

Pharmacologic treatment of anaphylaxis: can the evidence base be strengthened?

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Purpose of review

To evaluate the evidence base for the pharmacologic treatment of anaphylaxis.

Recent findings

In this review, we focus on four classes of medications (the alpha/beta-agonist epinephrine (adrenaline), H₁-antihistamines, H₂-antihistamines, and glucocorticoids) that are used in healthcare settings for the initial treatment of anaphylaxis. Epinephrine and many H₁-antihistamines and glucocorticoids were introduced before the era of randomized controlled trials and before the era of evidence-based medicine. In anaphylaxis, no randomized controlled trials that are free from methodological problems and meet current standards have been performed with these medications, or with H₂-antihistamines. The evidence base for epinephrine injection is stronger than the evidence base for use of other medications in anaphylaxis. Guidelines unanimously recommend prompt injection of epinephrine as the life-saving first-line medication in anaphylaxis; however, they differ in their recommendations for H₁-antihistamines, H₂-antihistamines, and glucocorticoids. Epinephrine is the only medication that is universally available for anaphylaxis treatment in healthcare settings worldwide. Paradoxically, it is underused in anaphylaxis treatment.

Summary

For ethical reasons, there should never be a placebo-controlled trial of epinephrine in anaphylaxis. We discuss why the possibility of conducting randomized placebo-controlled trials with H₁-antihistamines, H₂-antihistamines, and particularly with glucocorticoids in anaphylaxis should be considered in order to improve the evidence base for treatment and guide clinical decision-making. We also describe the precautions that will be needed if randomized controlled trials are conducted in anaphylaxis.

Keywords

anaphylaxis, epinephrine (adrenaline), evidence-based medicine, glucocorticoid, H₁-antihistamine, H₂-antihistamine

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Introduction

In this review, we focus on the four main classes of medications (the alpha/beta-agonist epinephrine, H₁-antihistamines, H₂-antihistamines, and glucocorticoids) that are used in healthcare settings for the initial treatment of anaphylaxis [1•,2–4]. Due to space constraints, additional classes of medications such as beta-2 adrenergic agonists and other bronchodilators, atropine, glucagon, and vasopressors such as dopamine, metaraminol, noradrenaline, vasopressin, and methylene blue will not be discussed. Epinephrine and many H₁-antihistamines and glucocorticoids were introduced before the era of randomized controlled trials and before the era of evidence-based medicine. Here we review the evidence base for their use in anaphylaxis and note the disconnect

tion between universal recommendations for prompt injection of epinephrine as a life-saving first-line medication and the reality of underuse of epinephrine in treatment. We list some of the reasons for lack of randomized controlled trials in anaphylaxis, and discuss why the possibility of conducting randomized placebo-controlled trials of H₁-antihistamines, H₂-antihistamines, and glucocorticoids in anaphylaxis should be considered in order to improve the evidence base for treatment and guide clinical decision-making.

Evidence-based medicine

Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The

practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence and systematic research [5].

Many different systems for grading the quality of evidence and the strength of recommendations have been published, and there may be poor agreement among systems [6]. Higher-quality evidence is based on systematic reviews of randomized controlled trials or individual randomized controlled trials, followed by nonrandomized uncontrolled trials, prospective cohort studies, and retrospective case-control studies. Lower-quality evidence consists of retrospective studies, including fatality studies, analyses of emergency department visits and hospital admissions, population-based cohort studies, and surveys. Case reports, clinical experience, and expert opinion rank at the bottom of most hierarchies (Table 1) [1*,7–13,14*,15–30]. Randomized controlled clinical pharmacology studies in humans, randomized controlled studies in animal models, and in-vitro studies including molecular pharmacology studies also contribute strongly to the evidence base for treatment; however, these types of studies are generally antecedent to randomized controlled trials and are seldom included in hierarchies of evidence.

In the absence of randomized controlled trials, the best available external evidence with which to answer clinical questions needs to be used. Some questions about treatment, for example, successful interventions in otherwise fatal conditions, might not require randomized trials [5].

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach clearly separates the quality of the evidence from the strength of the recommendations and is applicable to anaphylaxis [31].

