Treatment with Epinephrine (Adrenaline) in Suspected Anaphylaxis during Anesthesia in Denmark

Lene H. Garvey, M.D., Ph.D.,* Bo Belhage, M.D., D.Msc.,† Mogens Krøigaard, M.D.,* Bent Husum, M.D., D.Msc.,‡ Hans-Jørgen Malling, M.D., D.Msc.,§ Holger Mosbech, M.D., D.Msc.§

ABSTRACT

Background: Literature on the use of epinephrine in the treatment of anaphylaxis during anesthesia is very limited. The objective of this study was to investigate how often epinephrine is used in the treatment of suspected anaphylaxis during anesthesia in Denmark and whether timing of treatment is important.

Methods: A retrospective study of 270 patients investigated at the Danish Anaesthesia Allergy Centre after referral due to suspected anaphylaxis during anesthesia was performed. Reactions had been graded by severity: C1, mild reactions; C2, moderate reactions; C3, anaphylactic shock with circulatory instability; C4, cardiac arrest. Use of epinephrine, dosage, route of administration, and time between onset of circulatory instability and epinephrine administration were noted.

Results: A total of 122 (45.2%) of referred patients had C3 or C4 reactions; of those, 101 (82.8%) received epinephrine. Route of administration was intravenous in 95 (94%) patients. Median time from onset of reported hypotension to treatment with epinephrine was 10 min (range, 1–70 min). Defining epinephrine treatment less than or equal to 10 min after onset of hypotension as early, and more than 10 min as late, infusion was needed in 12 of 60 patients (20%) treated early *versus* 12 of 35 patients (34%) treated late (odds ratio, 2.09) (95% confidence interval, 0.81–5.35).

Conclusion: Anaphylaxis may be difficult to diagnose during anesthesia, and treatment with epinephrine can be delayed as a consequence. Anaphylaxis should be considered and treated in patients with circulatory instability during anesthesia of no apparent cause who do not respond to the usual treatments.

What We Already Know about This Topic

- Anaphylactic reactions during anesthesia are rare events. Clinical data on timing, dosage, and route of administration of epinephrine for intraoperative treatment of anaphylaxis are scarce.

What This Article Tells Us That Is New

- This retrospective study shows that treatment with epinephrine is often delayed. A lack of a consistent response to suspected anaphylactic reactions during anesthesia is documented.

ANAPHYLAXIS has been defined as a "severe life-threatening generalized or systemic hypersensitivity reaction";[1] however, there is no universally agreed definition, and several other definitions have been proposed.[2–4] It can be triggered by a multitude of factors including foods, venoms, and drugs and can also occur in the setting of surgery and anesthesia caused by drugs, latex, disinfectants, or other substances used perioperatively.[5]

The incidence of anaphylaxis during anesthesia depends on the definition of anaphylaxis used and has been reported to be in the range of 1:3,180 to 1:20,000 anesthetics.[6] Anaphylaxis in the perioperative setting differs from anaphylaxis outside the operating room in several ways. Allergic signs and symptoms may be masked by the effect of anesthesia and surgery or hidden under surgical drapes. A large number of drugs and substances are administered simultaneously, making it very difficult to guess which substance caused the reaction.[7] The patient is usually fully monitored, has an intravenous access, and is under observation by anesthetic personnel. Thus, although the diagnosis of anaphylaxis during anesthesia is difficult to make and the cause will not be

* Consultant, Danish Anaesthesia Allergy Centre, Allergy Clinic KAA-816, Department of Dermato-Allergology, Copenhagen University Hospital, Gentofte Hospital, and Department of Anaesthesia, Centre for Head and Orthopaedics, Copenhagen University Hospital, Rigshospitalet. † Consultant, Department of Anaesthesiology, Copenhagen University Hospital, Bispebjerg Hospital. ‡ Consultant, Department of Anaesthesiology, Frederikssund Hospital, Denmark. § Consultant, Danish Anaesthesia Allergy Centre, Allergy Clinic KAA-816, Department of Dermato-Allergology, Copenhagen University Hospital, Gentofte Hospital.

