Position paper

Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization

Epinephrine is the treatment of choice and the first drug that should be administered in acute anaphylaxis. Some state that properly administered epinephrine has no absolute contraindication in this clinical setting. A committee of anaphylaxis experts assembled by the World Allergy Organization has examined the evidence from the medical literature concerning the appropriate use of epinephrine for anaphylaxis. The Committee strongly believes that epinephrine is currently underutilized and often dosed suboptimally to treat anaphylaxis, is under-prescribed for potential future self-administration, that most of the reasons proposed to withhold its clinical use are flawed, and that the therapeutic benefits of epinephrine exceed the risk when given in appropriate i.m. doses.

Anaphylaxis is an acute and potentially lethal multi-system allergic reaction. Most consensus guidelines for the past 30 years have held that epinephrine is the drug of choice and the first drug that should be administered in acute anaphylaxis. Some state that properly administered epinephrine has no absolute contraindication in this clinical setting. A committee of anaphylaxis experts assembled by the World Allergy Organization has examined the evidence from the medical literature concerning the appropriate use of epinephrine for anaphylaxis. The Committee strongly believes that epinephrine is currently underutilized and often dosed suboptimally to treat anaphylaxis, is under-prescribed for potential future self-administration, that most of the reasons proposed to withhold its clinical use are flawed, and that the therapeutic benefits of epinephrine exceed the risk when given in appropriate i.m. doses.

Few controlled clinical trials, and no placebo-controlled trials, have been performed in anaphylaxis because of the nature of the disease (19). Randomization to a nonepinephrine treatment would be unethical because of the preponderance of data showing that expeditious treatment with epinephrine is optimal, if not critical, for survival in many instances (20–25). The following discussion reviews the current evidence for the use of epinephrine in anaphylaxis.

Definition
The traditional nomenclature for anaphylaxis reserves the term anaphylactic for IgE-dependent reactions and the term anaphylactoid for IgE-independent events, which are...
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### Categorization of evidence

- **IA** Evidence from meta-analysis of randomized controlled trials
- **IB** Evidence from at least one randomized controlled trial
- **IIa** Evidence from at least one controlled study without randomization
- **IIb** Evidence from at least one other type of quasi-experimental study
- **III** Evidence from nonexperimental descriptive studies, such as comparative studies
- **IV** Evidence from expert committee reports or opinions or clinical experience of respected authorities or both
- **NR** Not rated

### Figure 1. Categorization of evidence.

A literature search of Medline (1966 to present) was conducted using the keywords anaphylaxis and epinephrine and articles from the personal anaphylaxis file collections of the authors were also included. Cross-references were accessed when deemed appropriate. References have been categorized by degree of evidence, where possible (27; Fig. 1).

### Methods

A literature search of Medline (1966 to present) was conducted using the keywords anaphylaxis and epinephrine and articles from the personal anaphylaxis file collections of the authors were also included. Cross-references were accessed when deemed appropriate. References have been categorized by degree of evidence, where possible (27; Fig. 1).

### Anaphylaxis in perspective

Anaphylaxis is an acute and potentially lethal multi-system allergic reaction in which some or all of the following signs and symptoms occur: diffuse erythema, pruritus, urticaria, and/or angioedema; bronchospasm; laryngeal edema; hypotension; cardiac arrhythmias; feeling of impending doom; unconsciousness and shock. Other earlier or concomitant signs and symptoms can include: itchy nose, eyes, pharynx, genitalia, palms, and soles; rhinorrhea; change in voice; metallic taste; nausea, vomiting, diarrhea, abdominal cramps and bloating; lightheadedness; headache; uterine cramps, and generalized warmth.