Evidence base for pharmacologic treatment of anaphylaxis

Cochrane systematic reviews have confirmed the absence of optimal randomized controlled trials of epinephrine, H₁-antihistamines, and glucocorticoids in anaphylaxis [32*,33,34*].

These reviews considered all randomized or quasi-randomized controlled trials comparing the intervention with a placebo or another medication in all ages of patients, all types of anaphylaxis episodes regardless of trigger or mechanism, all settings in which anaphylaxis occurs, and all potential outcome measures, including mortality rate and clinical improvement by any objective measure. In the absence of randomized controlled trials, current strategies for the pharmacologic treatment of anaphylaxis are based on best available evidence [5],

which differs from one medication class to another (Table 1), and on extrapolation from use of the medications in other diseases.

Recommendations for the use of epinephrine, H₁-antihistamines, H₂-antihistamines, and glucocorticoids have been outlined in anaphylaxis guidelines [35–39] (Table 2). Although some of these guidelines are published in indexed, peer-reviewed journals, many appear in the so-called ‘grey literature’, for example, in journals that are peer-reviewed but not indexed and cannot be retrieved by searching databases such as Medline, Scirus, EMBASE, ISI Web of Science, and Google Scholar. The scope and comprehensiveness of the guidelines vary. The problem of lack of randomized controlled trials and of high-quality evidence for anaphylaxis treatment recommendations is compounded by the use of many different systems for grading the best available evidence, and lack of clarity with regard to the strength of the evidence underlying the recommendations [35–39]. Although global guidelines for the assessment and management of asthma and allergic rhinitis based on randomized controlled trials were published decades ago and are regularly updated and widely promulgated [40–42], global anaphylaxis guidelines will be published for the first time in 2010 (F.E.R. Simons, L.R.F. Arduoso, M.B. Bilo, *et al.*, for the World Allergy Organization, manuscript in preparation).

The availability of epinephrine, H₁-antihistamines, H₂-antihistamines, and glucocorticoids for treatment of anaphylaxis has been assessed worldwide in low-resource countries as well as in high-resource countries [43*]. Prescribing patterns for these medications in acute anaphylaxis have been documented in hospital emergency departments in some countries [44] (Table 3).

Why there are no randomized controlled trials in anaphylaxis

Due to ethical, clinical, and logistical considerations, there is understandable reluctance to perform randomized controlled trials in anaphylaxis.

The main ethical concern is about potential delay in treatment, which is unacceptable in a disease that can lead to fatality within minutes [45–49]. Median times to death are reported to be 5 min in iatrogenic anaphylaxis, 15 min in stinging insect venom-induced anaphylaxis, and 30 min in food-induced anaphylaxis [45]. Fatalities are often attributed to delay in epinephrine injection [45–49].

Clinical concerns also contribute to reluctance to perform randomized controlled trials in anaphylaxis. A major factor is the unpredictable nature of the disease, invol-

Table 1 Pharmacologic treatment of anaphylaxis: little high-quality evidence to be found

	Epinephrine	H ₁ -antihistamines	H ₂ -antihistamines	Glucocorticoids
Systematic review or meta-analysis of randomized controlled trials in anaphylaxis ^a	No	No	No	No
Individual randomized controlled trials in anaphylaxis (without methodological problems) ^a	No	No	No	No
Observational studies in anaphylaxis (nonrandomized uncontrolled, cohort, or case control studies)	Yes	No	No	No
Retrospective analysis of fatalities ^b	Yes	No	No	No
Retrospective analysis of emergency department admissions ^b	Yes	Yes	Yes	Yes
Retrospective population-based cohort studies ^b	Yes	Yes	Yes	Yes
Retrospective surveys ^b	Yes	Yes	Yes	Yes
Clinical experience (nonsystematic clinical observations, including case reports) ^b	Yes	Yes	Yes	Yes
Qualitative studies ^b	Yes	Yes	Yes	Yes
Expert opinion ^b	Yes	Yes	Yes	Yes
Clinical pharmacology studies ^c in patients with a history of anaphylaxis but not experiencing it at the time of study	Yes	No	No	No
Studies in animal models of anaphylaxis, ^c including blinded controlled studies	Yes	Yes	No	No
In-vitro studies/molecular pharmacology studies ^c	Yes	Yes	Yes	Yes
References	[1 [•] ,7–13,14 [•] ,15–25]	[2,3,26,27]	[3,26,27]	[4,28–30]

