Practice parameter

Anaphylaxis—a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis

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Anaphylaxis is an acute, potential life-threatening systemic allergic reaction that may have a wide range of clinical manifestations. Severe anaphylaxis and/or the need for repeated doses of epinephrine to treat anaphylaxis are risk factors for biphasic anaphylaxis. Antihistamines and/or glucocorticoids are not reliable interventions to prevent biphasic anaphylaxis,

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although evidence supports a role for antihistamine and/or glucocorticoid premedication in specific chemotherapy protocols and rush aeroallergen immunotherapy. Evidence is lacking to support the role of antihistamines and/or glucocorticoid routine premedication in patients receiving low- or iso-osmolar contrast material to prevent recurrent radiocontrast media anaphylaxis. Epinephrine is the first-line pharmacotherapy for uniphasic and/or biphasic anaphylaxis. After diagnosis and treatment of anaphylaxis, all patients should be kept under observation until symptoms have fully resolved. All patients with anaphylaxis should receive education on anaphylaxis and risk of recurrence, trigger avoidance,

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self-injectable epinephrine education, referral to an allergist, and be educated about thresholds for further care. (J Allergy Clin Immunol 2020;145:1082-123.)

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Abbreviations used

AAAAI:	American Academy of Allergy, Asthma & Immunology
ACAAI:	American College of Allergy, Asthma, and Immunology
ADR:	Adverse drug reaction
C3a (4a, 5a):	Complement 3a (4a, 5a)
DHR:	Drug hypersensitivity reaction
ED:	Emergency department
EMS:	Emergency medical services
FAAN:	Food Allergy and Anaphylaxis Network
FIA:	Food-induced anaphylaxis
GRADE:	Grading of Recommendations, Assessment, Development and Evaluation
H1 (2, 3, 4):	Histamine 1 (2, 3, 4)
HSR:	Hypersensitivity reaction
HVA:	Hymenoptera venom allergy
I^2:	Inconsistency of studies' results
IQR:	Interquartile range
JTFPP:	Joint Task Force on Practice Parameters
LL:	Large local
LT:	Leukotriene
NIAID:	National Institute of Allergy and Infectious Diseases
NNT:	Number needed to treat
NPV:	Negative predictive value
OR:	Odds ratio
PAF:	Platelet-activating factor
PEER:	Patient expected event rate
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCM:	Radiocontrast media
RIT:	Rush immunotherapy
RR:	Relative risk

EXECUTIVE SUMMARY

Anaphylaxis is an acute, life-threatening systemic allergic reaction that may have a wide range of clinical manifestations.[1] The clinical criteria proposed in 2006 by National Institute of Allergy and Infectious Diseases (NIAID) continue to provide a helpful framework in approaching patients with acute allergic symptoms, because diagnosis and management of anaphylaxis must occur rapidly and confirmatory testing for anaphylaxis has poor sensitivity.[2] While NIAID anaphylaxis diagnostic criteria have a sensitivity of 95% with a specificity of 71% in an emergency department (ED) setting,[3] fulfilling diagnostic criteria is not a prerequisite for epinephrine administration in a patient experiencing an acute allergic reaction.

The lifetime prevalence of anaphylaxis has been estimated at 1.6% to 5.1%.[1,4] Risk factors for severe anaphylaxis include cardiovascular disease, asthma, older age, and additional coexisting, comorbid conditions.[5-9] Medications and stinging insects are the leading triggers in adults, with foods and stinging insects the most frequently implicated triggers in children and adolescents.[1,10-12] Food allergy impacts 8% to 11% of children and adults in the United States,[13-15] while adverse drug reactions (ADRs) affect up to 10% of the population (and 20% of hospitalized patients), with hypersensitivity reactions (HSRs) accounting for 10% of all ADRs.[16] Although medical complexity increases for patients with prior HSRs to radiocontrast media (RCM), fortunately the prevalence of RCM ADRs has decreased in recent decades.[17] Systemic reactions to Hymenoptera venom occur in 0.5% to 3.3% of the US population, with most fatalities occurring in patients who have no prior history of systemic allergic reaction to Hymenoptera.[16]

IgE binding and cross-linking of the high affinity IgE receptor (FcεRI) on the surface of mast cells and basophils is an important mechanism in many cases of anaphylaxis.[18] Some patients with anaphylaxis have low or undetectable circulating allergen-specific IgE.[19] Anaphylaxis involves additional cell types that may include neutrophils, monocytes, macrophages, and platelets and signaling through mediators that include complement components, cysteinyl leukotrienes (LTs), platelet activating factor, IL-6, IL-10, and TNF-receptor 1.[20,21]

Epinephrine administered intramuscularly (in a dose of 0.01 mg/kg of a 1:1000 [1 mg/mL] solution to a maximum of 0.5 mg in adults and 0.3 mg in children) into the anterolateral thigh is the first-line treatment for anaphylaxis.[22] Epinephrine is the cornerstone of anaphylaxis management but continues to be underutilized.[23-25] As a nonselective adrenergic agonist, epinephrine works rapidly to increase peripheral vascular resistance through vasoconstriction, to increase cardiac output, to reverse bronchoconstriction and mucosal edema, and to stabilize mast cells and basophils.[26,27] Despite underuse of rapidly acting epinephrine as first-line treatment, fatal anaphylaxis is a rare outcome, with population prevalence rates between 0.47 and 0.69 per million persons (0.25%-0.33% of anaphylaxis hospitalizations or ED visits).[9,28-31] Antihistamine agents are considered second-line treatment for anaphylaxis, given their slow onset of action and inability to stabilize or prevent mast cell degranulation or to target additional mediators of anaphylaxis.[32] Unlike epinephrine, antihistamines will not effectively treat cardiovascular and respiratory symptoms such as hypotension or bronchospasm. Although glucocorticoids are frequently used as an adjunctive therapy for anaphylaxis, evidence is lacking to support clinical benefit, and they should not be administered in place of epinephrine in the treatment of acute anaphylaxis.[33,34]

Biphasic anaphylaxis is recurrent anaphylaxis occurring 1 to 72 hours after resolution of an initial anaphylactic episode, though an outside limit of 78 hours has also been suggested.[35,36] Estimates of biphasic anaphylaxis vary from <1% to 20% of patients; however, the ability of antihistamines and glucocorticoids to affect this outcome is unclear.[37-44] Despite a lack of clear evidence supporting the role of antihistamines and glucocorticoids in anaphylaxis, these agents continue to be routinely used in anaphylaxis management. To evaluate the role for these second-line, supplemental therapies, the Joint Task

Box 1. Key questions assessed by this systematic review on anaphylaxis

Topic area 1. Identification and mitigation of risk factors for biphasic anaphylaxis

Question 1. What risk factors should clinicians take into consideration in determining the likelihood of biphasic anaphylaxis?

Topic area 2. Evaluation of the use of supplemental glucocorticoids and/or antihistamine premedication for the prevention of anaphylaxis

Question 2. Should antihistamines and/or glucocorticoids be used to prevent biphasic anaphylaxis?

Question 3. Should antihistamine and/or glucocorticoid premedication be used to prevent index hypersensitivity/infusion reactions to chemotherapy?

Question 4. Should antihistamine and/or glucocorticoid premedication be used to prevent recurrent HSRs to RCM?

Question 5. Should antihistamine and/or glucocorticoid premedication be used to prevent HSRs to allergen immunotherapy or other agents?

Force on Practice Parameters (JTFPP) undertook a systematic review and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis of antihistamines and glucocorticoids in anaphylaxis. Specifically, the JTFPP sought to better inform the practice of anaphylaxis prevention in 2 broad topic areas through (1) identification and mitigation of risk factors for biphasic anaphylaxis and (2) evaluation of the use of supplemental glucocorticoid and/or antihistamine premedication (see Box 1). Although the goal of the JTFPP was to rigorously evaluate the literature to form evidence-based recommendations, there are limits to the available evidence in human anaphylaxis due to ethical considerations and the absence of double-blind studies in a potentially fatal, acute condition. This GRADE analysis incorporated the balance of relative benefits and harms of treatments under consideration, the certainty of the evidence, and the impact of patient preferences and values. Box 2 provides a summary of key clinical advice.

Question 1. What risk factors should clinicians take into consideration in determining the likelihood of biphasic anaphylaxis?

Recommendation 1. We suggest that a clinician incorporate severity of anaphylaxis presentation and/or the administration of >1 dose of epinephrine for the treatment of initial anaphylaxis as a guide to determining a patient's risk for developing biphasic anaphylaxis. Conditional recommendation. Certainty rating of evidence: very low.

Even though the ability to accurately predict which patients with resolved initial anaphylaxis will experience biphasic anaphylaxis is imperfect, an understanding of risk factors allows a more tailored approach to patient management. Risk factors also provide useful parameters to incorporate into decision making regarding duration of observation following initial resolution of anaphylaxis.

The JTFPP findings suggest biphasic anaphylaxis is associated with a more severe initial presentation of anaphylaxis (odds ratio [OR], 2.11; 95% CI, 1.23-3.61) or repeated epinephrine doses (ie, >1 dose of epinephrine) required with the initial presentation (OR, 4.82; 95% CI, 2.70-8.58). Additional risk factors include wide pulse pressure (OR, 2.11; 95% CI, 1.32-3.37), unknown anaphylaxis trigger (OR, 1.63; 95% CI, 1.14-2.33), cutaneous signs and symptoms (OR, 2.54; 95% CI, 1.25-5.15), and drug trigger in children (OR, 2.35; 95% CI, 1.16-4.76). While presence of dyspnea on presentation was associated with a decreased risk for anaphylaxis, overall confidence in this estimate was low (OR, 0.6; 95% CI, 0.38-0.96). Prompt and adequate treatment of anaphylaxis appears central to reducing biphasic anaphylaxis risk, in the opinion of the JTFPP. While the possibility of biphasic anaphylaxis should be emphasized in this higher risk group, it is important to educate all patients regarding the chance of a biphasic reaction as well as avoiding known triggers, identification of symptoms of anaphylaxis, the use of auto-injector epinephrine for the treatment of anaphylaxis, and timely follow-up with an allergist.

Recommendation 2. We suggest extended clinical observation in a setting capable of managing anaphylaxis (to detect a biphasic reaction) for patients with resolved severe anaphylaxis and/or those who need >1 dose of epinephrine. Conditional recommendation. Certainty rating of evidence: very low.

While wide pulse pressures may be considered a marker for severe anaphylaxis, the clinician may also consider extended observation for patients with an unknown anaphylaxis trigger and children with a drug trigger. Incorporating cutaneous signs and symptoms into a clinical decision for extended observation may be limited by the common occurrence of cutaneous signs and symptoms in patients presenting with anaphylaxis. The estimated number needed to monitor with extended observation to be able to detect 1 episode of biphasic anaphylaxis before discharge would be 41 (range, 18-195) for patients with a more severe initial presentation of anaphylaxis and 13 (range, 7-27) for patients with multiple epinephrine doses. The implication for the clinician, based on this systematic review and meta-analysis, is that the patient presenting with severe anaphylaxis and/or requiring more aggressive treatment (eg, >1 dose of epinephrine) should be considered for longer observation time for a potential biphasic reaction following complete resolution of signs and symptoms. At present, evidence is lacking to clearly define the optimal duration of observation (eg, number of hours) that would prove to be cost-effective for patients with initial resolution of severe anaphylaxis and/or those requiring multiple doses of epinephrine. However, for patients without severe risk features, discharge after a 1-hour asymptomatic observation may be reasonable. If the clinical impression is that a patient has a higher risk of biphasic reaction (ie, 17% or greater) or risk factors for anaphylaxis fatality (eg, cardiovascular comorbidity, lack of access to epinephrine, lack of access to emergency medical services (EMS), poor self-management skills), then extended observation of up to 6 hours or longer (including hospital admission) may be appropriate. Regardless of severity, after diagnosis and treatment of anaphylaxis, all patients should be kept under observation until signs and symptoms have fully resolved.