The US National Institute of Allergy and Infectious Diseases (Bethesda, MD, USA) and the Food Allergy and Anaphylaxis Network (Chantilly, VA, USA) convened symposia in 2004 and 2005, during which an international and interdisciplinary group of representatives and experts from 16 professional, government and lay organizations attempted, among other tasks, to establish clinical criteria that would increase diagnostic precision in anaphylaxis (16). The working definition proposed is the following: ‘Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death’. The group proposed that anaphylaxis is likely to be present clinically if any one of three criteria is satisfied within minutes to hours: (i) acute onset of illness with involvement of skin, mucosal surface, or both, and at least one of the following: respiratory compromise, hypotension, or end-organ dysfunction; (ii) two or more of the following occur rapidly after exposure to a likely allergen: involvement of skin or mucosal surface, respiratory compromise, hypotension, or persistent gastrointestinal symptoms; and (iii) hypotension develops after exposure to a known allergen for that patient: age-specific low blood pressure or decline of systolic blood pressure of > 30% compared to baseline (16). The group concluded that these criteria ‘are likely to capture more than 95% of cases of anaphylaxis’. The implication from this definition could be interpreted to mean that more than just cutaneous and other even less severe symptoms need to be present before epinephrine is administered. However, the Anaphylaxis Working Group report also states that ‘there undoubtedly will be patients who present with symptoms not yet fulfilling the criteria of anaphylaxis yet in whom it would be appropriate to initiate therapy with epinephrine, such as a patient with a history of near-fatal anaphylaxis to peanut who ingested peanut and within minutes is experiencing urticaria and generalized flushing’.

In summary, anaphylaxis occurs as part of a clinical continuum. It can begin with relatively minor symptoms and rapidly progress to a life-threatening respiratory and cardiovascular reaction. Delaying treatment until the development of multi-organ symptoms, as under the clinical criteria for diagnosis by the Anaphylaxis Working Group report, may be risky since the ultimate severity of anaphylaxis is difficult or impossible to predict at the time of onset of the episode. Therefore, some of the authors and Committee members of the WAO Ad Hoc Committee on Epinephrine and Anaphylaxis recommend that any symptoms of anaphylaxis, such as generalized pruritus, erythema, urticaria, and angioedema alone, and any other systemic symptom including those not involving vital organs, should be treated immediately and as necessary with appropriate i.m. doses of epinephrine in an attempt to prevent more severe anaphylaxis from occurring.

Conversely, symptoms clearly attributable to another diagnosis for which the clinical probability is much
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Respiratory compromise and cardiovascular collapse cause most fatalities (28, 34). An analysis of 202 anaphylaxis fatalities occurring in the UK from 1992 to 2001 ascertained that the interval between initial onset of food anaphylaxis symptoms and fatal cardiopulmonary arrest averaged 25–35 min, which was longer than for insect stings (10–15 min) or for drugs (mean, 5 min in hospital; 10–20 min prehospital) (34).

Increased vascular permeability during anaphylaxis can shift up to 35% of intravascular fluid to the extravascular space within 10 min (35). The intrinsic compensatory response to anaphylaxis (endogenous epinephrine and other catecholamines, as well as angiotensin II, endothelin 1, etc.) also influences the extent of clinical manifestations and, when adequate, may be life-saving independent of medical intervention, which sometimes contributes to diagnostic and therapeutic confusion. Because mast cells accumulate at sites of coronary atherosclerotic plaques and IgE antibodies bound to mast cells can trigger mast cell degranulation, some investigators have suggested that anaphylaxis may lead to myocardial ischemia by promoting plaque rupture (36, 37). Stimulation of the H1 histamine receptor may also produce coronary artery vasospasm (37, 38).

Pharmacology of epinephrine

The pharmacology of epinephrine is reviewed in detail elsewhere (39, 40; Fig. 2). At recommended dosages and routes of administration, the α-adrenergic vasoconstrictive effects reverse peripheral vasodilation, which alleviates hypotension and also reduces erythema, urticaria, and angioedema. Local injection of epinephrine may also minimize further absorption of antigen from a sting or injection, but this has not been studied systematically. The β-adrenergic properties of epinephrine cause bronchodilation, increase myocardial output and contractility, and suppress further mediator release from mast cells and basophils (41, 42). Epinephrine administered in low concentrations (e.g. 0.1 μg/kg) paradoxically can produce vasodilation, hypotension, and increased release of inflammatory mediators (39, 43).