^a Higher quality evidence.^b Lower quality evidence.^c Clinical pharmacology studies, studies in animal models, and in-vitro studies are not typically found in hierarchies of evidence; however, some of these studies have only recently been performed for the anaphylaxis medications introduced more than half a century ago, and they do contribute to the evidence base.

ving sudden onset of multisystem subjective symptoms and nonspecific signs which vary in chronology, severity, and duration from one person to another, and in the same person from one anaphylaxis episode to another [50,51,52[•]]. No specific laboratory test is available to confirm the diagnosis of an acute anaphylaxis episode at point of care [50,51,52[•]]. At the onset of an anaphylaxis episode, there are few clues about its eventual outcome (Table 4). Patient-related factors that are reported to increase the risk of severe or fatal anaphylaxis episodes include age, for example, infants [53], adolescents [47], pregnant women [54], and the elderly [49]; concomitant diseases such as asthma [55], cardiovascular diseases [56], and mastocytosis [57]; and concurrent medications such as beta-blockers and angiotensin-converting enzyme inhibitors [56,57].

In addition, logistical issues contribute to reluctance to perform randomized controlled trials in anaphylaxis (Table 4). Despite the increased rate of occurrence of anaphylaxis in recent years, few medical centers treat enough patients with acute anaphylaxis episodes to be able to perform adequately powered single-center clinical trials [44]. Although new definitions of anaphylaxis, for example, ‘a serious allergic reaction that is rapid in onset and might cause death’ [50] are now widely accepted, old definitions and terminology, for example, anaphylactic shock, are still in use and might impact inclusion and exclusion criteria for randomized controlled trials. Anaphylaxis now occurs commonly in community settings,

and patients present to hospital emergency departments at different time intervals after symptom onset, often with resolving or partially treated symptoms, and without baseline measurements of vital signs and oxygenation [50,51,52[•]].

The evidence base for epinephrine injection in anaphylaxis

The multiple beneficial pharmacologic actions of epinephrine have been extensively documented. They include alpha-1 adrenergic effects (increased vasoconstriction and increased peripheral vascular resistance leading to increased blood pressure and decreased mucosal edema in the upper airway), beta-1 adrenergic effects (increased force and rate of cardiac contractions), and beta-2 adrenergic effects (increased bronchodilation and decreased release of mediators of inflammation) [1[•]].

In a Cochrane systematic review, no randomized controlled trials of epinephrine treatment in acute anaphylaxis were identified [32[•]]; however, epinephrine use was deemed to be based firmly on other types of studies and on expert opinion [7–10] (Table 3). The evidence from fatality studies was considered to be particularly strong [32[•]]; most people who die from anaphylaxis have not received an epinephrine injection before their symptoms progress to cardiac arrest [45–49]. The experience of anesthesiologists was also considered to be relevant; these specialists treat anaphylaxis relatively frequently and

Table 2 Pharmacologic treatment of anaphylaxis: what the anaphylaxis guidelines say^{a,b}