Box 2. Suggested key clinical advice

- Severe anaphylaxis and/or the need for >1 dose of epinephrine to treat anaphylaxis are risk factors for biphasic anaphylaxis. Additional risk factors include wide pulse pressure, unknown anaphylaxis trigger, cutaneous signs and symptoms, and drug trigger in children.
- Extended observation is suggested for patients with resolved severe anaphylaxis and/or those with need for >1 dose of epinephrine.
- Antihistamines and/or glucocorticoids are not reliable interventions to prevent biphasic anaphylaxis but may be considered as secondary treatment.
- Evidence supports a role for antihistamine and/or glucocorticoid premedication in specific chemotherapy protocols and rush aeroallergen immunotherapy.
- Evidence is lacking to support the routine use of antihistamines and/or glucocorticoid premedication in patients receiving low- or iso-osmolar contrast material to prevent recurrent RCM anaphylaxis.
- Administer epinephrine as the first-line pharmacotherapy for uniphasic and/or biphasic anaphylaxis.
- Do not delay the administration of epinephrine for anaphylaxis.
- After diagnosis and treatment of anaphylaxis, all patients should be kept under observation until symptoms have fully resolved.
- All patients with anaphylaxis should receive education about anaphylaxis, risk of recurrence, trigger avoidance, self-injectable epinephrine, and thresholds for further care, and they should be referred to an allergist for follow-up evaluation.

Question 2. Should antihistamines or glucocorticoids be used to prevent biphasic anaphylaxis?

Recommendation. We suggest against administering glucocorticoids or antihistamines as an intervention to prevent biphasic anaphylaxis. Conditional recommendation. Certainty rating of evidence: very low.

Although we suggest against the use of antihistamines and/or glucocorticoids as an intervention to prevent biphasic anaphylaxis, these may be considered for the secondary treatment of anaphylaxis.[45] In particular, antihistamines may treat urticaria and itching to improve comfort during anaphylaxis, but if used prior to epinephrine administration, antihistamine administration could lead to a delay in first-line treatment of anaphylaxis. The JTFPP analysis did not identify clear benefit in prevention of biphasic anaphylaxis from histamine 1 (H1) antihistamines (OR, 0.71; 95% CI, 0.47-1.06), H2 antihistamines (OR, 1.21; 95% CI, 0.80-1.83), or glucocorticoids (OR, 0.87; 95% CI, 0.74-1.02). An interaction was identified between age and glucocorticoid use, with glucocorticoids actually increasing risk for biphasic anaphylaxis in children (OR, 1.55; 95% CI, 1.01-2.38); however, a confounding effect of severity could not be excluded. At a biphasic anaphylaxis patient expected event rate (PEER) of 5%, the number needed to treat (NNT) for H1 antihistamines and glucocorticoids is 72 and 161 to prevent 1 episode of biphasic anaphylaxis, with significant uncertainty in the estimate.

Question 3. Should antihistamine and/or glucocorticoid premedication be used to prevent index hypersensitivity/infusion reactions to chemotherapy?

Recommendation. We suggest in favor of administering glucocorticoids and/or antihistamines to prevent anaphylaxis or infusion-related reactions when indicated for specific agents in chemotherapy protocols. Conditional recommendation. Certainty rating of evidence: very low.

The JTFPP analysis did identify a significant change in rates of anaphylaxis and/or infusion reactions for some chemotherapy protocols. The use of premedication was associated with a decreased rate of HSRs for chemotherapy (OR, 0.49; 95% CI, 0.37-0.66). In contrast to chemotherapy premedication, benefit was not observed when using premedication to prevent anaphylaxis in the setting of infliximab without prior reaction to the administered agent (relative risk [RR], 1.58; 95% CI, 0.87-2.87). We did not evaluate premedication in the context of desensitization to chemotherapy agents and to monoclonal antibodies. Furthermore, the use of premedication in patients who had previously experienced anaphylaxis from these agents was not evaluated.

Question 4. Should antihistamine and/or glucocorticoid premedication be used to prevent recurrent HSRs to RCM?

Recommendation. We suggest against routinely administering glucocorticoids and/or antihistamines to prevent anaphylaxis in patients with prior radiocontrast HSRs when readministration of a low- or iso-osmolar, nonionic RCM agent is required. Conditional recommendation. Certainty rating of evidence: very low.

The JTFPP analysis did not identify significant benefit from the use of premedication prior to RCM administration to prevent anaphylaxis (RR, 1.07; 95% CI, 0.67-1.71). The absence of benefit of premedication in patients with prior immediate HSRs to RCM who are receiving a different low- or iso-osmolar agent is consistent with prior literature; however, it is important to distinguish the immediate index reaction associated with RCM from a severe, delayed, cutaneous T-cell-mediated reaction, where premedication may add value to management.[17] Given the diversity of clinical circumstances evaluated and low confidence in the literature base, higher certainty evidence is needed to better inform practice, and future recommendations could potentially change as a result of new information. As such, clinicians may reasonably consider premedication in clinical circumstances associated with a high level of perceived risk of anaphylaxis or comorbidities associated with greater anaphylaxis fatality risk (such as underlying cardiovascular disease, use of beta-blockers, or prior severe anaphylaxis), although evidence is lacking to clearly support this practice.

This analysis evaluated patients with both mild and severe prior RCM reactions, but we were unable to stratify prophylaxis by severity of index reaction. Furthermore, only low- and iso-osmolar nonionic radiocontrast agents were evaluated because these are the most commonly used agents at present. This recommendation does not apply to patients receiving high-osmolar contrast agents for whom prophylaxis may be appropriate in some circumstances.

Question 5. Should antihistamine and/or glucocorticoid premedication be used to prevent HSRs to allergen immunotherapy or other agents?

Recommendation. We suggest the administration of glucocorticoids and/or antihistamines as an intervention to prevent anaphylaxis in patients undergoing aeroallergen rush immunotherapy (RIT). Conditional recommendation. Certainty rating of evidence: very low.

Evidence suggests that in the setting of aeroallergen RIT, premedication may provide value in reducing systemic reactions and anaphylaxis (immunotherapy analysis including RIT: RR, 0.62; 95% CI, 0.41-0.94). The evidence base for premedication before conventional aeroallergen immunotherapy is limited; however, 1 study[46] suggested some benefit with fexofenadine pretreatment 2 hours before conventional immunotherapy using cedar pollen or dust mite allergens. The JTFPP is unable to exclude the possibility that specific situations and subpopulations may exist where premedication could provide benefit to immunotherapy in those with concomitant risk factors (eg, in situations associated with higher rates of systemic reactions). As such, clinicians may reasonably consider immunotherapy premedication in other clinical circumstances associated with a high level of perceived risk of anaphylaxis or comorbidities associated with greater anaphylaxis fatality risk (such as underlying cardiovascular disease or use of beta-blockers), although high-certainty evidence is lacking to support this practice.

Additional good practice statements

Good practice statement 1. Administer epinephrine as the first-line pharmacotherapy for uniphasic and/or biphasic anaphylaxis.

Good practice statement 2. Do not delay the administration of epinephrine for anaphylaxis, as doing so may be associated with higher morbidity and mortality.

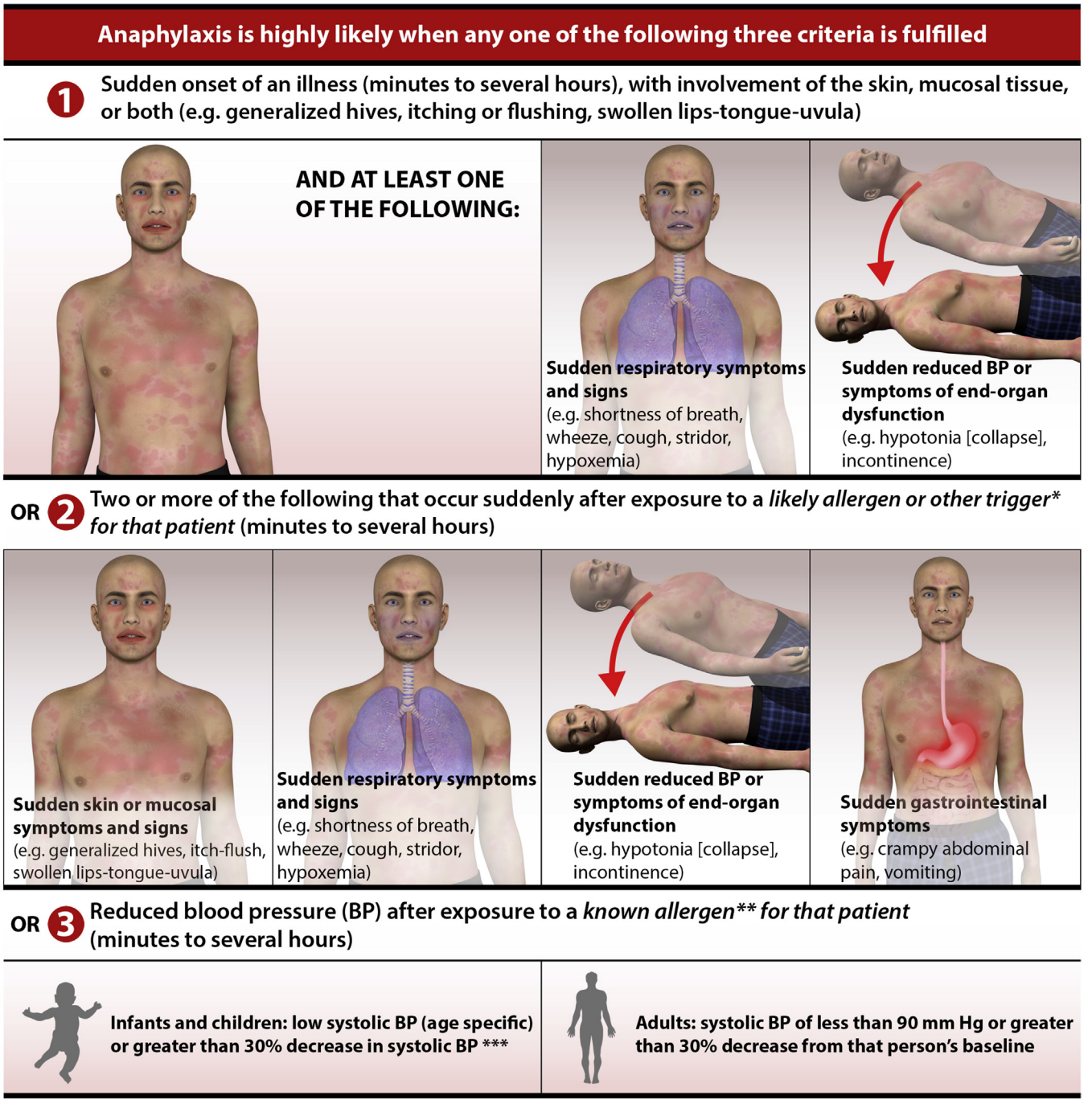
Good practice statement 3. After diagnosis and treatment of anaphylaxis, all patients should be kept under observation in a setting capable of managing anaphylaxis until symptoms have fully resolved.

Good practice statement 4. All patients with anaphylaxis should receive education on anaphylaxis, including avoidance of identified triggers, presenting signs and symptoms, biphasic anaphylaxis, treatment with epinephrine, and the use of epinephrine auto-injectors, and they should be referred to an allergist. Of note, there may be some circumstances where self-injectable epinephrine is deferred (ie, resolved anaphylaxis and drug trigger with high likelihood of successful avoidance) and shared decision making may play a role in some circumstances.

INTRODUCTION TO AND DIAGNOSIS OF ANAPHYLAXIS

Anaphylaxis is an acute, life-threatening systemic allergic reaction associated with different mechanisms, triggers, clinical presentations, and severity.[1] The wide range of clinical manifestations and complex underlying mechanisms of anaphylaxis contribute to the difficulty in establishing a definition and diagnostic criteria for anaphylaxis. The poor sensitivity of confirmatory laboratory testing further complicates accurate diagnosis of anaphylaxis. Furthermore, a lack of use of established diagnostic criteria plays a major role in the underdiagnosis and inconsistent management of anaphylaxis.[47-49] In 2005, a multinational and multidisciplinary work group that included allergist-immunologists, emergency physicians, pediatricians, critical care specialists, internists, and key stakeholders was assembled by the NIAID and Food Allergy and Anaphylaxis Network (FAAN) to address the need for universally accepted anaphylaxis diagnostic criteria. The diagnostic criteria proposed by this work group were published in 2006[22] and describe anaphylaxis as likely when 1 of 3 criteria are fulfilled: (1) acute onset of an illness (minutes to hours) with involvement of the skin, mucosal tissue, or both with either respiratory involvement or reduced blood pressure and/or associated symptoms of end-organ dysfunction; or (2) 2 or more of the following that occur rapidly after exposure to a likely allergen for the patient, including (i) involvement of skin-mucosal tissue, (ii) respiratory involvement, (iii) reduced blood pressure or associated symptoms, or (iv) gastrointestinal symptoms; or (3) reduced blood pressure as a result of exposure to a known allergen trigger. These criteria have since been recognized and endorsed by the American Academy of Allergy, Asthma & Immunology (AAAAI), American College of Allergy, Asthma, and Immunology (ACAAI),[50] and the World Allergy Organization.[51]

The NIAID/FAAN criteria were developed to facilitate rapid diagnosis of anaphylaxis. The criteria (shown in Fig 1) incorporate features related to the onset of the reaction, exposure to an inciting trigger, as well as signs and symptoms. Importantly, using these criteria, anaphylaxis can be identified among patients lacking hemodynamic compromise, patients lacking cutaneous manifestations, and patients with mild presentations (eg, those with a rash and vomiting after exposure to a likely trigger). The NIAID/FAAN anaphylaxis diagnostic criteria were prospectively validated in patients seeking care for an allergic reaction and possible anaphylaxis in an ED setting and were shown to provide a positive likelihood ratio of 3.26 and negative likelihood ratio of 0.07.[3] Thus, although these criteria are helpful clinically, they should not replace clinician judgment. It is important to recognize, as acknowledged by those who developed the criteria, that epinephrine administration is not limited to those patients meeting the NIAID/FAAN diagnostic criteria. For example, a patient undergoing immunotherapy who immediately develops generalized urticaria after an injection may appropriately receive epinephrine if impending anaphylaxis is suspected, despite the fact that the diagnostic criteria for anaphylaxis have not yet been met. In such instances, management relies heavily on clinical judgment. However, the role of preemptive epinephrine prior to the development of anaphylaxis has been questioned.[52-54] Isolated allergen-associated urticaria, which may respond to antihistamines, should be distinguished from anaphylaxis for which prompt epinephrine administration is indicated.