Epinephrine administration enhances coronary blood flow. Two mechanisms are probably responsible: an

Figure 2. Adrenergic effects of epinephrine (40). Reproduced with permission.
increased duration of diastole compared to that of systole and a vasodilator effect due to increased myocardial contractility. These actions usually offset the vasoconstrictor effects of epinephrine on the coronary arteries (39, 44). Rapid achievement of peak plasma and tissue epinephrine levels appears to optimize survival, as retrospective human studies demonstrate that delayed administration is associated with poor outcomes (20, 21). However, epinephrine administration during anaphylaxis is not always effective and patients may still die (20–25). Reasons may be multifactorial and include delayed administration, inadequate doses, inappropriate route of administration, use of epinephrine that has passed its expiry date, leading to inadvertent administration of an inadequate dose, or an underlying disease, such as poorly controlled asthma, cardiovascular disease, mastocytosis, and perhaps other serious systemic disorders (40, 45). A study performed in a canine model also demonstrates that achievement of peak epinephrine plasma levels and hemodynamic recovery is not as effective when epinephrine administration is delayed until hypotension has developed (46).

Epinephrine has a relatively narrow therapeutic window (relative benefit vs risk) (Fig. 3). Common pharmacologic effects that occur at recommended doses via any route of administration include agitation, anxiety, tremulousness, headache, dizziness, pallor, or palpitations (39). Rarely, and usually associated with overdosage, or overly rapid rate of intravenous infusion, epinephrine administration might contribute to or cause myocardial ischemia or infarction (47–52), pulmonary edema (53, 54), prolonged QTc interval [QTc = QT interval divided by the square root of the RR interval (in seconds) on the electrocardiogram] (55), ventricular arrhythmias, accelerated hypertension, and intracranial hemorrhage in adults and children alike (41, 56). Nonetheless, some patients have survived massive overdoses of epinephrine with no evidence of myocardial ischemia (57, 58). Particularly vulnerable populations are those individuals at the extremes of age and those with hypertension, peripheral vascular disease, ischemic heart disease, or untreated hyperthyroidism (increased number of β-adrenergic receptors in the vasculature of these individuals render the myocardium more sensitive to β-adrenergic effects of epinephrine) (59). Certain medications might also increase the risk of adverse events from drug interactions (13, 18, 42, 59). Some medications decrease the effectiveness of endogenous catecholamine stores or exogenously administered epinephrine (β-adrenergic blockers), interfere with intrinsic compensatory responses to hypotension (angiotensin-converting enzyme inhibitors and possibly angiotensin-II receptor blockers), or impede epinephrine metabolism and lead to increased plasma and tissue concentrations (tricyclic antidepressants and monoamine oxidase inhibitors). β-adrenergic antagonists and α-adrenergic antagonists also potentially can exaggerate pharmacologic effects of epinephrine by permitting unopposed α-adrenergic (vasoconstrictor) and β-adrenergic (vasodilator) effects, respectively. Cocaine and amphetamines sensititize the myocardium to effects of epinephrine, thus increasing the risk of toxicity.

However, none of these circumstances poses an absolute contraindication to epinephrine administration for anaphylaxis (13).

Management of anaphylaxis
Physicians and other healthcare professionals who perform procedures or administer medications should have available the basic therapeutic agents used to treat anaphylaxis (4, 7, 13): (i) stethoscope and sphygmomanometer; (ii) tourniquets, syringes, hypodermic needles, large-bore needles (e.g. 14- or 16-gauge); (iii) injectable aqueous epinephrine 1 : 1000 (1 mg in 1 ml) (physicians are being urged to express doses in mass concentration, e.g. 1 mg in ml, rather than as ratios, e.g. 1 : 1000, which have been identified as a source of dosing errors with epinephrine and other medications); (iv) equipment and supplies for administering supplemental oxygen; (v) equipment and supplies for administering intravenous fluids; (vi) oral or laryngeal mask airway; (vii) diphenhydramine or similar injectable antihistamine; (viii) ranitidine or other injectable H2 antihistamine; (ix) corticosteroids for i.v. injection; and (x) vasopressor (e.g. dopamine or norepinephrine). Glucagon, an automatic defibrillator, and one-way valve facemask with oxygen inlet port are other supplies that some clinicians might find desirable depending on the individual clinical setting (13).