Guidelines	Epinephrine	H ₁ -antihistamines	H ₂ -antihistamines	Glucocorticoids
Australia [35]	IM 0.01 mg/kg, to a maximum of 0.5 mg; repeat at 3–5 min intervals; IV infusion per hospital protocol only if cardiac arrest is imminent; nebulization (in addition to injected epinephrine) for persistent stridor	No proven impact on the immediate and dangerous symptoms of anaphylaxis; restrict use to oral nondrowsy H ₁ -antihistamines in mild allergic skin reactions; promethazine use not advised due to potential vasodilation and hypotension	No proven impact; no H ₂ -antihistamines listed	No proven impact; no evidence to support use in reducing the risk of biphasic reactions; no glucocorticoids listed
UK [36]	IM 0.01 mg/kg, adult dose 0.5 mg; repeat at 5 min intervals; IM route has greater margin of safety than IV route, which should be used only by experienced specialists	Chlorpheniramine adult dose 10 mg, IM, or slow IV	Little evidence to support routine use of ranitidine or cimetidine in emergency treatment of anaphylaxis	Hydrocortisone IM or slow IV; adult dose 200 mg; dosing extrapolated from acute asthma treatment
US [37]	IM or SC, 1 : 1000 dilution, adult dose, 0.2–0.5 mg; repeat at 5 min intervals; or IV infusion	Diphenhydramine adult dose 25–50 mg IV or po	Ranitidine adult dose 1 mg/kg, infused over 10–15 min	Methylprednisolone adult dose 125 mg IV; prednisone adult dose 50 mg po
EAACI (pediatric guidelines) [38]	IM 0.01 mg/kg, to a maximum of 0.5 mg, repeat at 5–10 min intervals; IV infusion (restrictions apply) nebulization (restrictions apply)	Diphenhydramine or chlorpheniramine available IV; six additional H ₁ -antihistamines listed for po use; IM and IO routes also mentioned	H ₂ -antihistamines are not adequately tested in children	Hydrocortisone or methylprednisolone IV, prednisolone po; nebulized and IO routes also mentioned; not first-line treatment; do not act fast enough; efficacy not fully proven in anaphylaxis

EAACI, European Academy of Allergy and Clinical Immunology; IM, intramuscular; IO, intraosseous; IV, intravenous; po, by mouth.

^a The rationale for selecting the guidelines listed in this table is that they are published in indexed, peer-reviewed journals [35–38] and are used beyond the countries in which they were developed; for example, the Australian guidelines are used throughout southeast Asia, the UK guidelines are used in some other European countries, and the US guidelines are used throughout North America and Latin America. At the time of publication, the EAACI pediatric guidelines were the only published guidelines focused on children.

^b Different systems of grading the quality of the evidence and the strength of the recommendations are used in the Australian, US, UK, and EAACI guidelines.

Table 3 Pharmacologic treatment of anaphylaxis: recommendations versus reality

	Epinephrine	H ₁ -antihistamines	H ₂ -antihistamines	Glucocorticoids
Recommendations				
Cochrane systematic reviews [32*,33,34*]	First-line	Second-line	No Cochrane review	Second-line
What anaphylaxis guidelines recommend [35–39]	First-line	Second-line	Second-line	Second-line
World Health Organization – list of essential medications (www.who.int)	Yes	No	No	No
World Allergy Organization survey: availability for anaphylaxis, % of countries [43*]	100	77 (IV formulations); 86 (oral formulations)	70	89
Reality				
Actual prescriptions for anaphylaxis in US emergency departments showing trends from 1993 to 2004, expressed as % of visits for anaphylaxis [44]	19→7	59→62	7→18	22→50

IV, intravenous.

invariably document a rapid objective response to epinephrine in their closely monitored patients [32*].

Recommendations for prompt epinephrine injection are based on prospective, nonrandomized uncontrolled studies in patients with anaphylaxis [11,12], retrospective studies including fatality studies [45–49], analyses of emergency department visits and hospital admissions [13,44], population-based cohort studies [14*], and surveys [15–18], as well as on nonsystematic clinical observations and expert opinion [1*,7–10,35–39] (Table 1). They are also based on randomized masked controlled clinical pharmacology studies in patients at risk for anaphylaxis although not experiencing it at the time of study [1*,19–22], randomized controlled studies in animal models of anaphylaxis [23], and in-vitro studies relevant to anaphylaxis [24].