* For example, immunological but IgE-independent, or non-immunologic (direct mast cell activation)

** For example, after an insect sting, reduced blood pressure might be the only manifestation of anaphylaxis; or after allergen immunotherapy, generalized hives might be the only initial manifestation of anaphylaxis.

*** Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years and less than 90 mm Hg from 11 to 17 years. Normal heart rate ranges from 80 - 120 beats/minute at age 3 years; and from 70 -115 beats/minute after age 3 years. In infants and children, respiratory compromise is more likely than hypotension or shock and shock is more likely to be manifest initially by tachycardia than by hypotension.

FIG 1. Clinical criteria for the diagnosis of anaphylaxis. Anaphylaxis is likely when 1 of 3 criteria are fulfilled: (1) acute onset of an illness (minutes to hours) with involvement of the skin, mucosal tissue, or both with either respiratory involvement or reduced blood pressure (*BP*)/associated symptom of end-organ dysfunction; or (2) ≥2 of the following that occur rapidly after exposure to a likely allergen for the patient, including (i) involvement of skin-mucosal tissue, (ii) respiratory involvement, (iii) reduced blood pressure or associated symptoms, or (iv) gastrointestinal symptoms; or (3) reduced blood pressure as a result of exposure to a known allergen trigger. Adapted from Simons et al.[61]

Additionally, in the ED, a stable, asymptomatic patient who provides a history of symptoms meeting NIAID/FAAN anaphylaxis diagnostic criteria but whose symptoms have completely resolved prior to arrival, should still be given an anaphylaxis diagnosis despite the fact that epinephrine administration is no longer acutely indicated.

Biphasic anaphylaxis is a well-recognized potential complication of anaphylaxis and has been defined as recurrent anaphylaxis after complete improvement; this has been reported to occur between 1 and 78 hours after the onset of the initial anaphylactic reaction, and this must be clinically differentiated from a reaction that does not fully respond to initial treatment and persists or quickly returns.[35,36,55,56] Some earlier studies of biphasic reactions, prior to the NIAID/FAAN criteria, which included patients with severe anaphylaxis, reported rates of biphasic anaphylaxis as high as 20%.[37-39] More contemporary studies of biphasic anaphylaxis utilizing the NIAID/FAAN diagnostic criteria or similar criteria for diagnosis of both the initial anaphylactic reaction and the biphasic reaction have demonstrated lower rates of biphasic reactions closer to 4% to 5% (range, 0.18%-14.7%).[40-44] No studies have systematically evaluated therapies for the second-phase reaction; however, therapy for the second phase is similar to that for the initial phase.[36] Optimal duration of extended observation following resolution of biphasic anaphylaxis is unknown.[36] One recent meta-analysis[57] of 12 studies including 2890 adult patients with anaphylaxis suggested the pooled negative predictive value (NPV) of 1-hour observation was 95%, with an NPV for biphasic anaphylaxis after ≥6 hours of observation (following resolved anaphylaxis) of 97.3%. A recent cost-effectiveness analysis suggested that extended observation could be cost-effective (ie, not exceeding $10 million per death prevented) at high rates of fatality risk reduction (76%) from an additional 5 hours of asymptomatic observation.[58]

EPIDEMIOLOGY AND RISK FACTORS

Prevalence estimates of anaphylaxis vary widely, and many studies suggest that the prevalence is increasing, particularly in developed countries. The lifetime prevalence of anaphylaxis has been estimated at 1.6% to 5.1%,[1,4,11] with an incidence rate of 42 per 100,000 person-years, but estimates may be susceptible to ascertainment bias.[59] Data from a European anaphylaxis registry revealed that over one-quarter of cases occurs in patients under 18 years of age.[60] As indicated in an international consensus on anaphylaxis document, cardiovascular disease and asthma are well-recognized risk factors for severe anaphylaxis.[5] Additional risk factors potentially associated with severe or fatal anaphylaxis include older age, mast cell disorder, and beta-blocker or angiotensin-converting enzyme inhibitor use.[6-9] Atopy is a risk factor for anaphylaxis triggered by food, exercise, and latex.[61] While 1 survey[62] of Turkish beekeepers (n = 29 subjects with systemic reactions, 9 with anaphylaxis, of 444 subjects with a history of a sting exposure in the prior 12 months) suggested atopic disease as a risk factor for systemic reactions (OR, 3.3; 95% CI, 1.2-8.7), it has not been otherwise established that atopic disease increases the risk for Hymenoptera sting-associated anaphylaxis.

Medications and stinging insect venom are leading causes of adult anaphylaxis,[1] while foods and stinging insect venom are the most common triggers of anaphylaxis in children and adolescents.[10-12] In the middle-age adult population, anaphylaxis most often occurs at home.[1] Medications most frequently implicated in the United States are antibiotics, nonsteroidal anti-inflammatory drugs, immunomodulators, and biological agents.[63] In contrast, in Portugal, a review[64] of 313 patients with a history of drug-induced anaphylaxis revealed the most common trigger to be nonsteroidal anti-inflammatory drugs, followed by antibiotics and anesthetics. An anaphylaxis registry[65] of German-speaking countries (Germany, Austria, and Switzerland) reported the most common trigger to be insect venom, followed by food and drugs, respectively (when all age groups are considered). In studies of food-induced anaphylaxis (FIA), incidence ranges from as low as 1 per 100,000 to as high as 70 per 100,000 have been reported by using data from hospitalizations, ED visits, and medical record reviews.[66-68] When examining anaphylaxis etiology, the proportion due to foods varied between 13% and 65% depending on age and study.[66-71] The specific trigger may not be identified during the acute anaphylactic event or in subsequent evaluations, especially if the reaction is occurring for the first time, and the trigger may only be identified retrospectively at a follow-up evaluation. For example, 1 study[72] of ED records in Florida found that only 37% of patients could pinpoint a specific trigger on initial presentation. Futhermore, initial suspected culprits are often not confirmed on subsequent allergy testing, which suggests caution in presumption of potential triggers and supports the necessity of follow-up evaluation by an allergy specialist.[47,73,74]

With respect to treatment, delayed use of epinephrine has been associated with increased risk for fatality, and several observational studies and case reports series[48,75-88] suggest a continued disparity between the diagnosis of anaphylaxis and frequency of appropriate epinephrine treatment. In 1 study[76] of drug-induced anaphylaxis evaluated and managed in an ED, only 8% of patients received epinephrine. While early epinephrine is the bedrock of anaphylaxis management, anaphylaxis fatality is fortunately a rare outcome. The overall prevalence of fatal anaphylaxis in recent years in the United States and United Kingdom is between 0.47 and 0.69 per million persons.[8,9,28-30] The 3 leading causes of fatal anaphylaxis are drugs (29%-58.5%),[8,28,89,90] insect stings (3.3%-54%),[8,28,89,90] and food (2%-6.7%).[8,28,90] While anaphylaxis-related hospitalizations have increased, general case fatality rates have been stable in the range of 0.25% to 0.33% of hospitalizations or ED presentations for anaphylaxis.[31] However, in contrast to other causes of fatal anaphylaxis, drug-induced anaphylaxis rates have increased.[8] In the United Kingdom, fatal drug anaphylaxis has been reported to be mostly due to general anesthetics,[91] whereas antibiotics predominate in Australia[28] and France.[92] A review by Pichichero et al[93] described the population incident risk of anaphylaxis to penicillin between 0.004% and 0.015% with a fatality rate of 0.0002% to 0.0015%. The UK fatal anaphylaxis registry reported that while those dying from food anaphylaxis often have a prior history of a food reaction, those with fatal Hymenoptera venom and drug anaphylaxis usually do not.[91,94] Additional observational case series have shown patients dying from food anaphylaxis often have a history of previous food-induced allergic reactions.[28,38,95] Notably, respiratory arrest may occur more commonly with foods (86% of fatalities in the UK registry), with shock more common in fatalities due to medications and venom reactions.[91] It is important to note that most fatal reactions are unpredictable and statistically occur very rarely; however, appropriate trigger identification after

recovery from a severe reaction may decrease the risk for a subsequent severe reaction, including fatality.[94] Referral to an allergy specialist after recovery from anaphylaxis is recommended to confirm the diagnosis, evaluate for potential triggers, and educate the patient on the risk of future reactions and measures to reduce that risk, including self-injectable epinephrine access and auto-injector education.

BURDEN OF DISEASE

Food-induced anaphylaxis

Prevalence. Food allergy (or presumed food allergy) is a leading cause of anaphylaxis presenting to US EDs, with an estimated 30,000 cases per year.[96] Food allergy (assessed through a nationally representative Internet self-report study) is estimated to affect up to 8% to 11% of the US population.[13-15] Food allergens may be attributed to upward of 50% of ED-reported anaphylaxis cases in developed countries, including the United States.[97]

Trends. According to the Centers for Disease Control and Prevention, rates of food allergies in US children increased by about 50% between 1997 and 2011.[98] Whereas Clark et al[99] reported stable trends in the frequency of US ED visits for food allergy in the period of 2001 to 2009, they did find a statistically significant decline among individuals ≥18 years of age. In a retrospective cohort study[100] of 37 pediatric hospitals from 2007 to 2012, an increasing rate of FIA-related ED visits was reported but without any increase in the proportion of ED patients hospitalized or admitted to the intensive care unit. This decrease in the proportional rate of ED visits to utilization of inpatient and intensive care unit facilities may be due to the increased utilization of ED or inpatient observation units, as approximately 36% of US EDs reported having observation units in 2007.[101] More recently, Motosue et al[102] reported a fourfold increase in FIA-related ED visits for adolescents from 2005 through 2014.