Assessment and maintenance of airway, breathing, circulation, and mentation are necessary before proceeding to other management steps. Patients are monitored continuously to facilitate prompt detection of any clinical changes or treatment complications. Place-
ment of a patient in the recumbent position with elevation of the lower extremities is strongly recommended as management in the sitting or upright position has contributed to poor outcomes in some patients (34).

When to administer epinephrine

Epinephrine should be administered simultaneously with the above measures (12–14). By expert consensus based on anecdotal evidence, there is no absolute contraindication to epinephrine administration in anaphylaxis (13). It can be administered in doses appropriate for the severity of the reaction, regardless of the initial signs and symptoms of anaphylaxis. All subsequent therapeutic interventions depend on the initial response to epinephrine. Development of toxicity or inadequate response to epinephrine injections indicates that additional therapeutic modalities are necessary (13). Table 1 outlines a sequential approach to anaphylaxis treatment. Modalities used in concert with epinephrine are reviewed in detail elsewhere (10–14).

_Epinephrine injections_. Expert consensus and anecdotal evidence indicate aqueous epinephrine 1 : 1000 dilution (1 mg in 1 ml), 0.2–0.5 mg (0.01 mg/kg in children; maximum dose, 0.3 mg) administered intramuscularly every 5–15 min or as necessary, depending on the severity of the reaction, regardless of the initial signs and symptoms of anaphylaxis. Every subsequent therapeutic intervention depends on the initial response to epinephrine. Development of toxicity or inadequate response to epinephrine injections indicates that additional therapeutic modalities are necessary (13). Table 1 outlines a sequential approach to anaphylaxis treatment. Modalities used in concert with epinephrine are reviewed in detail elsewhere (10–14).

Table 1. Management of acute anaphylaxis

| I. Immediate intervention                      |
|-----------------------------------------------|
| a. Assessment of airway, breathing, circulation, and adequacy of mentation |
| b. Administer epinephrine intramuscularly every 5–15 min, in appropriate doses, as necessary, depending on the presenting signs and symptoms of anaphylaxis, to control signs and symptoms and prevent progression to more severe symptoms such as respiratory distress, hypotension, shock and unconsciousness. |

| II. Possibly appropriate, subsequent measures depending on response to epinephrine                      |
|------------------------------------------------------------------------------------------------|
| a. Place patient in recumbent position and elevate lower extremities. |
| b. Establish and maintain airway. |
| c. Administer oxygen. |
| d. Establish venous access. |
| e. Normal saline i.v. for fluid replacement. |

| III. Specific measures to consider after epinephrine injections, where appropriate                      |
|------------------------------------------------------------------------------------------------|
| a. Consider epinephrine infusion. |
| b. Consider H$_2$ and H$_3$ antihistamines. |
| c. Consider nebulized $f_2$ agonist (e.g. albuterol (salbutamol)) for bronchospasm resistant to epinephrine. |
| d. Consider systemic corticosteroids. |
| e. Consider diuretic. |
| f. Consider glucagon for patient taking $\beta$-blocker. |
| g. Consider atropine for symptomatic bradycardia. |
| h. Consider transportation to an emergency department or an intensive care facility. |
| i. For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary. |

See reference (13) for specific details.

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_Intravenous epinephrine_. Epinephrine (1 : 10 000 or 1 : 100 000 dilutions) should be administered by infusion during cardiac arrest, or to unresponsive or severely hypotensive patients who have failed to respond to intravenous volume replacement and several epinephrine injections (13). One group of investigators suggest that the early use of intravenous epinephrine is safe, effective, and well tolerated when the rate is titrated to clinical response, but this has not been evaluated systematically in a cohort study comparing this modality to epinephrine i.m. injections (67).

_Inhaled epinephrine_. Some physicians recommend inhalation of epinephrine as an alternative to injection during anaphylaxis, but perioral paresthesias, bad taste, and gastrointestinal effects are dose-limiting and it may not achieve prompt, significant increases in plasma epinephrine concentrations (68, 69). No direct comparisons have been made between the inhaled and the intramuscular routes of epinephrine administration.