The unique life-saving effects of epinephrine in anaphylaxis are promulgated in all anaphylaxis guidelines

published in indexed, peer-reviewed allergy journals. The recommended initial dose of epinephrine in anaphylaxis is 0.01 mg/kg [35–39]. Recommendations for the *maximum* initial dose vary from 0.3 to 0.5 mg in adults (Table 2). Recommendations for the preferred route of injection also differ; most but not all [37] guidelines suggest the intramuscular route initially. When intravenous infusion of epinephrine is required, some guidelines now recommend that due to its poor benefit-to-risk ratio when administered by this route, it should be given only by specialists who are experienced in dose titration of vasopressors through an infusion pump versus continuously monitored blood pressure, cardiac rate and function, and oxygenation [35,36] Table 2. Many experts now recommend intravenous bolus doses of epinephrine for use in anaphylaxis only if cardiac arrest has occurred [25].

Anaphylaxis guidelines are in universal agreement with regard to prompt injection of epinephrine in anaphylaxis

Table 4 Why there are no randomized controlled trials in anaphylaxis

Ethical Factors
Rarely, anaphylaxis can be fatal within minutes.
Patient Factors
Anaphylaxis episodes have a sudden onset.
Symptoms and signs differ from one person to another and from one episode to another in the same person, with regard to: - time of onset after exposure to trigger (minutes to hours) - body organ systems involved
Symptoms range from mild to severe. They can be transient, prolonged, or biphasic.
Diagnosis is based on chronology, subjective symptoms, and non-specific signs. There is no specific laboratory test to confirm the diagnosis at point of care. ^a
The ultimate severity of an episode cannot be predicted at the onset.
Logistical Factors
Old definitions and terminology, eg. anaphylactic shock, are still in use.
Anaphylaxis commonly occurs in community settings (home, restaurant, school, etc.): - patients often present to emergency departments with resolving and/or partially treated symptoms. - baseline measurements of vital signs and oxygenation are not available
Few medical centers treat sufficient numbers of patients with anaphylaxis to perform adequately powered, single-center, randomized controlled trials.

Adapted from reference [29].

^a The most widely used test is measurement of serum tryptase levels for which blood samples should optimally be obtained within 15 minutes to 3 hours of symptom onset. The test is not available on a stat basis. It is not specific for anaphylaxis. Tryptase levels can be within normal limits in many patients with anaphylaxis, eg. those with food-triggered anaphylaxis, however, this cannot be used to refute the clinical diagnosis of anaphylaxis.

[35–39] (Table 2). The World Health Organization (www.who.int) lists epinephrine as an essential medication (Table 3). In a survey of 44 countries on six continents, including low-resource countries, allergy/immunology specialists reported that epinephrine *ampules* were universally available in healthcare settings worldwide; in contrast, other medications, equipment, and supplies needed for optimal management of anaphylaxis were not universally available [43•] (Table 3).

Recommendations and reality differ. In a nationally representative sample of 12.4 million visits to US hospital emergency departments for treatment of acute allergic reactions (anaphylaxis), epinephrine prescriptions actually declined from 19 to 7% of visits from 1993 to 2004 [44] (Table 3).

The evidence base for H₁-antihistamine treatment in anaphylaxis

H₁-antihistamines are inverse agonists, not competitive antagonists or blockers as originally reported. They have a preferential affinity for the inactive state of H₁-receptors, stabilize the receptors in this conformation, and consequently shift the equilibrium toward the inactive state [2]. More than 40 H₁-antihistamines are in use worldwide. As documented in positron emission tomography studies, first-generation, sedating H₁-antihistamines such as chlorpheniramine, diphenhydramine, hydroxyzine, and promethazine cross the blood–brain barrier readily due to their lipophilicity, relatively low-molecular weight, and lack of recognition by the P glycoprotein efflux pump expressed on the luminal surfaces of endothelial cells in the central nervous system (CNS) vasculature. They potentially interfere with the neurotransmitter effect of histamine, cause drowsiness, and impair cognitive function. Second-generation, relatively non-sedating newer H₁-antihistamines cross the blood–brain barrier to a minimal degree and are significantly less likely to cause adverse effects. They are therefore the preferred medications for oral use; however, they are not available in formulations for intravenous injection [2].

In a Cochrane systematic review of 2070 studies, no high-quality evidence from randomized controlled trials that were free from methodological problems was found to support the use of H₁-antihistamines in anaphylaxis. Concern was expressed about the potential harmful CNS effects caused by the first-generation H₁-antihistamines even when given in usual doses [33] (Table 3).