Economic burden. Food allergies can burden patients and families by affecting finances, social relationships, and personal perceptions of health.[103] Patients with food allergies and their families experience anxiety and other stresses that affect quality of life given the risk of potentially severe reactions and inability to completely control these risks.[16] The impact of food allergies is not limited to just the patients and their families but can also lead to a significant economic effect on society and the health care system. Food-induced anaphylaxis can result in prehospital emergency care by ambulance personnel, ED visits, hospitalizations, or even death. Mild as well as more severe allergic reactions require comprehensive evaluation, including diagnostic studies, and regular follow-up outpatient visits.[104]

In 2011, Patel et al[104] estimated total annual direct medical costs of food allergy and anaphylaxis at $225 million (2007 US dollars). Office visits accounted for 52.5% of direct medical costs, and the remaining was split among ED visits (20%), inpatient hospitalizations (11.8%), outpatient department visits (3.9%), ambulance runs (3%), and epinephrine devices (8.7%). Children accounted for 46.6% of the total inpatient costs, 31.5% of the ED visit costs, 67.3% of the office visit costs, and 97.7% of the total outpatient department visit costs. US national estimates for epinephrine auto-injector use after a suspected reaction triggered by a food allergy obtained from the published literature suggest that between 30% and 86% of patients at risk for a severe allergic reaction are prescribed an epinephrine auto-injector and have it available when needed.[95,105] Prevalence estimates and mean costs for office, inpatient, and ED visits have the largest effect on total societal direct costs. Indirect costs have been estimated at $115 million[104] with morbidity-related costs accounting for 85% of indirect costs, resulting from disease-related sick days (lost productivity and wages).[104] Simulations from probabilistic sensitivity analyses have generated mean annual direct costs of $307 million and indirect costs of $203 million in the United States.[104] While evidence suggests that activation of EMS and prolonged ED observation of resolved food anaphylaxis is a low-value practice, prompt EMS activation is appropriate for patients who do not immediately completely respond to timely epinephrine, or for recurrence of symptoms.[106]

Drug-induced anaphylaxis

ADRs may affect up to one-tenth of the general population and up to 20% of all hospitalized patients. More than 10% of all ADRs are drug hypersensitivity reactions (DHRs). In a systematic review, 53 observational studies were synthesized to estimate that 8% of patients self-report drug allergy, and that 11% of self-reported drug allergy is reported to be anaphylaxis.[107] The most common DHR involves antibiotics such as penicillins, cephalosporins, sulfonamides, aspirin, and other nonsteroidal anti-inflammatory drugs. DHRs can be severe and life-threatening and are associated with significant mortality rates. The incidence of anaphylaxis due to medication triggers is increasing over time.[59] DHRs have a significant socioeconomic impact related to both direct costs (management of reactions and hospitalizations) and indirect costs (missed work and/or school days; alternative drugs); however, there is, overall, a major gap in the literature for summarizing the economic burden of DHRs.[16] A US nationwide cross-sectional telephone self-reported survey[1] reported a prevalence of anaphylaxis in the general population of 1.6% with medications being the most common trigger (35%). Excluding pediatric cohorts (where food is the most common trigger), medications are the most frequent cause of fatal anaphylaxis in reports from the United States, as well as the United Kingdom, Australia, and New Zealand.[8,16] Perioperative anaphylaxis presents unique challenges. Recently, the 6th National Audit Project of the Royal College of Anaesthetists reviewed 266 reports of grades 3 to 5 anaphylaxis across all UK National Health Service hospitals over the course of 1 year, reporting prompt recognition and treatment of anaphylaxis in 83% of cases.[108] Cardiac arrest occurred in 15% of cases reviewed, with fatalities occurring in 3.8% of patients.[108] Risk factors for perioperative anaphylaxis fatality included older age and cardiovascular disease.[108]

ADRs from RCM occur less frequently now than they did prior to 1990 when patients received high-osmolar, ionic RCM. Prior ADRs to RCM can contribute to burden of disease by creating medical complexity associated with premedication; however, while glucocorticoid premedication has become common practice for patients with prior RCM hypersensitivity, evidence supporting the use of prophylaxis in high-risk patients receiving low- or iso-osmolar, nonionic contrast agents is lacking. ADRs associated with RCM do not relate to iodine, and the term "iodine allergy" should not be used in the context of RCM reactions.

Insect-venom anaphylaxis

Hymenoptera venom allergy (HVA) describes both anaphylactic and nonanaphylactic HSRs to stings. Reaction types include sting-induced large local (LL) or systemic allergic reactions. LL reactions last over 24 hours in which signs and symptoms are confined to tissues contiguous with the sting site. In contrast to LL reactions, acute onset systemic reactions involve generalized signs and symptoms and include a spectrum of manifestations, ranging from mild urticarial reactions to life-threatening anaphylaxis. It is estimated that 2% to 3% of adults and up to 1% of children have had a systemic reaction to a sting, and LL reactions occur in >5% of adults.[109] In a review of 10 studies published between 2001 and 2009, Bilo et al[110] found that 23% of 2577 cases of anaphylaxis were caused by an insect sting. Fatal anaphylaxis can result from HVA; the reported average of 40 deaths per year in the United States is highly suspected to underestimate the true event rate.[53,111] Even the first reaction can be fatal, but no validated screening test is available because of the very high frequency of asymptomatic sensitization (>20% of adults have detectable venom-specific IgE).[112,113] Patients often express fears of anaphylaxis because of their family history or atopic history, but HVA has not been shown to be familial.[112]

Patients often present with concern about potential anaphylaxis after having LL or generalized cutaneous systemic reaction.[114] The morbidity of living with HVA may be underestimated.[114] Fear of life-threatening anaphylaxis whenever one is outdoors, and the burden of ensuring that injectable epinephrine is readily accessible at all times, affects the daily activities and level of stress in affected individuals.[115] Even people with nonanaphylactic (LL or cutaneous systemic) reactions to stings share the same concerns and can be impacted as severely as the patients with anaphylactic reactions.[114] These concerns persist in these mild reactors even though their risk of severe anaphylaxis is quite low, and the prescription of injectable epinephrine is not cost-effective in such cases.[53] Whether it is mild or severe, HVA impairs long-term quality of life and may be a cause of substantial socioeconomic impairment.[116] HVA can impact career choices, especially in beekeepers, groundskeepers, gardeners, and greenhouse workers.[117] HVA has important adverse consequences in terms of employment, earning capacity, and leisure and sporting activities.[117] For these reasons, discussion of HVA usually includes not only anaphylactic, but also mild systemic and nonanaphylactic reactions.[109]

PATHOGENESIS OF ANAPHYLAXIS

Data regarding pathophysiologic mechanisms and effector cells are limited on humans but mouse models have offered some insight.[118] IgE binding and cross-linking of FcεRI on the surface of mast cells and basophils is an important mechanism in many cases of anaphylaxis. This causes the immediate release of preformed mediators, as well as *de novo* synthesis of inflammatory mediators.[18] Interestingly, some patients with life-threatening anaphylaxis have low or undetectable circulating allergen-specific IgE and mouse models have demonstrated a potential role for IgG-dependent anaphylaxis.[19] Furthermore, the complement (C) system, anaphylatoxins C3a, C4a, C5a, and neutrophils[119] have also been shown to be involved in anaphylaxis in human subjects. Lastly, a newly recognized form of anaphylaxis occurring in patients receiving chemotherapy suggests a mixed type of reaction with both features of IgE and non-IgE-dependent anaphylaxis.[120] Cytokine storm-like reactions have recently been described for patients with chemotherapy-induced anaphylaxis.[120]

Animal and human studies have linked multiple mediators to the signs and symptoms of anaphylaxis. The most important effector cells involved in anaphylaxis are mast cells, but basophils, neutrophils, monocytes, macrophages, and platelets have also been implicated.[118,121] Histamine is an important mediator of anaphylaxis, and studies have demonstrated that intravenous histamine can induce symptoms of anaphylaxis, including flushing, airway obstruction, systemic hypotension, and tachycardia.[122,123] While histamine appears to play a significant role, other mediators have also been implicated. Therefore, pharmacologic targeting of histamine alone (eg, administration of antihistamines) is not appropriate and is thus considered second-line treatment for anaphylaxis and should not be used in place of epinephrine. Given the slow onset of antihistamine agents, ineffectiveness in treating cardiovascular and respiratory symptoms such as hypotension or bronchospasm, and the inability to stabilize or prevent mast cell degranulation, these agents should not delay definitive treatment of anaphylaxis.

Elevated tryptase levels have been less consistently found in patients presenting with anaphylaxis, particularly in cases triggered by allergic response to food.[124] While the positive predictive value of an elevated serum tryptase is high (93%), the NPV of a serum tryptase is low (17%).[2] However, several studies[125-129] have reported an association between elevation of tryptase and severity of anaphylaxis from food and other causes. In a study[20] of prospectively recruited ED patients with anaphylaxis, mediators in addition to tryptase correlated with hypotension, a symptom of severe anaphylaxis. These included histamine, IL-6, IL-10, and TNF-receptor 1.[20,21] Several other mediators have been shown to be important in murine models of anaphylaxis, but their contribution in human anaphylaxis has not been clearly demonstrated—these include platelet-activating factor (PAF), cysteinyl LTs, and anaphylatoxins. PAF is a lipid-derived mediator elevated in serum of patients with cold urticaria during cold challenge.[130] The role of PAF is supported by studies demonstrating that injection of PAF into the skin of healthy volunteers can induce early wheal and flare and late-phase flare responses.[131] These responses are not associated with increased dermal histamine levels,[132] suggesting that the effects of PAF are independent of mast cell degranulation. While some evidence suggests antihistamine attenuation of experimental intradermally injected PAF-mediated wheal and flare response, antihistamines had no protective effect against PAF-mediated bronchoconstriction during PAF bronchial provocation.[133] Associations have been noted with increased PAF in cases of anaphylaxis.[125] In 1 study,[134] increased PAF levels demonstrated the highest correlations with severe anaphylaxis (when compared with histamine and tryptase levels), with PAF elevations in 20%, 67%, and 100% of patients with grades 1, 2, and 3 allergic reactions, respectively (grade 1: acute allergic reactions with cutaneous signs and symptoms only; grade 2: mild to moderate anaphylaxis; grade 3: severe anaphylaxis). Data to support the role of cysteinyl LTs stem from studies showing that intradermal injection of LTB_4, LTC_4, and LTD_4 can induce wheal and flare responses[135] and aerosolized LTC_4 and LTD_4 can trigger

bronchoconstriction.[136,137] In a small study of insect sting challenges, elevated serum C3a was associated with severe anaphylaxis.[138] Additional studies suggest that specific allergens such as peanut can contribute to anaphylaxis by activating complement,[139] and tryptase can generate anaphylatoxins under specific conditions.[140] These findings are important because they demonstrate some of the pathophysiologic explanations that underpin why antihistamine use may be ineffective in management of anaphylaxis.

Less is understood about the pathophysiology of protracted reactions.[141] A prospective study of anaphylaxis cases seen in EDs in Australia reported delayed deterioration (defined as any worsening of the reaction while under observation in the ED) in 17% of reactions.[21] Of the delayed deteriorations, 53% were treated with epinephrine and 69% of these started within 4 hours of arriving in the ED. A delay in the administration of epinephrine or too small a dose of epinephrine are considered risk factors for delayed deterioration, though the "optimal" time frame for epinephrine delivery to prevent delayed deterioration has not been established.[36,142] Principal component analysis revealed an association between delayed deterioration with elevated levels of histamine, tryptase, IL-6, IL-10, and TNF-receptor 1 (peak concentrations on serial assessment at ED arrival, 1 hour later, and discharge). These are the same mediators found to be correlated with severe anaphylaxis,[20,21] lending support to the hypothesis that severity of the initial reaction may be intrinsically linked to protracted symptoms.

TREATMENT STRATEGIES AND PARADIGMS

Role of epinephrine

An understanding of the pathophysiology and effector cells involved in anaphylaxis reinforces the recommendation to use epinephrine as first-line treatment, while antihistamines and glucocorticoids are considered solely second-line therapy. Anaphylaxis is a clinical diagnosis that can present with any combination of symptoms affecting various organ systems.[22] The clinical presentation and severity of symptoms differ among individuals and may change over time within the same individual.

There is international consensus that the most effective treatment for anaphylaxis is epinephrine, with evidence supporting clinical guidelines based on observational studies, extrapolation from retrospective case reports, and limited clinical trials. However, a thorough understanding of the pathophysiology of anaphylaxis, existing evidence, and mechanisms of action for various medications provides the basis for treatment recommendations.

Epinephrine administered intramuscularly (in a dose of 0.01 mg/kg of a 1:1000 [1 mg/mL] solution to a maximum of 0.5 mg in adults and 0.3 mg in children) into the anterolateral thigh is the first-line treatment for anaphylaxis.[22] The availability of newer auto-injector dose formulations (0.1 mg for infants) allows greater epinephrine dosing accuracy; however, a 0.15-mg intramuscular dose is also widely prescribed for infants at risk for anaphylaxis.[105,143] Particularly in settings where a 0.1-mg auto-injector dose is not available, the speed and precision gained from a 0.15-mg auto-injector dose compared with having caregivers draw up doses using an ampule and syringe method may justify trade-offs in dosing accuracy, especially in infants weighing >7.5 kg.[105,143] Depending on response to the initial injection, the dose can be repeated every 5 to 15 minutes.[61] Epinephrine is a nonselective agonist of all adrenergic receptors, which are present within every organ system affected by anaphylaxis.[26] By increasing peripheral resistance via α-1 receptors and increasing cardiac output via β-1 receptors, epinephrine treats hypotension, shock, urticaria, angioedema, and upper airway mucosal edema. Epinephrine can reverse bronchoconstriction and treat lower respiratory symptoms through its effect on β-2 adrenergic receptors. In addition, epinephrine has been shown to activate β-2 adrenergic receptors on mast cells and basophils and prevent additional release of histamine and other mediators.[27] Thus, epinephrine not only treats all symptoms associated with anaphylaxis but also can prevent the escalation of symptoms.