Follow-up and observation postanaphylaxis

Observation periods should be individualized and based on such factors as co-morbid conditions and distance from the patient’s home to the closest emergency facility, particularly as there are no reliable predictors of biphasic anaphylaxis (13). After resolution of the acute episode,
patients should be discharged with an epinephrine auto-injector and properly instructed on how to self-administer it in case of a subsequent episode. They should receive an individualized Anaphylaxis Emergency Action Plan (18). Patients should also have ready access to emergency medical services to facilitate prompt transportation to the closest emergency department (ED) for treatment after injecting the additional epinephrine.

Use of epinephrine by healthcare professionals

Numerous guidelines on anaphylaxis have been published, but physicians and other healthcare professionals often do not follow them. For example, investigators determined by questionnaire that only 4 (5%) of 78 senior house officers beginning ED responsibilities in the UK would administer epinephrine appropriately and with the proper dose and route of administration, as outlined in the UK Resuscitation Council guidelines on anaphylaxis (70). Other reports have examined treatment patterns in the ED settings of civilian (71) and military hospitals (72) in the USA and observed that epinephrine injections were administered during acute anaphylaxis to 16% and 50% of patients, respectively, as recommended by consensus anaphylaxis guidelines. Retrospective analysis of a national reporting database on ED visits in the USA from 1993 to 2004 revealed 12.4 million allergy-related visits to the ED, approximately 1% of all ED visits based on ICD-9-CM coding. Anaphylaxis coding was rare (0.01% of all ED visits), although epinephrine was administered in 50% of those coded with anaphylaxis. Epinephrine administration documented in patients with acute allergic conditions was infrequent (11%) and the trend of use declined over the period of interest from 19% to 7% ($P = 0.04$) (73).

Primary care physicians have demonstrated similar knowledge gaps in their knowledge pertaining to anaphylaxis. For example, a questionnaire based on the clinical scenario of a child with peanut-induced anaphylaxis was utilized in a random sample of 468 pediatricians in the USA (74). About half (56%) agreed both that the scenario represented anaphylaxis and that treatment with epinephrine was indicated. Most (81%) correctly chose to discharge the child home with self-injectable epinephrine and either to refer to an allergist or to recommend further diagnostic testing (86%). Similar surveys have been performed in other countries [several studies are cited in ref. (75)].

Studies have also demonstrated that many healthcare professionals are uncertain about how to use an epinephrine auto-injector and thus cannot properly instruct their patients (76, 77). Available resources may help physicians develop treatment plans and resolve any therapeutic quandaries (17, 18, 65). Examples of written action plans can be downloaded over the Internet (see ‘Additional Resources’).
Underutilization of epinephrine by patients, parents, and caregivers

Fatalities during witnessed anaphylaxis, most of which occur outside of a medical facility, usually result from delayed administration of epinephrine. In a retrospective review of six fatal and seven nonfatal episodes of food-induced anaphylaxis in children and adolescents, all subjects who survived had received epinephrine before or within 5 min of developing severe respiratory symptoms. None of the subjects with fatal attacks received epinephrine prior to the onset of severe respiratory symptoms (20). Analysis of data from a national case registry of fatal food anaphylaxis in the U.S. indicates that very few individuals (7/63) had epinephrine auto-injectors available at the time of fatal reaction (23, 25). Similarly, Pumphrey (21) determined that although epinephrine was administered in 62% of the fatal anaphylactic reactions in the UK that he reviewed, in only 14% was it given prior to cardiac arrest. In a follow-up analysis of 48 cases of fatal food anaphylaxis from 1999 to 2006, Pumphrey and Gowland (24) reported 19 (40%) had received epinephrine auto-injectors, but over one-half of the fatalities occurred in patients whose previous clinical reactions had been so mild that, in the opinion of the investigators, it was unlikely that a physician would have prescribed a precautionary epinephrine syringe.

Multiple factors may contribute to the lack of available epinephrine for administration during anaphylaxis that occurs outside of a medical facility. An international survey conducted under the auspices of the WAO determined that epinephrine auto-injectors were available in about half of surveyed countries and that the cost of an auto-injector in some countries was equivalent to the monthly salary of an average citizen (78). Of 39 countries, auto-injectors containing 0.15 mg and 0.3 mg doses were available in 17 (44%) and 22 (56%), respectively.