Received from the Danish Anaesthesia Allergy Centre, Allergy Clinic KAA-816, Copenhagen University Hospital, Gentofte Hospital, Denmark. Submitted for publication March 28, 2010. Accepted for publication January 26, 2011. Support was provided solely from institutional/departmental sources. Presented as an abstract presentation at the Congress of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine, Odense, Denmark, June 12, 2009. Also presented at the Ph.D. defense by Lene Heise Garvey of the Ph.D. thesis "Allergic Reactions during Anaesthesia and Surgery," Gentofte, Denmark, June 24, 2010.

Address correspondence to Dr. Garvey: Danish Anaesthesia Allergy Centre, Allergy Clinic, Department of Dermato-Allergology, KAA 816, Gentofte Hospital, Niels Andersens Vej 65, DK-2900, Hellerup, Denmark. lene@heisegarvey.dk. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

 Anesthesiology 2011; 115:111–6

immediately obvious, the conditions for optimal management should be present once the diagnosis is made.

The recommended treatment guidelines for anaphylaxis, inside and outside the operating room, are all based on first-line treatment with epinephrine.[4,8–12] Not surprisingly, a recent Cochrane review could find no randomized or quasi-randomized trials of the use of epinephrine in anaphylaxis.[13] However, in anaphylaxis outside the operating room, delayed injection of epinephrine has been reported to be associated with mortality.[14,15] Only limited information on the management of anaphylaxis is available in the literature. A recent systematic review of gaps in the management of anaphylaxis covering a large number of databases over a time period spanning 1966–2008 could only identify 59 relevant studies.[16] In addition, very little is known of the management of anaphylaxis by anesthetists. One Danish study from a full-scale anesthesia simulator concluded that in anaphylaxis scenarios the diagnosis was made late by all teams and that no team had a structured plan for treatment.[17] Another study from the Australian Incident Monitoring Study concluded that there was a striking reluctance to administer epinephrine.[18]

In the Danish Anaesthesia Allergy Centre, detailed information on the treatment of suspected anaphylaxis in patients referred for investigation has been collected since 1999.

The aim of this retrospective study was to describe the use of epinephrine in the treatment of suspected anaphylaxis during anesthesia in Denmark from 1999 to 2008, with regard to dose, route of administration, and timing of administration.

Materials and Methods

A retrospective study of 270 adult patients investigated in the Danish Anaesthesia Allergy Centre after referral due to suspected anaphylaxis during anesthesia in the period 1999–2008 is presented. Institutional review board approval for this study was not needed according to Danish law. On referral, reactions were graded into reaction classes by one of two anesthesiologists in the Danish Anaesthesia Allergy Centre using the following classification (based on the classification proposed by J. Ring and K. Messmer in 1977)[19]:

C1, mild reactions, usually resolving spontaneously; C2, more severe reactions, resolving within 10–20 min with or without treatment; C3, anaphylactic shock usually requiring epinephrine to restore circulatory stability; and C4, cardiac arrest.

Grading of reactions was based on symptoms recorded in the referral papers, at the time of the reaction, by the attending anesthetist, combined with data from the anesthetic chart and other relevant notes. Details of treatment including use of epinephrine and other drugs, route of drug administration, dosage, and time between onset of circulatory instability and first epinephrine administration were also retrieved from referral papers. Total doses of epinephrine were based on cumulated bolus doses only, as cumulated doses of infused epinephrine were not reported by referring anesthetists. It was also noted whether serum tryptase had been measured in connection with the reaction.

The need for epinephrine infusion was used as a surrogate parameter for a severe prolonged reaction. Epinephrine treatment less than or equal to 10 min after onset of hypotension was defined as early, and epinephrine treatment more than 10 min after onset of hypotension was defined as late. This definition was made on the presumption that it takes up to 10 min to realize the lack of effect of the usual treatment modalities for hypotension during anesthesia (such as ephedrine, phenylephrine, fluids, decrease in anesthetic dose, *etc.*) and subsequently suspect the diagnosis of anaphylaxis.