US, European, and international anaphylaxis guidelines recommend intramuscular epinephrine in the anterolateral thigh rather than subcutaneous epinephrine in the deltoid region of the upper arm for the treatment of anaphylaxis.[5,75,144] This is based on a limited number of pharmacodynamic studies in volunteers (not in anaphylaxis) that demonstrated that when administered intramuscularly into the thigh, epinephrine works rapidly and reaches maximal pharmacodynamic efficacy within 10 minutes of injection, though no proof exists that subcutaneous delivery is not effective.[26] A small study[145] conducted in children 4 to 12 years of age demonstrated a higher mean peak plasma concentration (2136 ± 351 vs. 1802 ± 214 pg/mL) and faster onset of action (8 ± 2 vs. 34 ± 14 minutes) for intramuscular compared with subcutaneous administration of epinephrine. A similar study in adult males also demonstrated higher mean peak plasma concentration for intramuscular epinephrine in the thigh (9722 ± 4801 pg/mL) compared with both intramuscular administration in the deltoid (1821 ± 426 pg/mL) and subcutaneous administration in the deltoid region (2877 ± 567 pg/mL).[146] From these limited data, experts have advocated the intramuscular rather than the subcutaneous route of delivery, though for years subcutaneous delivery was the mainstay, without any evidence that it was not effective. Importantly, studies comparing intramuscular and subcutaneous injections in the thigh have not been completed.[146] Furthermore, the studies described above were conducted in healthy adults and children who were not experiencing anaphylaxis and were taken from small samples, and thus the generalizability of these findings to the clinical setting has not been established.[144] There are also no data that have evaluated whether the peak plasma concentration, the time to peak plasma concentration, or the area under the curve is the most important feature to effective epinephrine delivery in anaphylaxis. For pediatric patients, administration of epinephrine into the anterolateral thigh is preferred to the deltoid region as this likely decreases the risk for inadvertent intraosseous administration due to needle length.[147-150] Efforts to develop alternative epinephrine delivery routes (such as sublingual and intranasal epinephrine formulations) are underway.[151-154] Intravenous administration of epinephrine is also not recommended as first-line treatment of acute anaphylaxis, even in a medical setting, due to risk for cardiac adverse events such as arrhythmias and myocardial infarction.[155] However, for patients with inadequate response to intramuscular epinephrine and intravenous saline, intravenous epinephrine can be given by continuous infusion by microdrip, preferably using an infusion pump in a monitored hospital setting. In more remote settings when immediate treatment is required on an outpatient basis, one might consider adding 1 mg (1 mL of 1:1000) of epinephrine to 1000 mL of 0.9 normal saline; starting the infusion at 2 μg/min

(2 mL/min, equivalent of 120 mL/h) and increase up to 10 μg/min (10 mL/min, equivalent of 600 mL/h); titrating the dose continuously according to blood pressure, cardiac rate, and oxygenation. Although potential epinephrine-related adverse events must be balanced in high-risk patients (ie, elderly patients with multiple comorbidities and patients with complex congenital heart disease, pulmonary hypertension, prior epinephrine-associated cardiomyopathy), there is no absolute contraindication to epinephrine use in the treatment of anaphylaxis.[61,156] Providers should be aware of the need to appropriately counsel patients when using epinephrine. It is important to discuss technique of administration and the need to appropriately restrain young children and infants to avoid inadvertent epinephrine needle injuries.[157] While there is a lack of evidence to inform treatment approaches to biphasic anaphylaxis, the same treatment recommended for initial anaphylactic events applies to the biphasic response, with prompt epinephrine the cornerstone of management.[36]

An interesting conundrum surrounds those individuals who recover fully without sequelae despite never receiving treatment for anaphylaxis. Variations in the cause and severity of their symptoms and metabolism of mediators are likely involved but this remains poorly understood.[118] Given the inability to identify which individual is at risk for life-threatening or fatal anaphylaxis, particularly in the acute setting, and the well-recognized significant benefit from rapid administration of epinephrine, treatment should never be withheld for ongoing symptoms and this should be advocated as a best-practice strategy.[22] The mortality from anaphylaxis, though real, is remarkably low at <0.5% per episode of anaphylaxis.[158] Herein lies the anaphylaxis paradox —patients having anaphylaxis may survive despite lack of treatment (or "inappropriate" treatment), but delay in treatment is widely presumed to be associated with death (though limited by lack of studies that compare fatality to nonfatality situations where provoking conditions and treatment factors were identical to determine a relative risk).[31,158]

Role of antihistamines and glucocorticoids

Antihistamines are often included as adjunctive therapy for cutaneous signs and symptoms associated with anaphylaxis but should not be administered before, or in place of, epinephrine. Histamine is an important mediator released during anaphylaxis and can cause anaphylaxis when administered intravenously or when ingested (ie, scombroid poisoning).[122,159] There are 4 histamine receptors located throughout the body (H1, H2, H3, and H4), but H1 receptors are the most clinically relevant during anaphylaxis. H2 receptors are mostly found within the gastrointestinal tract with limited distribution in the vascular smooth muscle cells and play a minor role in the pathophysiology of anaphylaxis. H1 and H2 antihistamine medications are widely available and often administered concurrently for the treatment of anaphylaxis, without supporting data for their efficacy, in particular with H2 antihistamines. Compared with older first-generation H1 antihistamines, second-generation H1 antihistamines have a longer duration of action, less anticholinergic effects, and less sedation, yet similar onset of action.[32] Antihistamines act as inverse agonists at histamine receptors; they are effective therapy for patients with urticaria and can treat many of the cutaneous signs and symptoms associated with anaphylaxis including pruritus, flushing, and urticaria.[160] Unlike epinephrine, antihistamines are poorly effective in treating cardiovascular and respiratory symptoms such as hypotension or bronchospasm when used acutely as monotherapy. Epinephrine is the first-line treatment of anaphylaxis because it has a faster onset of action and more appropriate and robust pharmacologic action compared with antihistamines. When given orally, the onset of action of antihistamines may occur within 30 minutes,[161] but peak plasma concentrations are not reached until 60 to 120 minutes, and an additional 60 to 90 minutes may be necessary for diffusion of the medication into extravascular tissues to exert maximal effect.[32,162,163] Given the rapid and potentially fatal nature of anaphylaxis, the timing of onset for antihistamines is considered too slow and could lead to incomplete or ineffective treatment. Furthermore, antihistamines lack the vasoconstrictive, bronchodilatory, ionotropic, and mast cell stabilization properties of epinephrine. While intravenous administration of H1 antihistamines may be used in a medical setting or by EMS, it should never be utilized in place of timely intramuscular epinephrine administration, but it may have an adjunct role in treatment after epinephrine has been administered.[164]

Glucocorticoids are also frequently used as adjunctive (or sometimes primary) therapy in the treatment of anaphylaxis but also should not be administered prior to, or in place of, epinephrine. Glucocorticoids have no proven role in the treatment of an acute reaction as they work with slow onset of action by binding to the glucocorticoid receptor on cell membranes, translocating the glucocorticoid/glucocorticoid receptor complex to the nucleus, and inhibiting gene expression and production of new inflammatory mediators. They are nonselective, ineffective in treating acute symptoms, and have multiple adverse effects related to high doses and prolonged use. There is a scarcity of data demonstrating the efficacy of glucocorticoids in the treatment of acute anaphylaxis despite common anecdotal administration in this setting, and no studies have clearly established their benefit when combined with epinephrine and/or antihistamines.[34,164] Studies investigating the use of glucocorticoids for treatment of anaphylaxis have shown that their use is associated with reduced length of hospital stay but have not shown any benefit of preventing return visits to the ED following discharge.[165,166]

Given the mechanism of action, glucocorticoids may not result in clinical improvement for 4 to 6 hours after administration, regardless of route. Although animal studies and *in vitro* data have demonstrated inhibitory effects within 5 to 30 minutes through upregulation of anti-inflammatory mediators and by decreasing mast cell mediator release on a cellular level,[33,167] there are no data demonstrating similar rapid onset of action or clinical improvement in human subjects. As such, given the slow onset of action and inability to reverse acute symptoms, it is again emphasized that glucocorticoids have a limited role in the acute management of anaphylaxis.

REVIEW OF EVIDENCE FOR SUPPLEMENTAL THERAPIES IN ANAPHYLAXIS TREATMENT

Despite a lack of clear evidence supporting the use of antihistamines and glucocorticoids in anaphylaxis, these treatments continue to be a part of anaphylaxis management in routine practice. While it is critical to ensure that use of these agents does

not delay administration of epinephrine, the question of whether use of these therapies adds value in the management of anaphylaxis has not been subjected to rigorous methodologic assessment in previous anaphylaxis practice parameters. To evaluate the role of these supplemental therapies, the JTFPP undertook systematic reviews to better inform practitioners' treatment of anaphylaxis.

Methods and overview

The Anaphylaxis Workgroup that developed this guideline was composed of volunteers from the AAAAI and the ACAAI with a specific interest in the topic and the guideline process. The JTFPP and Anaphylaxis Workgroup were asked to submit questions regarding anaphylaxis that they considered to be of importance for both the clinician and the patient for which currently there was not a clear-cut answer. The work group used the Population, Intervention, Comparator, Outcome (PICO) evidence-based framework for formulating each question.[168] After all questions were discussed and informal preliminary searches completed, the work group used the modified Delphi process[169,170] to select and list top questions in priority order prior to presenting them to the AAAAI/ACAAI for consideration. The top questions chosen by the AAAAI/ACAAI were then submitted to the work group for GRADE analysis.[171]

Literature search: Design, inclusion and exclusion criteria, and databases

The work group agreed to include cohort and observational studies, nonrandomized clinical trials, and articles with multiple case studies provided a comparator was reported. While review articles, guidelines, and editorials were excluded from analysis, they were reviewed to locate primary research studies within the bibliography. The search was limited to human subjects and to articles published in the English language. For each of the questions, the described databases were searched and duplicates removed, the abstracts were uploaded into Covidence (Melbourne, Australia) or Rayyan (Doha, Qatar), web-based software platforms used by guideline writing groups (eg, Cochrane Reviews) to streamline the production of systematic reviews. Each abstract was reviewed by 2 work group members or collaborators and categorized as relevant or irrelevant based on the predetermined inclusion and exclusion criteria. When required, a third work group member resolved any disagreement by consensus. For all relevant abstracts, full-text articles were uploaded into Covidence or Rayyan. Two members assessed each full-text article for eligibility for qualitative analysis with any disagreement resolved by consensus of a third member. Supplemental searches were performed to address questions in more targeted areas including prophylaxis to prevent recurrence of anaphylaxis to nonionic low-osmolar or iso-osmolar, RCM, and prevention of index anaphylaxis with chemotherapeutic agents. The resultant studies were extracted by JTFPP members and methodology groups, who assessed each article to determine whether they were appropriate for quantitative meta-analysis. In that each question used varying databases, dates, and inclusion and exclusion criteria, these were discussed within the methodological review for each question. The evidence is summarized in this document with supplemental detail included in this article's Online Repository at www.jacionline.org.

Certainty assessment of the included studies: Risk of bias using GRADE analysis

An assessment of risk of bias factors (random sequence generation, allocation concealment, blinding adequacy, completeness of data, reporting, and other potential biases) that may contribute to risk of bias was performed by the JTFPP/methodology groups. The work groups and the JTFPP reviewed draft assessments, applied assessments of clinical importance for each patient-important outcome, and determined an overall certainty of evidence across outcomes. The level of methodologic certainty for the identified literature is summarized after each clinical question.

Certainty of the body of evidence using GRADE analysis

For GRADE analysis of the certainty of the evidence,[171] 5 areas were evaluated: inconsistency, indirectness, imprecision, risk of bias, and publication bias. For the purpose of this analysis, inconsistency, indirectness, and imprecision were defined as follows:

Inconsistency: Studies are reviewed in terms of populations, interventions, and outcomes for similarity, or consistency, among the compared studies.
Indirectness: Analysis occurs around comparisons, populations, and outcomes among intervention studies. Indirectness in comparisons occurs when one drug is compared with placebo and another drug is compared with placebo, but the researchers do not compare the first drug and the second drug in a head-to-head comparison. Indirectness in populations means that the population in which the drug was studied does not reflect the population in which the study drug would be used. Indirectness of outcome refers to a primary or secondary outcome that does not exactly measure the intended outcome and thus is not powered for the outcome of choice.
Imprecision: When too few study participants were enrolled or too few events occurred in the study, imprecision is detected as studies do not meet optimal information size (OIS). However, low OIS may be offset by critical versus important outcome or valued trade-off desirable/undesirable consequences. In systematic reviews, if the confidence interval crosses a threshold of 1.0, there will usually be downgrading for imprecision.