Adherence with an action plan to keep epinephrine available at all times and to inject it during anaphylaxis is another concern. Kemp et al. (79) determined in a follow-up survey of patients that 32 (47%) of 68 did not have the recommended epinephrine auto-injector with them when they again experienced anaphylaxis from a previously identified culprit. In contrast, 31 (91%) of 34 patients with idiopathic anaphylaxis (i.e. no culprit could be identified) had epinephrine available at the time of a subsequent episode. Implementation of an educational protocol with emphasis on carrying epinephrine increased the frequency of adherence from 53% to 92% over the ensuing 10 years (80). Other studies similarly have reported that 50–75% of patients prescribed epinephrine carry it with them, of whom 30–40% can demonstrate proper administration technique (81–84). Still others carry epinephrine but choose not to use it during anaphylaxis (32, 85–87) or prefer to seek emergency medical assistance (21).

Conclusions

Based on available evidence, the benefit of using appropriate doses of i.m. epinephrine in anaphylaxis far exceeds the risk (Evidence Category IV). Consensus opinion and anecdotal evidence recommend epinephrine administration ‘sooner rather than later’, i.e. when the initial signs and symptoms of anaphylaxis occur, regardless of their severity, because fatalities in anaphylaxis usually result

Table 3. Preventive measures to reduce the risk for anaphylaxis

| I. General measures |
|---------------------|
| Obtain thorough history to diagnose life-threatening food or drug allergy |
| Identify cause of anaphylaxis and those individuals at risk for future attacks |

| II. Specific measures for high-risk patients |
|-------------------------------------------|
| Individuals at high risk for anaphylaxis should carry self-injectable syringes of epinephrine at all times and receive instruction in proper use with placebo trainer |
| Substitute other agents for β-adrenergic blockers, angiotensin-converting enzyme inhibitors, tricyclic antidepressants and monoamine oxidase inhibitors, whenever possible |
| Agents suspected of causing anaphylaxis should be given orally if possible; if the i.v. route is needed, a slow, supervised rate of administration is required |

Modified from reference (88).

Few studies thus far have examined management of anaphylaxis in school or day care settings. These are reviewed in detail elsewhere (75). Protection of children at risk of anaphylaxis in school, day care, or other settings requires an interdisciplinary approach (9). Several resources are available for help in the school or day care setting (see ‘Additional Resources’).

Precautions for the patient at risk for anaphylaxis

Optimizing prevention (Table 3) is crucial since future anaphylaxis may be fatal despite appropriate management. An allergist–immunologist can provide comprehensive professional advice on these matters and should be consulted if he/she is not already involved in the anaphylaxis plan of care. All patients at risk for future anaphylaxis should carry at least one epinephrine syringe and know how to administer it.
from delayed or inadequate administration of epinephrine. Experts may differ on how they define the clinical threshold by which they define and treat anaphylaxis. However, they have no disagreement whatsoever that appropriate doses of i.m. epinephrine should be administered rapidly once that threshold is reached. There is no absolute contraindication to epinephrine administration in anaphylaxis, and all subsequent therapeutic interventions depend on the initial response to epinephrine. Development of toxicity or inadequate response to epinephrine injections indicates that additional therapeutic modalities are necessary. All individuals at increased risk of anaphylaxis should have an anaphylaxis action plan and carry epinephrine auto-injectors for self-administration. Such individuals (and their caregivers, as appropriate) should be assessed regularly for adherence with these recommendations and for the ability to demonstrate proper epinephrine administration technique with a placebo device.

Additional educational resources on anaphylaxis

Websites

World Allergy Organization (WAO) (http://www.worldallergy.org). Resuscitation Council (http://www.resus.org.uk/siteindx.htm). American Academy of Allergy, Asthma, and Immunology (AAAAI) (http://www.aaaai.org). American College of Allergy, Asthma, and Immunology (http://www.acaai.org). Joint Council of Allergy, Asthma, and Immunology (http://www.jcaai.org). Food Allergy and Anaphylaxis Network (FAAN) (http://www.foodallergy.org). Allergy UK (http://www.allergyuk.org). Anaphylaxis Canada (http://www.anaphylaxis.org) and the websites of other national and regional allergy/immunology organizations also provide useful perspectives.

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