Statistical Analysis

Continuous data were reported as median and range and statistical analysis of differences in age within sex, American Society of Anesthesiologists' physical status classification group, and reaction class was performed using either independent *t* test or analysis of variance (ANOVA). Because serum tryptase values are not normally distributed, data were reported using median and interquartile range, and statistical analysis was performed after logarithmic transformation to approximate a normal distribution. The study was based on consecutive inclusion of patients referred to the Danish Anaesthesia Allergy Centre in 1999–2008, and therefore no power calculation was performed before the study. Because anaphylaxis during anesthesia is a rare event, achieving sufficient power in this type of study represents a challenge, and the main focus of this study is on the descriptive aspects. A 2×2 contingency table analysis was carried out in the subgroup of 95 patients with class 3 or 4 reactions, who had intravenous epinephrine. Odds ratio estimation was performed on the risk of needing intravenous epinephrine infusion depending on the timing of initiation of treatment. Results are reported with 95% confidence interval. In addition, inference testing using two-tailed Fisher exact test was carried out.

P values of less than 0.05 were considered statistically significant. All analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

Results

A total of 270 patients (158 women, 112 men) with a median age of 49.5 yr (range, 17–86) were included in the study, and patient characteristics can be seen in table 1. There were more females (58.5%), and median age was significantly lower in females than in males with a median of 43 yr (range, 17–85 yr) *versus* 57.5 yr (range, 17–86 yr).

Most patients (87.4%) belonged to American Society of Anesthesiologists' physical status classification groups 1 and 2, and there was a statistically significant increase in age with increasing classification.

Severe reactions (C3 and C4) were seen in a total of 122 patients (45.2%), and a statistically significant increase in age was seen with increasing reaction class.

Table 1. Characteristics of Patients with Suspected Anaphylaxis during Anesthesia

	Patients No. (%)	Median Age (Range)	*P* Value
All patients	270 (100)	49.5 (17–86)	
Sex			
Female	158 (58.5)	43.0 (17–85)	<0.0001
Male	112 (41.5)	57.5 (17–86)	
ASA classification			
I	105 (38.9)	38.0 (17–76)	<0.0001
II	131 (48.5)	56.0 (18–86)	
III	34 (12.6)	62.5 (45–78)	
IV	0	0	
Reaction class			
1	83 (30.7)	40 (17–78)	<0.0001*
2	65 (24.1)	46 (18–86)	
3	113 (41.9)	56 (18–86)	
4	9 (3.3)	57 (33–62)	

Independent *t* test or ANOVA.

* Reaction classes 3 and 4 added together for statistical analysis.

ASA = American Society of Anesthesiologists physical status classification.

Across all four reaction classes a total of 123 patients (45.6%) received epinephrine (table 2). There was an increase in the proportion of patients receiving epinephrine with increasing reaction class, with 82.3% and 88.9% receiving epinephrine in C3 and C4 reactions, respectively.

The preferred route of administration was the intravenous route, and table 3 shows an overview of route of administration by reaction class. The inhalational route was used primarily in milder reaction classes (for patients with localized edema of the airways), and the intravenous route was used in patients with circulatory symptoms (C3 and C4 reactions). A total of 95 of 101 C3 and C4 reactions (94%) were treated with intravenous epinephrine. Median time to first treatment with epinephrine for these 95 patients was 10 min (range, 1–70 min). Treatment with epinephrine was given early (less than or equal to 10 min after onset of hypotension) in 60 of 95 patients (63.2%) and late (more than 10 min after onset of hypotension) in 35 of 95 patients (36.8%). Median times to first treatment with epinephrine were 5 min (range, 1–10) and 20 min (range, 15–70) for the early and late groups, respectively.