Levels of certainty of evidence

High (⊕⊕⊕⊕): The team is very confident that the true effect lies close to the estimate of the effect.
Moderate (⊕⊕⊕◯): The team is moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low (⊕⊕◯◯): The team confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low (⊕◯◯◯): The team has very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Implications of strong and weak recommendations.

The implications of a *strong* recommendation are:

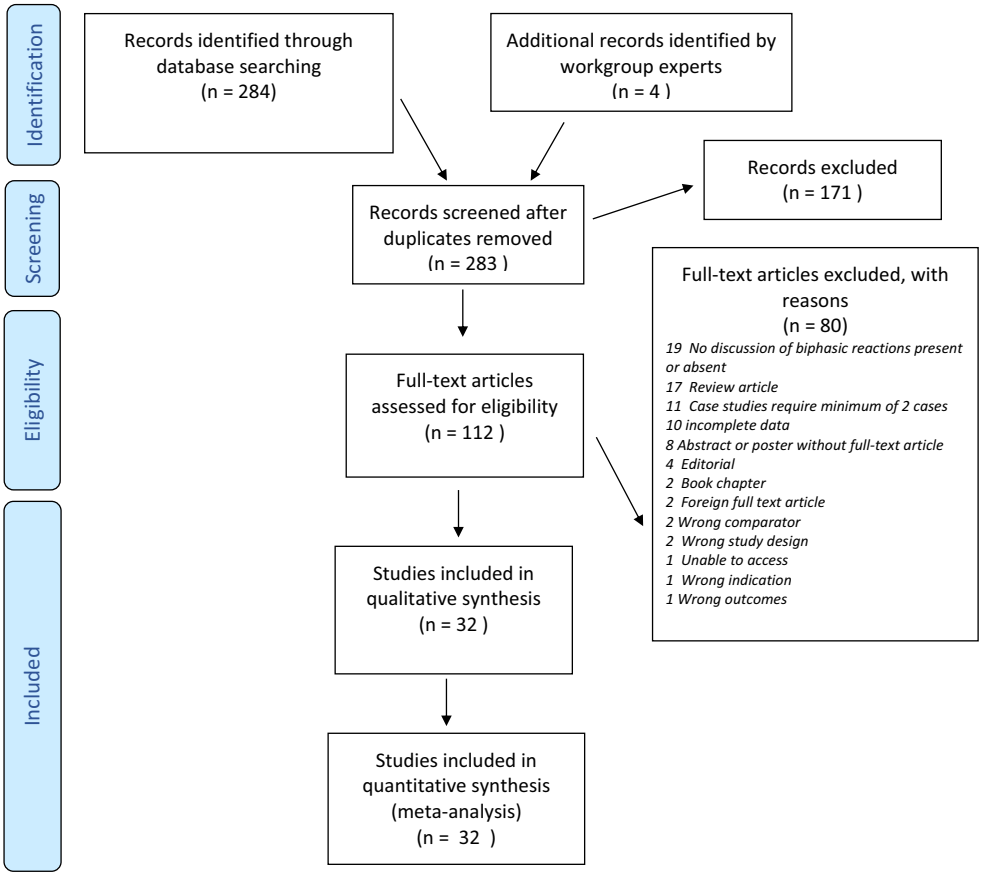


FIG 2. Topic area 1 PRISMA flow diagram.

For patients: Most people in this situation would want the recommended course of action and only a small proportion would not; patients should request discussion if the intervention is not offered.
For clinicians: Most patients should receive the recommended course of action.
For policy makers: The recommendation can be adopted as a policy in most situations.

The implications of a *weak (conditional)* recommendation (suggestion) are:

For patients: Most people in this situation would want the recommended course of action, but many would not.
For clinicians: Clinicians should recognize that different choices will be appropriate for different patients and that clinicians must help each patient to arrive at a management decision consistent with her or his values and preferences.
For policy makers: Policy making will require substantial debate and involvement of many stakeholders.

Reaching work group consensus on certainty of evidence, recommendations, clinical statement profiles and conclusions

To achieve consensus and resolve any differences in judgment within the work group and JTFPP, a modified Delphi method was used. The Delphi method is a structured, interactive, decision-making process used by a panel of experts to arrive at a consensus when there are differing views and perspectives.[169,170,172] The work group and/or JTFPP members discussed all the answers and were encouraged to modify their answers on the next round(s) of e-mail voting and anonymous "summary of the experts" feedback until a consensus was reached.

Determination of certainty of evidence for a specific outcome and across critical outcomes

The certainty of evidence indicates the extent to which one can be confident that an estimate of effect is correct. The GRADE system for evaluating the certainty of evidence (http://gdt.guidelinedevelopment.org/app) defines the elements that guideline writing groups need to consider when evaluating the certainty of references that address a specific outcome. These elements include factors that assess the risk of bias and the certainty of evidence as described above, as well as the article design (eg, randomized controlled trial or observation study). Methodology groups may designate a method of rating the certainty of individual references to assist in this analysis. Following a determination of the certainty of each individual reference, the GRADE handbook recommends that in the final analysis for each outcome of interest, the certainty of evidence for the entire group of references should be determined by the guideline writing group, using their collective expert opinion. The outcomes of interest are then categorized as "critical" or "important but not critical" to reaching a decision for a recommendation. For the

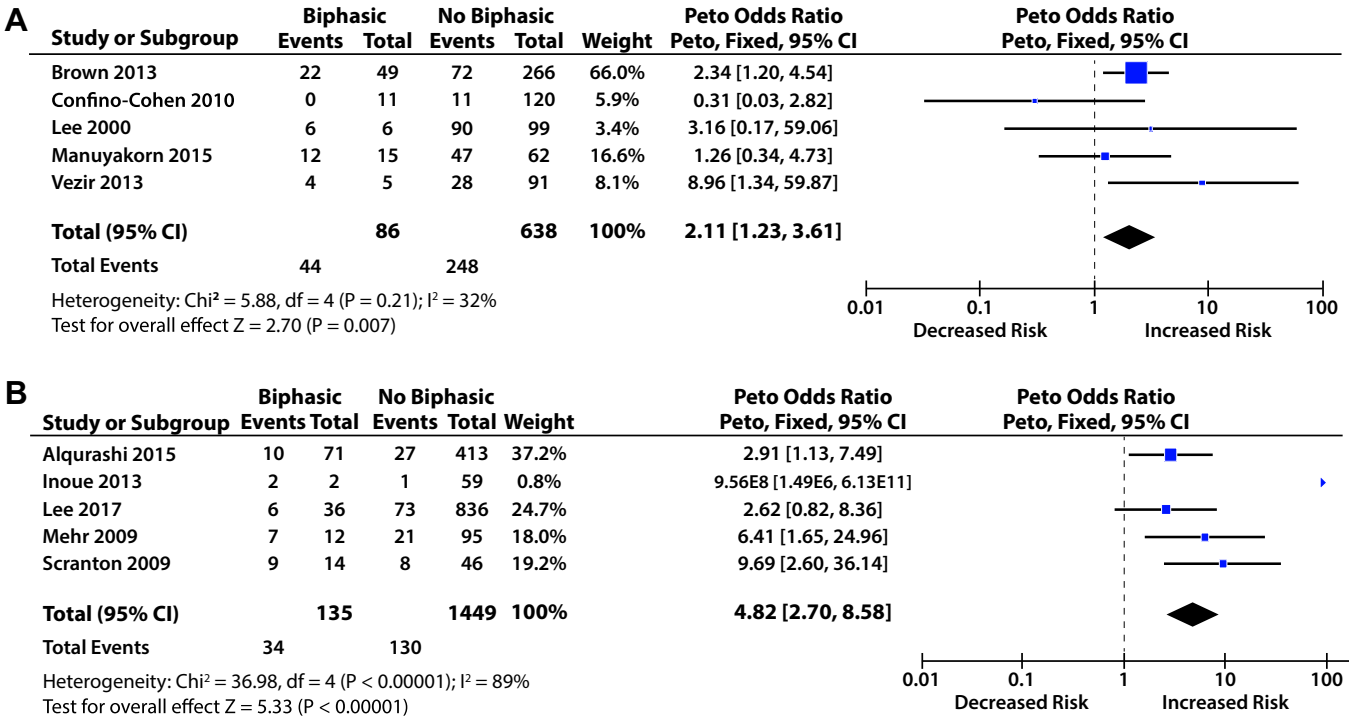


FIG 3. Question 1: Risk factors for biphasic anaphylaxis. Comparisons of biphasic versus no biphasic anaphylaxis. **A,** Outcome for severe initial symptoms. **B,** Outcomes for ≥1 dose of epinephrine.

determination of the "overall certainty of evidence" supporting a recommendation, all "critical" outcomes are reviewed together, and the lowest certainty grade assigned to any critical outcome of interest will determine the certainty assigned for the "overall certainty of evidence" to support a recommendation.

GRADE: FROM CERTAINTY OF EVIDENCE TO RECOMMENDATIONS FOR DIAGNOSIS, TREATMENT, OR COURSE OF ACTION

The strength of a recommendation indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm. After the certainty of evidence is evaluated, and before recommending or suggesting in favor or against a certain diagnostic strategy, therapeutic approach, or course of action, the GRADE analysis continues to consider additional factors: balance of desirable and undesirable effects, certainty of evidence, safety of the intervention, cost, likelihood of achieving adherence, acceptability, feasibility, equity, and patient's preference. The JTFPP primarily focused on the US population when reaching these conclusions. Therefore, the GRADE analysis is not only a system focused on grading the level of evidence but also a much more complete system aimed at formulating recommendations for specific populations. Individual subgroups drafted the recommendations and justifications based on the GRADE analysis. Subsequently, all recommendations were reviewed by the work group and JTFPP. Both groups were provided the opportunity to comment, propose changes, and approve or disapprove each statement. Consensus was sought and reached for each recommendation's direction and strength. Actual or potential conflicts of interest were disclosed semiannually and at the completion of the guideline with transparency maintained during all discussions.

External review

External peer review was through appointed official reviewers and membership at large of the AAAAI and the ACAAI. All comments were discussed by the JTFPP, and revisions made when the work group and JTFPP believed this to be appropriate.

Topic area 1: Identification and mitigation of risk factors for biphasic anaphylaxis

Topic area 1 deals solely with question 1.

Question 1. What risk factors should clinicians take into consideration in determining the likelihood of biphasic anaphylaxis?

- Patients: Adults and children treated for anaphylaxis.
- Intervention: Any treatment or characteristic associated with a decreased risk of biphasic anaphylaxis including medication or other trigger; epinephrine, antihistamine, glucocorticoid, or other treatment; age, severity, physical examination finding, or other patient characteristic.
- Comparator: Dichotomous comparator of characteristic under evaluation.
- Outcome: Occurrence of biphasic anaphylaxis.

Background. A prior single-center review of biphasic anaphylaxis in 103 patients suggested biphasic reactions were more common in patients who received less epinephrine ($P = .048$) and possibly less glucocorticoid ($P = .06$) treatment.[39] A systematic review by Lee et al.[43] found 27 observational studies

TABLE I. Question 1: GRADE summary of findings table: What are the risk factors are associated with biphasic anaphylaxis?