In anaphylaxis, H₁-antihistamines do not prevent or relieve upper or lower airway obstruction, hypotension, or shock, although they decrease itching, flushing, urticaria, and nasal symptoms. In pharmacodynamic studies, onset of significant wheal and flare suppression after oral

administration takes 0.7–2.6 h, depending on the H₁-antihistamine. In anaphylaxis, disappearance of urticaria and itching within a few minutes of ingestion of an oral H₁-antihistamine might therefore represent spontaneous improvement. First-generation, sedating H₁-antihistamines potentially cause drowsiness, confusion, and impairment of cognition, judgment, and self-recognition of symptoms by patients. In infants and children, their adverse effects such as drowsiness and seizures potentially complicate interpretation of the CNS symptoms and signs of anaphylaxis [2].

Guidelines published in indexed, peer-reviewed allergy/immunology journals differ with regard to recommendations for use of H₁-antihistamines in anaphylaxis [35–39] (Table 2). Some state that medications in this class have no proven benefit in anaphylaxis beyond relief of skin symptoms and signs [35]. Others list doses for up to eight different H₁-antihistamines: chlorpheniramine, cetirizine, diphenhydramine, levocetirizine, loratadine, desloratadine, fexofenadine, and oxatomide [38]. In the World Allergy Organization survey, H₁-antihistamines were reported to be widely available for use in anaphylaxis treatment globally [43•] (Table 3).

Recommendations and reality differ. In the nationally representative sample of emergency department visits for acute allergic reactions (anaphylaxis) described previously, H₁-antihistamines were prescribed in 59–62% of visits from 1993 to 2004, and were consistently the most commonly prescribed medications for anaphylaxis [44] (Table 3).

The evidence base for H₂-antihistamine treatment in anaphylaxis

H₂-antihistamines, like H₁-antihistamines, are inverse agonists, not competitive antagonists or blockers as originally reported. They have a preferential affinity for the inactive state of H₂-receptors, stabilize the receptors in this conformation, and consequently shift the equilibrium toward the inactive state [2]. In the treatment of anaphylaxis, they are used only in combination with H₁-antihistamines.

There is no Cochrane systematic review of H₂-antihistamines in anaphylaxis (Table 3). An H₂-antihistamine administered concurrently with an H₁-antihistamine in patients infused with histamine contributes to decreased urticaria, flushing, headache, hypotension, and rhinorrhea [2,3]. In patients with chronic urticaria, it increases wheal and flare suppression by 10–15%, but does not relieve itching [3]. In patients with mild acute allergic reactions, it enhances relief of urticaria and tachycardia, but has no significant effect on itching or other symptoms [26,27]. H₂-antihistamines have low potential to cause harm;

however, cimetidine can lead to hypotension if infused rapidly.

Few guidelines recommend H₂-antihistamines for anaphylaxis treatment [37] (Table 2). In the World Allergy Organization survey, H₂-antihistamines were reported to be less widely available than epinephrine, H₁-antihistamines, or glucocorticoids [43[•]] (Table 3).

Recommendations and reality differ. In the nationally representative sample of emergency department visits for acute allergic reactions (anaphylaxis) described previously, H₂-antihistamine prescriptions increased from 7 to 18% of visits from 1993 to 2004 [44] (Table 3).

The evidence base for glucocorticoid treatment in anaphylaxis

Glucocorticoids downregulate the allergic inflammatory response through coordinated molecular mechanisms, principally by switching off transcription of multiple genes that encode cytokines, chemokines, adhesion molecules, inflammatory enzymes, and other proteins. This occurs through inhibition of the transcription factors NF-kappa B and AP-1, as well as recruitment of histone D-acetylase-2 to the inflammatory gene complex and reversal of the histone acetylation associated with increased gene transcription. In addition, glucocorticoids activate anti-inflammatory genes such as mitogen-activated protein, chymase, and phosphatase-1 [4].