Table 2. Number of Cases and Total Dose of Epinephrine Administered in Patients with Anaphylaxis during Anesthesia

Reaction Class	Epinephrine Given/ Total Cases (%)	Total Epinephrine Dose in mg	
		No.	Median (Range)
1	4/83 (4.8)	1	0.01
2	18/65 (27.7)	10	0.125 (0.03–1.0)
3	93/113 (82.3)	83	0.2 (0.002–2.0)
4	8/9 (88.9)	8	1.95 (0.6–2.0)
Total	123/270 (45.6)	102	

Table 3. Route of Administration of Epinephrine in Suspected Anaphylaxis during Anesthesia According to Severity of Reactions

Route of Administration	Reaction Class				Total
	4	3	2	1	
Intravenous	8	87	10	1	106
Intramuscular	0	2	2	0	4
Subcutaneous	0	1	1	0	2
Inhalation	0	2	5	3	10
Not known	0	1	0	0	1
Total	8	93	18	4	123

Two-by-two table of timing of treatment with epinephrine and the need for intravenous infusion of epinephrine is shown in table 4. An odds ratio = 2.09 (95% confidence interval, 0.81–5.35) was found for needing intravenous infusion, when treatment with epinephrine was initiated more than 10 min after onset of hypotension. This finding did not reach statistical significance ($P = 0.15$). There was no significant difference in the distribution of age and sex between groups treated early and late. A serum tryptase was taken in 70 of 95 patients (73.7%), and median serum tryptase was 16.5 μg/l (interquartile range, 5.8–32.8) in patients treated early *versus* 16.1 μg/l (interquartile range 4.8–25.6) in patients treated late ($P = 0.72$); thus, no difference was found.

In 33 of 123 patients (26.8%) across all four reaction classes antihistamine and steroid treatment were given before treatment with epinephrine (table 5). For C3 and C4 reactions only, 17 of 101 patients (16.8%) with hypotension were treated with antihistamine and steroid before treatment with epinephrine. In most C3 reactions other vasoactive drugs such as ephedrine and phenylephrine were first-line treatment (data not shown), except in 22 patients (23.7%) in whom epinephrine was the first vasoactive drug administered.

Discussion

This is the first study describing details on timing, dosage, and route of administration of epinephrine in the treatment of suspected anaphylaxis during anesthesia. Our study indicates that treatment with epinephrine can be delayed, most likely

Table 4. Timing of Intravenous Epinephrine Treatment and Need for Epinephrine Infusion in Patients with Anaphylaxis during Anesthesia*

Timing of Epinephrine	Need for IV Infusion		Total
	Yes	No	
Late (>10 min)	12 (34%)	23 (66%)	35
Early (≤10 min)	12 (20%)	48 (80%)	60
Total	24	71	95

Odds ratio = 2.087 (95% CI 0.817–5.353).

* Class 3 and 4 reactions only (n = 95).

Table 5. Sequence of Drug Administration in the Treatment of Anaphylaxis during Anesthesia According to Reaction Class (n = 123)

Sequence of Drug Administration	Reaction Class				
	4	3	2	1	Total
Epinephrine first drug administered*	4	22	5	0	31
Epinephrine administered before AH/S	1	45	0	0	46
Epinephrine administered after AH/S	1	16	12	4	33
AH/S not administered	2	10	1	0	13
Total	8	93	18	4	123

* Epinephrine administered as first vasoactive drug (before efedrine, phenylephrine, *etc.*).
AH = antihistamine; S = steroid.

because of the difficulties in diagnosing anaphylaxis during anesthesia and surgery. Other factors may contribute to the delay in treatment, such as a reluctance to administer epinephrine, even when the diagnosis of anaphylaxis has been made and antihistamine and steroids have been given. Epinephrine was administered in 82.1% of C3 and C4 reactions, and in 94% of these patients it was given intravenously. However, median doses used in C3 reactions of 0.2 mg (range, 0.002–2.0 mg) were high compared with current recommendations of an intravenous start dose of 0.01–0.05 mg.[8]

The reasons for the large variability in the doses are unclear, but could be a reflection on the lack of clear guidelines on the treatment on anaphylaxis during anesthesia in Scandinavia until 2007.[8]

In milder C1 and C2 reactions with skin symptoms only or self-limiting tachycardia or bronchospasm, a first-line treatment with antihistamine and steroids would be acceptable. However, the patient should be observed for progression in symptoms and relevant doses of epinephrine should be made ready for use. Our study showed that in 16 of 22 (72.7%) C1 and C2 reactions where epinephrine was needed, it was administered after antihistamines and steroids, perhaps reflecting a progression in symptoms from mild symptoms to a more severe reaction requiring epinephrine.