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no biphasic	With biphasic	Relative effect (95% CI)	Risk with no biphasic	Risk difference with biphasic
Unknown trigger											
4275 (21 observational studies)	Very serious*†‡§	Serious‖	Not serious	Not serious	None	⊕◯◯◯ Very low	624 of 4005 (15.6%)	56 of 270 (20.7%)	OR 1.63 (1.14 to 2.33)	156 per 1000	75 more per 1000 (18 more to 145 more)
Drug trigger ≤18 y old											
996 (5 observational studies)	Very serious*†	Serious‖	Not serious	Serious†	None	⊕◯◯◯ Very low	135 of 886 (15.2%)	18 of 110 (16.4%)	OR 2.35 (1.16 to 4.76)	152 per 1000	145 more per 1000 (20 more to 309 more)
Cutaneous signs and symptoms											
1949 (6 observational studies)	Very serious*†‡	Very serious‖#	Not serious	Very serious¶**	None	⊕◯◯◯ Very low	1546 of 1838 (84.1%)	104 of 111 (93.7%)	OR 2.54 (1.25 to 5.15)	841 per 1000	90 more per 1000 (28 more to 123 more)
Dyspnea symptoms											
1841 (6 observational studies)	Serious*†	Serious††	Not serious	Serious¶	None	⊕◯◯◯ Very low	831 of 1743 (47.7%)	34 of 98 (34.7%)	OR 0.60 (0.38 to 0.96)	477 per 1000	123 fewer per 1000 (220 fewer to 10 fewer)
Wide pulse pressure											
1356 (2 observational studies)	Serious*	Not serious	Not serious	Serious¶	None	⊕◯◯◯ Very low	247 of 1249 (19.8%)	40 of 107 (37.4%)	OR 2.11 (1.32 to 3.37)	198 per 1000	144 more per 1000 (48 more to 256 more)
Severe initial symptoms											
724 (5 observational studies)	Very serious*‡	Very serious‖ ‡‡	Not serious	Serious¶	None	⊕◯◯◯ Very low	248 of 638 (38.9%)	44 of 86 (51.2%)	OR 2.11 (1.23 to 3.61)	389 per 1000	184 more per 1000 (50 more to 308 more)
>1 Dose of epinephrine											
1584 (5 observational studies)	Very serious*†	Very serious††	Not serious	Serious¶	None	⊕◯◯◯ Very low	130 of 1449 (9.0%)	34 of 135 (25.2%)	OR 4.82 (2.70 to 8.58)	90 per 1000	232 more per 1000 (120 more to 368 more)
Glucocorticoids ≤18 y old											
1203 (7 observational studies)	Very serious*†‡	Not serious	Not serious	Serious¶	None	⊕◯◯◯ Very low	632 of 1089 (58.0%)	78 of 114 (68.4%)	OR 1.55 (1.01 to 2.38)	580 per 1000	102 more per 1000 (2 more to 187 more)

*Retrospective data may introduce selection bias and increase possible confounding errors.
†Included study or studies with limited follow-up of 24 hours or no follow-up resulting in possible missed biphasic patients.
‡Included study or studies with limited patient selection including patients from inpatient setting or from a specialty clinic.
§Included study or studies with larger exclusion of patients due to missing data.
‖Moderate heterogeneity as evidence by I^2 of 30% to 60%.
¶Low number of events (<250 biphasic reactions).
#Different definitions of cutaneous signs and symptoms.
**Wide confidence interval.
††Substantial heterogeneity as evidence by I^2 of 50% to 90%.
‡‡Different scales for measuring severity of anaphylactic reaction.

that reviewed predictors of biphasic anaphylactic reactions. Of the studied predictors, food as an anaphylactic trigger was associated with a decreased risk of a biphasic reaction (OR, 0.62; 95% CI, 0.4-0.94) and the "unknown" anaphylactic trigger was associated with increased risk of a biphasic reaction (OR, 1.72; 95% CI, 1.0-2.95). An initial presentation with hypotension was also associated with an increased risk of a biphasic reaction (OR, 2.18; 95% CI, 1.14-4.15).

Study characteristics. The search for suitable studies was completed by the JTFPP. In the search 283 articles were identified after removal of duplicates, with full text eligibility assessed in 112 studies, and 32 studies included in the quantitative evidence synthesis. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) system was used (see Fig 2 for PRISMA diagram).

Question 1 included studies. The following studies were included in the analysis of question 1: Alqurashi et al,[42] Brady et al,[173] Brazil and MacNamara,[174] Brown et al,[21] Calvani et al,[175] Cianferoni et al,[176] Confino-Cohen and Goldberg,[177] Douglas et al,[178] Ellis and Day,[39] Grunau et al,[40] Inoue and Yamamoto,[179] Jirapongsananuruk et al,[180] Ko et al,[181] Lee et al,[182] Lee et al,[59] Lertnawapan and Maek-a-nantawat,[183]

TABLE II. Evidence to recommendations: Topic area 1

Identification and mitigation of risk factors for biphasic anaphylaxis	
Population:	Adults and children with anaphylaxis.
Intervention:	Using the presence of risk factors associated with biphasic anaphylaxis to advise regarding medical observation time following resolution of the initial phase of anaphylaxis.
Comparison:	Standard medical observation without risk factor stratification following resolved initial anaphylaxis.
Main outcomes:	The occurrence of biphasic anaphylaxis.
Setting:	Emergency departments, allergy clinics, and primary care offices.
Perspective:	Health care providers and patients want to know what risk factors predict biphasic anaphylaxis and how best to prevent it.
Background:	Biphasic reactions may occur in up to 20% of patients with anaphylaxis but can be difficult to predict. Because biphasic anaphylaxis may occur from 1 to 78 h after anaphylaxis resolution, there is uncertainty as to optimal medical observation to detect biphasic reactions. Prior studies have suggested more severe initial presentation (including hypotension) is associated with a greater risk for biphasic anaphylaxis.
Conflict of interests:	None

Clinical statement

Very low-certainty evidence suggests patients with severe initial anaphylaxis and those requiring >1 dose of epinephrine are at risk for biphasic anaphylaxis after resolution of initial anaphylaxis.

Very low-certainty evidence suggests extended observation is appropriate for patients with severe initial anaphylaxis and/or who have required >1 dose of epinephrine. For patients with resolved nonsevere anaphylaxis who are without significant comorbidities that would increase the risk for fatal anaphylaxis, who have had a prompt response to epinephrine, and will have reliable access to medical care following discharge, a 1-h observation may be reasonable.

Prior to discharge all patients should be prescribed and receive education on how and when to use self-injectable epinephrine, the risk of biphasic anaphylaxis, trigger avoidance, and the need for follow-up care with an allergist.

Assessment

Judgment	Research evidence	Additional considerations
Problem: Is the problem a priority?		
No Probably no Probably yes **Yes** Varies Do not know	The lifetime prevalence of anaphylaxis is estimated between 1.6% to 5.1%, and biphasic anaphylaxis may occur in up to 20% of patients.[1,4] Medications are a leading trigger of anaphylaxis in adults.[1,11] The prevalence of fatal anaphylaxis is between 0.47 to 0.69 per million persons 0.25% to 0.33% of ED visits or hospitalizations.[9,10,29-31]	There is some uncertainty as to the exact rate of biphasic anaphylaxis and evidence regarding optimal treatment for biphasic anaphylaxis is scant.
Desirable effects: How substantial are the desirable anticipated effects?		
Trivial Small **Moderate** Large Varies Do not know	Understanding risk factors that could predict patients more likely to have biphasic reactions may allow more focused triage for patients who could benefit from additional education or medical observation. Very low-certainty evidence suggests biphasic anaphylaxis is associated with: (1) severe initial anaphylaxis symptoms, OR = 2.11 (95% CI, 1.23-3.61); (2) >1 dose of epinephrine, OR = 4.82 (95% CI, 2.70-8.58); and (3) wide pulse pressures, OR = 2.11 (95% CI, 1.32-3.37). Additional associations include: (4) anaphylaxis caused by any drug in patients <18 y of age, OR = 2.35 (95% CI, 1.16-4.76); (5) anaphylaxis caused by an unknown trigger, OR = 1.63 (95% CI, 1.14-2.33); (6) anaphylaxis symptoms with cutaneous manifestations, OR = 2.54 (95% CI, 1.25-5.15); and (7) anaphylaxis in patients <18 y of age treated with glucocorticoids, OR = 1.55 (95% CI, 1.01-2.38).	More severe anaphylaxis carries a greater risk for biphasic anaphylaxis. Additional associations are quite broad (eg, cutaneous signs and symptoms) or may be confounded by anaphylaxis severity (eg, wide pulse pressure and children receiving glucocorticoids).
Undesirable effects: How substantial are the undesirable anticipated effects?		
Large Moderate Small Trivial **Varies** Do not know	For ED or hospital presentations of anaphylaxis, the case-fatality rate is estimated at 0.25% to 0.33%, including both uniphasic and biphasic anaphylaxis.[31] To reduce the fatality rate for biphasic anaphylaxis, one would ideally have the patient under direct observation; however, it is not cost-effective to observe all patients for a prolonged time following resolution of uniphasic anaphylaxis. Furthermore, it has been shown that the majority of patients monitored for 1 asymptomatic hour after resolved anaphylaxis will not experience a biphasic reaction.[57] Therefore the risks and benefits need to be balanced. While harm may result from missed cases of anaphylaxis in	Patients identified to have risk factors may be observed much longer in the ED or admitted, increasing the cost of anaphylaxis treatment. Patients with these risk factors may be reluctant to go the ED for fear of having an extended stay.

(Continued)

TABLE II. *(Continued)*

Assessment		
Judgment	**Research evidence**	**Additional considerations**
	discharged patients, an overly cautious observation time for patients at low risk for both biphasic anaphylaxis and anaphylaxis fatality would be very costly. Depending on how evidence is incorporated into clinical practice, undesirable effects could include adoption of prolonged periods of medical observation, which would be unnecessary for the majority of patients with resolved anaphylaxis.	
Certainty of evidence (intentional vagueness): What is the overall certainty of the evidence of effects?		
Very low Low Moderate High No included studies	Across variables evaluated, heterogeneity ranged from low (I^2 = 0%) to high (I^2 = 89%). Due to very low certainty of evidence and absence of a randomized controlled trial to address this question, there remains uncertainty as to the degree of benefit and fatality risk reduction obtained from extended observation in patients with resolved anaphylaxis. However, when comparing a 1-h to a ≥6 h observation, the NNT by extended observation to prevent 1 biphasic reaction following discharge is 41 (range, 18-195) for patients presenting with severe anaphylaxis and 13 (range, 7-27) for those requiring >1 dose of epinephrine.[57,195]	Patients with severe initial anaphylaxis are likely to experience the greatest potential benefit from more extended observation. All patients should receive anaphylaxis education, including the risk for biphasic anaphylaxis. Patients should be prescribed self-injectable epinephrine and provided with an action plan, instructing them on how and when to administer epinephrine. On discharge, patients should be instructed to see an allergist-immunologist.[45]
Values (value judgments): Is there important uncertainty about or variability in how much people value the main outcomes?		
Important uncertainty or variability **Possibly important uncertainty or variability** Probably no important uncertainty or variability No important uncertainty or variability	All patients would prefer to avert biphasic anaphylaxis. Apart from prompt and appropriate treatment of initial anaphylaxis with epinephrine, evidence is lacking to support a clear role for any additional therapy or management strategy to decrease biphasic anaphylaxis risk. However, if initial anaphylaxis was severe, if the clinical impression is that a patient has a higher risk of biphasic reaction (ie, 17% or greater), or if risk factors for anaphylaxis fatality are present (eg, cardiovascular comorbidity, lack of access to epinephrine, lack of access to EMS, poor self-management skills) then extended observation of up to 6 h or longer (including hospital admission) may be appropriate.[58] There is an absence of patient-preference sensitive evidence to inform physicians of the relative valuation of trade-offs when prolonged observation is compared with the risk of biphasic anaphylaxis following discharge.	While all patients would choose to minimize biphasic anaphylaxis, a differential value may be placed on the importance of prolonged observation even for patients having experienced severe anaphylaxis. Conversely, patients with nonsevere anaphylaxis may prefer more extended observation (beyond 1 h). Development of a patient-decision aid could facilitate shared decision making.
Balance of effects (benefit-harm assessment): Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Favors the comparison Probably favors the comparison Does not favor either the intervention or the comparison **Probably favors the intervention** Favors the intervention Varies Do not know	Potential harm could result from overreliance of risk factors. While universal prolonged observation could lead to patients delaying medical care (or avoiding medical observation all together), triage of patients with severe index anaphylaxis may facilitate a balance of benefits and harms.	Biphasic anaphylaxis may occur in any patient with anaphylaxis and all patients should seek care if anaphylaxis recurs after initial resolution.
Resources required: How large are the resource requirements (costs)?		
Large costs Moderate costs Negligible costs and savings Moderate savings Large savings **Varies** Do not know	Direct and indirect costs may vary depending on how risk factors are incorporated into patient management. Prolonged ED observation or inpatient admission could dramatically increase costs of anaphylaxis management. Biphasic anaphylaxis occurring outside of medical observation may be more severe and life-threatening, leading to greater costs of care; however, availability of self-injectable epinephrine would be expected to mitigate these risks and costs.	Anaphylaxis patient education, referral to an allergist, and prescription of an epinephrine auto-injector at discharge are important for all patients with anaphylaxis.[45]
Certainty of evidence of required resources: What is the certainty of the evidence of resource requirements (costs)?		
Very low **Low** Moderate	There is low certainty in evidence of resource requirements due to variation in treatment setting, costs, duration of observation, and incorporation of risk factors. However, a time-dependent	Indirect costs involve job-related opportunity costs and may vary significantly across patient populations. Additional costs would