The onset of glucocorticoid action takes hours, regardless of route of administration. These medications do not relieve the initial symptoms and signs of anaphylaxis. They are traditionally given to reduce the likelihood and severity of protracted symptoms and of biphasic symptoms that occur without further exposure to the trigger in 0–23% of acute anaphylaxis episodes, up to 72 h after resolution of initial signs and symptoms [28].

A Cochrane systematic review [34[•]] failed to identify any evidence from randomized controlled trials to confirm the effectiveness of glucocorticoids in anaphylaxis and raised concerns that they are often inappropriately used as first-line medications in place of epinephrine (Table 3).

On the basis of case reports, there is evidence both for and against the efficacy of glucocorticoids in reducing the occurrence and severity of protracted anaphylaxis and biphasic anaphylaxis [28–30]. Harmful effects are unlikely during a short course of glucocorticoid treatment.

Guidelines published in indexed, peer-reviewed allergy/immunology journals differ with regard to advice about glucocorticoid use in anaphylaxis [35–39] (Table 2). Some state that these medications have no proven benefit

in anaphylaxis [35,38]. Others recommend different glucocorticoids (hydrocortisone or methylprednisolone intravenously; prednisone, methylprednisolone, or dexamethasone orally), different routes of administration (including slow intravenous injection, intramuscular injection, and oral), and different dose regimens (1 dose – 3 days) [35–39] (Table 2). In the World Allergy Organization survey [43[•]], glucocorticoids were reported to be the second most widely available medications (after epinephrine) for anaphylaxis treatment globally (Table 3).

Recommendations and reality differ. In the nationally representative sample of emergency department visits for acute allergic reactions (anaphylaxis) described previously, glucocorticoids were the second most commonly prescribed medications (after H₁-antihistamines), with an increase from 22% of visits in 1993 to 50% in 2004 [44] (Table 3).

Can the evidence base for the pharmacologic treatment of anaphylaxis be strengthened?

In anaphylaxis, the evidence base for epinephrine injection is stronger than the evidence base for administration of H₁-antihistamines, H₂-antihistamines, or glucocorticoids, although the latter three medications have been appropriately studied in randomized controlled trials in other diseases. It is clear that randomized placebo-controlled trials of epinephrine in anaphylaxis would be unethical. In contrast, it might be ethical and reasonable to consider the possibility of conducting randomized placebo-controlled trials in anaphylaxis with representative H₁-antihistamines, H₂-antihistamines, and glucocorticoids in an attempt to improve the evidence base for anaphylaxis treatment and guide clinical decision-making [50,51,52[•],58].

Discussion of the possibility of conducting randomized controlled trials of any medications in anaphylaxis will be fraught with complexities due to the ethical, patient-related, and logistical considerations described previously. Such deliberations should involve not only allergy/immunology specialists, emergency medicine specialists, and other physicians, but also allied health personnel, ethicists, statisticians, and patients who have experienced anaphylaxis. Anaphylaxis/acute systemic allergic reactions account for fewer than 1% of emergency department visits [44]; therefore, multicenter trials will likely be needed.

Pros and cons of randomized controlled trials of medications in anaphylaxis

As noted previously, epinephrine is not a candidate for randomized placebo-controlled trials in anaphylaxis because of the evidence that delay in epinephrine

injection, even by a few minutes, increases the likelihood of fatality [32[•],45–49,58]. Also as noted previously, successful interventions in otherwise fatal conditions might not require randomized controlled trials [5]. Indeed, if consideration is given to performing randomized controlled trials of medications such as antihistamines or glucocorticoids in acute anaphylaxis episodes, epinephrine injection should be considered to be mandatory in all patients in such trials [58]. Eventually, consideration might be given to discussing the possibility of conducting randomized trials of epinephrine, without a placebo control in anaphylaxis, comparing different epinephrine doses, for example, the different initial adult maximum intramuscular doses (0.3 versus 0.5 mg), or comparing different initial routes of injection (intramuscular versus subcutaneous) [51,52[•],58]. These aspects of epinephrine treatment have been previously studied in patients not experiencing anaphylaxis at the time of the investigation [19–21].