As inclusion of patients in our study depended on referral to the Danish Anaesthesia Allergy Centre after the reaction, only patients surviving the reaction have been referred and included. We are only aware of one adverse incident, the development of hemiplegia after a prolonged resuscitation attempt in a 47-yr-old woman. However, we have not looked at other consequences for patients such as prolonged admissions, unplanned admission to the intensive care unit, canceled operations, or changes to indications for surgery, which are likely to occur after anaphylaxis during anesthesia.

Postmortem studies of anaphylaxis conclude that severe reactions progress rapidly and are more likely to have a fatal outcome in older patients with comorbid conditions such as ischemic heart disease.[14] A postmortem study from the United Kingdom reported that in patients in whom the allergen was administered intravenously (including anesthetic reactions), presentation was more likely to be as shock with a median time to cardiac arrest of 5 min from administration of the allergen.[15] The same study looked at treatment given during reactions and reported that in the 55 reactions to drugs, treatment with epinephrine was given before the cardiac arrest in only 16% of patients. In 73% of patients epinephrine was administered after cardiac arrest occurred; in the remaining 11% epinephrine was not administered at all. In contrast, a few patients with inappropriately high doses of epinephrine (1–2.5 mg given intravenously) administered for relatively mild reactions also had a fatal outcome, related to adverse effects of epinephrine. This has been reported before.[20]

The rare and unexpected occurrence of anaphylaxis combined with lack of knowledge of the most effective treatment, especially with regard to dosage, timing, and route of epinephrine administration, thus unfortunately still leads to deaths. Only a few studies have looked at the knowledge of treatment with epinephrine among doctors. A questionnaire study of 78 doctors starting in training posts in emergency medicine showed that 100% would use epinephrine in the treatment of anaphylaxis, but only 5% identified the correct dose and route of administration.[21] Conclusions from a recent questionnaire study of 91 doctors working in acute specialties in an Australian hospital indicated that 92% would give epinephrine as first-line treatment, but only 20% knew the correct dose and route of administration. Interestingly, 20% of doctors would administer epinephrine in doses used for cardiac arrest to a conscious patient.[22]

Even though most doctors know that epinephrine is the first-line treatment of anaphylaxis, retrospective studies of patients with anaphylaxis generally show a reluctance to administer epinephrine. This has been found in reactions to food,[23] in emergency departments,[24] in pediatric patients,[25] in insect venom allergy,[26] and in patients with mastocytosis at high risk of developing anaphylaxis.[27] This reluctance to administer epinephrine is even reflected in our study of the treatment of anaphylaxis during anesthesia, where anesthetists chose to administer antihistamines and steroids before epinephrine in 16.8% of patients and did not administer epinephrine at all in 17.2% of patients having C3 and C4 reactions with cardiovascular instability. Reasons for this are unclear, but could be because of limited knowledge of the treatment algorithm for anaphylaxis, lack of experience with the use of epinephrine outside the cardiac arrest setting, or a reluctance to treat a tachycardic patient with a drug with a positive chronotropic effect. Because there is no proven benefit of antihistamines and steroids in anaphylactic shock,[28,29] the administration of epinephrine should always precede treatment with antihistamines and steroids once the diagnosis of anaphylaxis has been made.[8]

Only one other study could be found examining the management of anaphylaxis during anesthesia,[18] and the authors reported that anesthetists showed a striking reluc-

tance in administering epinephrine as an appropriate early intervention. This study also showed that antihistamines and steroids conferred no separate benefit in the acute phase. One of the main conclusions was that anesthetists should always suspect anaphylaxis in patients with sudden, unexpected, or severe hypotension.

The data in this study could not support our theory, that in patients in whom the diagnosis is not made or treatment with epinephrine is delayed for other reasons, the risk of needing prolonged treatment could be increased. This theory is often mentioned in the literature but very little evidence can be found. The only studies come from experimental animal models of anaphylaxis, which have shown conflicting results. Some studies showed that a single-bolus dose of epinephrine did not hasten recovery in dogs,[30,31] and another study showed that early (less than 5 min) bolus doses of epinephrine followed by titrated infusion of epinephrine provided the best survival in rats.[32] It could be speculated that in untreated patients or in those treated late, the immune response is magnified by the prolonged release of inflammatory mediators. In our study there was no difference between serum tryptase values in reactions treated early or late. This could indicate that tryptase release is related to initiation of the allergic reaction and initial reaction severity, but not to the prolonged allergic response. However, this has never been reported before and remains speculative.

No human studies of timing of treatment of anaphylaxis could be found, but a study of litigations related to drug errors in anesthesia in the United Kingdom in the period 1995–2007 may be interpreted to show a worse outcome in patients treated late.[33] In this study anaphylaxis was reported in 31 patients, and in 20 of these a drug was given despite a known allergy; there were no deaths or sequelae in this group. However, in the remaining 11 patients, the cause of the reaction was unknown, and thus the reaction was unexpected. In that group there were five deaths and four cardiac arrests, with two resulting in severe neurologic damage. One could speculate that when a drug is given despite a known allergy it is either an oversight or a conscious decision by the anesthesiologist deciding to give a test dose. In both cases a rapid diagnosis of anaphylaxis is likely to be made because of a high index of suspicion, and consequently treatment will be initiated promptly. On the other hand, unexpected anaphylaxis occurring during anesthesia may be difficult to diagnose, and the delay in diagnosis and treatment might be speculated to be the cause of the poorer outcome in this group. Therefore, as previously suggested[18] in patients with sudden, severe hypotension during anesthesia who are unresponsive to the usual treatment with ephedrine and fluids, anaphylaxis should be suspected and treatment with epinephrine considered. Intravenous bolus doses of epinephrine starting at 0.01–0.05 mg (10–50 μg) should be administered, and doses should be repeated or increased according to clinical response.[8]

It is recommended that the intravenous route for epinephrine treatment should be reserved for monitored patients and for specialists with experience in this treatment (anesthetists and intensivists or physicians in emergency departments). In all other circumstances the recommendation is to use intramuscular epinephrine.[4,34]

In the United Kingdom postmortem study, 56% of fatal reactions to drugs occurred in an operating theater, *i.e.*, with a fully monitored patient, with intravenous access and anesthetic personnel within reach.[15] There are no recent similar studies of deaths related to anaphylaxis in Denmark, but we are not aware of any fatalities caused by anaphylaxis during anesthesia in Denmark in our study period 1999–2008. However, because patients who might have died from anaphylaxis during anesthesia would not be referred to the Danish Anaesthesia Allergy Centre, such patients may not have come to our attention. A closed claims study analyzing deaths related to anesthesia in the period 1996–2004 in Denmark did not identify any cases of suspected perioperative anaphylaxis leading to a claim in the patient insurance association.[35]

Data on mortality from anaphylaxis during anesthesia varies in the literature, but because of the rarity of these events and the many potential sources of error in obtaining mortality data, it is uncertain whether there are differences in mortality in different countries. It is, however, important to note that geographic differences exist in the causes found on investigation of anaphylaxis during anesthesia. In Denmark there is a much lower incidence of reactions to neuromuscular blocking agents than is seen in other countries such as France, Australia, United Kingdom, and Norway. Because reactions to neuromuscular blocking agents are often very severe, this difference should be kept in mind when interpreting the Danish data presented in this article.

In conclusion, anaphylaxis during anesthesia may be difficult to diagnose. Because prompt and correct treatment seems a prerequisite for a good outcome, it is imperative that anesthetic personnel are trained to diagnose and treat anaphylaxis in the difficult setting of surgery and anesthesia. Because the first-line treatment is epinephrine, which has a narrow therapeutic profile, it is important that anesthetic personnel are familiar with correct dosing and route of administration. Although our study shows that anesthetic personnel on the whole manage anaphylaxis satisfactorily, there is room for improvement regarding the early use of titrated doses of intravenous epinephrine in suspected anaphylaxis during anesthesia.