It might be reasonable to consider the possibility of conducting randomized placebo-controlled trials of H₁-antihistamines in anaphylaxis, perhaps comparing one intravenously administered H₁-antihistamine versus another, for example, diphenhydramine versus chlorpheniramine, or one oral non-sedating H₁-antihistamine versus another, for example, cetirizine versus loratadine [33,50,51,52[•],58]. Due to the potential CNS adverse effects of first-generation H₁-antihistamines [2], masking and concealment of allocation are problematic in clinical trials involving these medications.

It might also be reasonable to consider the possibility of conducting a randomized placebo-controlled trial of the H₂-antihistamine ranitidine, perhaps including a comparison with cimetidine [50,51,52[•],58].

The most likely initial candidate medications for randomized placebo-controlled trials in anaphylaxis are glucocorticoids, perhaps comparing one intravenous glucocorticoid with another, for example, methylprednisolone versus hydrocortisone, or one oral glucocorticoid versus another, for example, prednisone versus methylprednisolone [34[•],50,51,52[•],58]. Randomized placebo-controlled trials of glucocorticoids have been conducted in patients presenting to emergency departments with acute asthma [59]. The relatively slow onset of action of glucocorticoids compared with epinephrine provides a window of time, for example, 1 h [59], for patient assessment, institution of optimal treatment according to protocol (epinephrine injection, supplemental oxygen, and other interventions, as outlined below) and for establishing continuous non-invasive monitoring of heart rate, blood pressure, and oxygenation, and obtaining informed consent. In any randomized controlled trial of glucocorticoids in anaphylaxis, outcomes should be monitored for 72 h.

Precautions needed in randomized controlled trials in anaphylaxis

If randomized controlled trials are contemplated in anaphylaxis, it will be critically important to design them with careful attention to detail in all aspects of patient assessment and management. In addition to objective outcomes such as cardiac rate and function, blood pressure, respiratory rate, and oxygen saturation, validated clinically useful severity scoring systems and validated instruments to measure outcomes are needed for use in such studies [50]. Patients at increased risk of severe or fatal anaphylaxis on the basis of age (for example, children, pregnant women, elderly people), concomitant health problems (for example, cardiovascular disease), or concurrently used medications (for example, beta-blockers) that increase the risk of severe or fatal anaphylaxis should be excluded from these trials [50,51,52[•],53–57]. All patients enrolled, and the physicians caring for them, should clearly understand that they can withdraw from the trial without penalty at any time.

The trials will need to be conducted in centers where healthcare professionals have extensive experience in diagnosing and treating anaphylaxis, and where rigorous precautions are taken to ensure that all patients have prompt injection of epinephrine and continuous noninvasive monitoring with state-of-the-art equipment [35–37,43[•],50,51,52[•],58]. Simultaneously, patients should be placed in the recumbent position with the lower extremities elevated, or placed in a position of comfort if they are experiencing respiratory distress or vomiting. If clinically indicated, administration of supplemental oxygen and airway management should be prioritized. If clinically indicated, insertion of one or more large bore (#14 or #16) needles or intravenous catheters for infusion of large volumes of fluid (for example, up to 1–2 liters of isotonic saline in the first 5–10 min) should be prioritized [35–37,43[•],50,51,52[•],58]. Backup from a critical care team should be readily available, in the event that mechanical ventilation or continuous infusion of intravenous epinephrine or another vasopressor is needed [35–37].

Conclusion

All guidelines recommend prompt injection of epinephrine as the first-line treatment in anaphylaxis. For ethical reasons, randomized placebo-controlled trials of epinephrine should not even be considered. Guidelines differ in their recommendations for administration of H₁-antihistamines, H₂-antihistamines, and glucocorticoids in anaphylaxis; and they generally do not state the paucity of evidence for use of these medications in anaphylaxis. Paradoxically, epinephrine is less likely to be given than H₁-antihistamines, H₂-antihistamines, and glucocorticoids in anaphylaxis. It is not known whether medications

in the latter three classes provide significant added benefit to epinephrine. For this reason, consideration should be given to discussing the possibility of studying them prospectively in randomized placebo-controlled trials, perhaps beginning with glucocorticoids because investigation of this class of medications is the most feasible.

Acknowledgement

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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