References

1. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J, Thien F, Van Cauwenberge P, Williams HC: Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol 2004; 113:832–6
2. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, Brown SG, Camargo CA Jr, Cydulka R, Galli SJ, Gidudu J, Gruchalla RS, Harlor AD Jr, Hepner DL, Lewis LM, Lieberman PL, Metcalfe DD, O'Connor R, Muraro A, Rudman A, Schmitt C, Scherrer D, Simons FE, Thomas S, Wood JP, Decker WW: Second symposium on the definition and management of anaphylaxis: Summary report – Second National Institute of Allergy and Infectious Disease/Food

Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117:391–7

3. Rüggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, de Souza Brito G, Heininger U, Imoukhuede B, Khamesipour A, Erlewyn-Lajeunesse M, Martin S, Mäkelä M, Nell P, Pool V, Simpson N, Brighton Collaboration Anaphylaxis Working Group: Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007; 25:5675–84
4. Simons FE: Anaphylaxis. J Allergy Clin Immunol 2010; 125: S161–81
5. Mertes PM, Lambert M, Guéant-Rodriguez RM, Aimone-Gastin I, Mouton-Faivre C, Moneret-Vautrin DA, Guéant JL, Malinovsky JM, Demoly P: Perioperative anaphylaxis. Immunol Allergy Clin North Am 2009; 29:429–51
6. Malinovsky JM, Decagny S, Wessel F, Guilloux L, Mertes PM: Systematic follow-up increases incidence of anaphylaxis during adverse reactions in anesthetized patients. Acta Anaesthesiol Scand 2008; 52:175–81
7. Krøigaard M, Garvey LH, Menné T, Husum B: Allergic reactions in anaesthesia: Are suspected causes confirmed on subsequent testing? Br J Anaesth 2005; 4:468–71
8. Kroigaard M, Garvey LH, Gillberg L, Johansson SG, Mosbech H, Florvaag E, Harboe T, Eriksson LI, Dahlgren G, Seeman-Lodding H, Takala R, Wattwil M, Hirlekar G, Dahlén B, Guttormsen AB: Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. Acta Anaesthesiol Scand 2007; 51:655–70
9. Mertes PM, Laxenaire MC, Lienhart A, Aberer W, Ring J, Pichler WJ, Demoly P, Working Group for the SFAR, ENDA, EAACI Interest Group on Drug Hypersensitivity: Reducing the risk of anaphylaxis during anaesthesia: Guidelines for clinical practice. J Investig Allergol Clin Immunol 2005; 15:91–101
10. Harper NJ, Dixon T, Dugué P, Edgar DM, Fay A, Gooi HC, Herriot R, Hopkins P, Hunter JM, Mirakian R, Pumphrey S, Seneviratne SL, Walls AF, Williams P, Wildsmith JA, Wood P, Nasser AS, Powell RK, Mirakhur R, Soar J, Working Party of the Association of Anaesthetists of Great Britain and Ireland: Suspected anaphylactic reactions associated with anaesthesia. Anaesthesia 2009; 64:199–211
11. Kemp SF, Lockey RF, Simons FE, World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis: Epinephrine: The drug of choice for anaphylaxis. A statement of the World Allergy Organization. Allergy 2008; 63:1061–70
12. Soar J, Pumphrey R, Cant A, Clarke S, Corbett A, Dawson P, Ewan P, Foëx B, Gabbott D, Griffiths M, Hall J, Harper N, Jewkes F, Maconochie I, Mitchell S, Nasser S, Nolan J, Rylance G, Sheikh A, Unsworth DJ, Warrell D: Working Group of the Rescusitation Council (UK): Emergency treatment of anaphylactic reactions – Guidelines for healthcare providers Resuscitation 2008; 77:157–9
13. Sheikh A, Shehata YA, Brown SG, Simons FE: Adrenaline for the treatment of anaphylaxis: Cochrane systematic review. Allergy 2009; 64:204–12
14. Greenberger PA, Rotskoff BD, Lifschultz B: Fatal anaphylaxis: Post- mortem findings and associated comorbid diseases. Ann Allergy Asthma Immunol 2007; 98:252–7
15. Pumphrey RS: Lessons for the management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy 2000; 30: 1144–50
16. Kastner M, Harada L, Waserman S: Gaps in anaphylaxis management at the level of physicians, patients, and the community: A systematic review of the literature. Allergy 2010; 65:435–44
17. Jacobsen J, Lindekær AL, Østergaard HT, Nielsen K, Østergaard D, Laub M, Jensen PF, Johannessen N: Management of anaphylactic shock evaluated using a full-scale anaesthesia simulator. Acta Anesthesiol Scand 2001; 45:315–9
18. Currie M, Kerridge RK, Bacon AK, Williamson JA: Crisis management during anaesthesia: Anaphylaxis and allergy. Qual Saf Health Care 2005; 14:e19
19. Ring J, Messmer K: Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet 1977; 1:466–9
20. Johnston SL, Unsworth J, Gompels MM: Adrenaline given outside the context of life threatening allergic reactions. BMJ 2003; 326:589–90
21. Gompels LL, Bethune C, Johnston SL, Gompels MM: Proposed use of adrenaline (epinephrine) in anaphylaxis and related conditions: A study of senior house officers starting accident and emergency posts. Postgrad Med J 2002; 78: 416–8
22. Thain S, Rubython J: Treatment of anaphylaxis in adults: Results of a survey of doctors at Dunedin Hospital, New Zealand. N Z Med J 2007; 120:U2492
23. Le TM, van Hoffen E, Pasmans SG, Bruijnzeel-Koomen CA, Knulst AC: Suboptimal management of acute food-allergic reactions by patients, emergency departments and general practitioners. Allergy 2009; 64:1226–35
24. Wang J, Sampson HA: Food anaphylaxis. Clin Exp Allergy 2007; 37:651–60
25. Mehl A, Wahn U, Niggemann B: Anaphylactic reactions in children–a questionnaire-based survey in Germany. Allergy 2005; 60:1440–5
26. Clark S, Long AA, Gaeta TJ, Camargo CA Jr: Multicenter study of emergency department visits for insect sting allergies. J Allergy Clin Immunol 2005; 116:643–9
27. Brockow K, Jofer C, Behrendt H, Ring J: Anaphylaxis in patients with mastocytosis: A study on history, clinical features and risk factors in 120 patients. Allergy 2008; 63:226–32
28. Sheikh A, ten Broek V, Brown SGA, Simons FER: H_1-antihistamines for the treatment of anaphylaxis: Cochrane systematic review. Allergy 2007; 62:830–7
29. Andreae DA, Andreae MH: Should antihistamines be used to treat anaphylaxis? BMJ 2009; 339:b2489
30. Mink SN, Bands C, Becker A, Elkin J, Sharma S, Unruh H, Kepron W: Effect of bolus epinephrine on systemic hemodynamics in canine anaphylactic shock. Cardiovasc Res 1998; 40:546–56
31. Bautista E, Simons FE, Simons KJ, Becker AB, Duke K, Tillett M, Kepron W, Mink SN: Epinephrine fails to hasten hemodynamic recovery in fully developed canine anaphylactic shock. Int Arch Allergy Immunol 2002; 128:151–64
32. Dewachter P, Raëth-Fries I, Jouan-Hureaux V, Menu P, Vigneron C, Longrois D, Mertes PM: A comparison of epinephrine only, arginine vasopressin only, and epinephrine followed by arginine vasopressin on the survival rate in a rat model of anaphylactic shock. ANESTHESIOLOGY 2007; 106:977–83
33. Cranshaw J, Gupta KJ, Cook TM: Litigation related to drug errors in anaesthesia: An analysis of claims against the NHS in England 1995–2007. Anaesthesia 2009; 64:1317–23
34. Mirakian R, Ewan PW, Durham SR, Youlten LJ, Dugué P, Friedmann PS, English JS, Huber PA, Nasser SM, BSACI: BSACI guidelines for the management of drug allergy. Clin Exp Allergy 2009; 39:43–61
35. Hove LD, Steinmetz J, Christoffersen JK, Møller A, Nielsen J, Schmidt H: Analysis of deaths related to anesthesia in the period 1996–2004 from closed claims registered by the Danish Patient Insurance Association. ANESTHESIOLOGY 2007; 106: 675–80