(Continued)

TABLE II. *(Continued)*

Assessment		
Judgment	**Research evidence**	**Additional considerations**
High No included studies	activity-based cost strategy can be used to estimate hourly costs from allergy clinic or ED observation.[196,197]	be incurred for patients receiving overnight hospital admission for postanaphylaxis monitoring.
Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
Favors the comparison Probably favors the comparison Does not favor either the intervention or the comparison **Probably favors the intervention** Favors the intervention Varies Do not know No included studies	Medical observation of patients with severe anaphylaxis for ≥6 h can be a cost-effective strategy if it provides at least a 76% fatality risk reduction compared with a shorter, for example, 1 h, observation.[58]	Cost-effectiveness may be sensitive to rates of biphasic reactions, cost of observation, hospitalization rates, and anaphylaxis fatalities.
Equity: What would be the impact on health equity?		
Reduced Probably reduced Probably no impact Probably increased Increased **Varies** Do not know	The impact on equity may vary depending on how risk factors are incorporated into patient management. Prolonged periods of medical observation in patients with resolved anaphylaxis could negatively impact equity and may discourage patients from seeking medical care.	All patients experiencing anaphylaxis should be closely observed until they are stable and suitable for discharge. Recognizing that a biphasic anaphylaxis may only develop many hours following total resolution of symptoms, it is difficult to determine the most appropriate and cost-effective time for medical observation. A risk-stratified approach to observation following resolved anaphylaxis should include a shared decision-making conversation with the patient and family, as both the medical risks and patient values and preference must be taken into consideration.
Acceptability and quality improvement opportunity: Is the intervention acceptable to key stakeholders?		
No Probably no Probably yes **Yes** Varies Do not know	Evidence suggests that a 1-h symptom-free observation period of nonsevere anaphylaxis has a 95% NPV for biphasic anaphylaxis.[57]	The concept that more severe anaphylaxis is associated with a greater risk for biphasic anaphylaxis is intuitive and would be acceptable to most stakeholders.
Feasibility: Is the intervention feasible to implement?		
No Probably no Probably yes Yes **Varies** Do not know	One recent meta-analysis suggests a 95% NPV associated with a 1-h medical observation, and a 97.3% NPV associated with an observation period of at least 6 h.[57]	Given the prolonged duration of possible biphasic reactions, it would not be feasible to observe all patients for the entire duration of risk (up to 78 h).
Intentional vagueness		
No Probably no Probably yes **Yes** Varies Do not know	Evidence was drawn from a heterogeneous population of nonrandomized clinical studies and is susceptible to methodologic bias. The optimal extended observation time following resolved anaphylaxis is poorly defined. While a ≥6-h observation period could be suggested in higher-risk patients, uncertainty remains regarding the cost-effectiveness of such an approach in many circumstances.[58]	Due to very low certainty of evidence and absence of a randomized controlled trial to address this question, there remains uncertainty and potential bias. A role for shared decision making in relation to extended observation may exist in some clinical situations of resolved anaphylaxis.
Role of patient preference		
No Probably no **Probably yes** Yes Varies Do not know	Patients with resolved severe anaphylaxis may reasonably choose to defer prolonged observation beyond 6 h.[58] Furthermore, an aversion to prolonged medical observation may deter some patients from seeking appropriate care. However, other patients, including those with less severe anaphylaxis, may prefer an extended period of observation based on fear, anxiety, past experiences, or specific psychosocial circumstances.	While patients with more severe anaphylaxis have a greater risk for biphasic reactions, the management of this increased risk may warrant practice variation based on a construct of shared decision making. In addition, patients with nonsevere anaphylaxis should have the option for more extended observation.

(Continued)

TABLE II. *(Continued)*

	Assessment	
Judgment	**Research evidence**	**Additional considerations**
Exclusions		
No **Probably no** Probably yes Yes Varies Do not know	It is important to distinguish biphasic anaphylaxis from uniphasic anaphylaxis without complete resolution (protracted anaphylaxis). Specific subpopulations were not excluded.	Additional factors associated with biphasic anaphylaxis would be difficult to incorporate into clinical triage strategies, such as anaphylaxis caused by a drug trigger in children, anaphylaxis with cutaneous signs and symptoms, and use of glucocorticoids in children. Some clinical associations identified may be confounded by anaphylaxis severity. Given the low certainty of evidence it is not possible to completely exclude that subpopulations may benefit from extended observation.
Policy level		
No **Probably no** Probably yes Yes Varies Do not know	We would not recommend policy-level interventions to mandate specific observation times or incorporate specific risk factors to predict biphasic anaphylaxis, as the certainty of evidence relating to this question is very low.	Well-performed future randomized controlled trials would better inform practice and understanding of risk factors to predict biphasic anaphylaxis.

Boldface indicates guideline group judgement in each domain.

Manivannan et al,[184] Manuyakorn et al,[185] Mehr et al,[186] Noone et al,[187] Orhan et al,[188] Poachanukoon and Paopairochanakorn,[189] Rohacek et al,[41] Sampson et al,[38] Scranton et al,[190] Smit et al,[191] Sricharoen et al,[55] Stark and Sullivan,[37] Vezir et al,[192] Yang et al.[193]

Key results. Based on very low-certainty evidence, the following associated factors significantly increase the risk of biphasic anaphylaxis: (1) anaphylaxis caused by any drug in patients <18 years of age (Peto OR, 2.35; 95% CI, 1.16-4.76); (2) anaphylaxis caused by an unknown trigger (Peto OR, 1.63; 95% CI, 1.14-2.33); (3) anaphylaxis symptoms with cutaneous manifestations (Peto OR, 2.54; 95% CI, 1.25-5.15); (4) wide pulse pressures (Peto OR, 2.11; 95% CI, 1.32-3.37); (5) severe initial anaphylaxis symptoms (Peto OR, 2.11; 95% CI, 1.23-3.61); (6) anaphylaxis in patients <18 years of age treated with glucocorticoids (Peto OR, 1.55; 95% CI, 1.01-2.38); and (7) patients requiring >1 dose of epinephrine (Peto OR, 4.82; 95% CI, 2.70-8.58) (see Fig 3). The bias of the studies ranged from moderate to high due to retrospective data, exclusions due to missing data, limited patient populations, and limited follow-up (Table I). The evidence to recommendations (Table II) and summary of judgements (Table III) assessments were used to develop strength of recommendations.[194-202]

Summary by predictive variable. Twenty-six predictive variables were analyzed. Nine outcomes showed a positive or negative association with biphasic anaphylaxis. Of these outcomes, time to first epinephrine was reviewed qualitatively due to the heterogeneity of the data.

Unknown trigger. Twenty-one retrospective observational studies (n = 4275) are included for this outcome: Alqurashi et al,[42] Brady et al,[173] Brazil and MacNamara,[174] Cianferoni et al,[176] Douglas et al,[178] Ellis and Day,[39] Grunau et al,[40] Inoue and Yamamoto,[179] Jirapongsananuruk et al,[180] Lee and Greenes,[142] Lee et al,[194] Lertnawapan and Maek-a-nantawat,[183] Manivannan et al,[184] Manuyakorn et al,[185] Mehr et al,[186] Rohacek et al,[41] Smit et al,[191] Sricharoen et al,[55] Stark and Sullivan,[37] Vezir et al,[192] Yang et al.[193] The pooled Peto OR was 1.63 (95% CI, 1.14-2.33). Using a fixed-effect analysis, patients with anaphylaxis from an unknown trigger have a higher risk of having a biphasic reaction. The evidence is graded very low certainty based on very serious risk of bias and serious inconsistency between the included studies. Biases include (1) the use of retrospective data, (2) limited or no follow-up, (3) limited patient selection (inpatient setting), and (4) exclusion of subjects due to missing data. Inconsistency was graded as serious due to moderate heterogeneity as evidenced by an $I^2 = 45\%$.

Drug trigger in patients ≤18 years of age. Five retrospective observational studies (n = 996) measured this outcome: Alqurashi et al,[42] Manuyakorn et al,[185] Mehr et al,[186] Orhan et al,[188] Vezir et al.[192] The pooled Peto OR was 2.35 (95% CI, 1.16-4.76). Using a fixed-effect analysis, patients ≤18 years of age who have anaphylaxis from a drug trigger are at a higher risk of having a biphasic reaction than patients ≥18 years of age with a drug trigger. The evidence is graded very low certainty based on (1) very serious risk of bias as the studies were retrospective in nature with limited or no follow-up, (2) serious inconsistency as the studies had moderate heterogeneity ($I^2 = 46\%$), and (3) serious imprecision as the studies had a low number of events.

Cutaneous signs and symptoms. Six retrospective observational studies (n = 1949) are included for this outcome: Alqurashi et al,[42] Grunau et al,[40] Inoue and Yamamoto,[179] Lee et al,[182] Manuyakorn et al,[185] Mehr et al.[186] The pooled Peto OR was 2.54 (95% CI, 1.25-5.15). Using a fixed-effect analysis, patients with cutaneous signs and symptoms are at higher risk of having a biphasic reaction than are patients without cutaneous signs and symptoms. The evidence is graded very low certainty based on very serious risk of bias and inconsistency, as well as serious imprecision. The biases include (1) the use of retrospective data, (2) limited or no follow-up, and (3) limited patient selection (inpatient setting). Inconsistency is graded as very serious because the definition of cutaneous signs and symptoms varied across studies and the $I^2 = 43\%$. Finally, the included studies are downgraded for serious imprecision, as there was a low number of events and the confidence interval for the summary statistic is wide.

Dyspnea. Six retrospective observational studies (n = 1841) are included for this outcome: Brazil and MacNamara,[174] Inoue and Yamamoto,[179] Lee et al,[194] Rohacek et al,[41] Smit et al,[191]

TABLE III. Topic area 1: Summary of judgments

	Judgment						
Problem is a priority	No	Probably no	Probably yes	**Yes**	Varies	Do not know	
Desirable effects	Trivial	Small	**Moderate**	Large	Varies	Do not know	
Undesirable effects	Large	Moderate	Small	Trivial	**Varies**	Do not know	
Certainty of evidence	**Very low**	Low	Moderate	High	No included studies		
Values	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects, benefits, harms and burdens	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Do not know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Do not know
Certainty of evidence of required resources	Very low	**Low**	Moderate	High	No included studies		
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Do not know
Acceptability	No	Probably no	Probably yes	**Yes**	Varies	Do not know	
Feasibility	No	Probably no	Probably yes	Yes	**Varies**	**Do not know**	

Boldface indicates guideline group judgment in each domain.

Sricharoen et al.[55] The pooled Peto OR was 0.6 (95% CI, 0.38-0.96). Using a fixed-effect analysis, patients with dyspnea are at lower risk of having a biphasic reaction than are patients without dyspnea. The evidence is graded very low certainty based on (1) serious risk of bias as the studies are retrospective observational studies and included studies had limited or no follow-up, (2) serious inconsistency as the studies had substantial heterogeneity (I^2 = 73%) and (3) serious imprecision as the studies had a low number of events.

Wide pulse pressure. Two retrospective observational studies (n = 1356) are included for this outcome: Alqurashi et al,[42] Lee et al.[194] The pooled Peto OR was 2.11 (95% CI, 1.32-3.37). Using a fixed-effect analysis, patients with a wide pulse pressure are at higher risk of having a biphasic reaction than are patients without a wide pulse pressure. The evidence is graded very low certainty based on (1) serious risk of bias as the studies are retrospective observational studies and (2) serious imprecision as the studies had a low number of events.

Severe initial anaphylaxis. Five retrospective observational studies (n = 724) are included for this outcome: Brown et al,[21] Confino-Cohen and Goldberg,[177] Lee and Greenes,[142] Manuyakorn et al,[185] Vezir et al.[192] The pooled Peto OR was 2.11 (95% CI, 1.23-3.61). Using a fixed-effect analysis, patients with a severe initial anaphylaxis are at higher risk of having a biphasic reaction than are patients without severe anaphylaxis. The evidence is graded very low certainty based on (1) very serious risk of bias as the studies are retrospective observational studies and included studies with limited or no follow-up, (2) serious inconsistency as the studies used different definitions for severe anaphylaxis, and (3) serious imprecision as the studies had a low number of events.

Greater than 1 epinephrine treatment. Five retrospective observational studies (n = 1584) are included for this outcome: Alqurashi et al,[42] Inoue and Yamamoto,[179] Lee et al,[203] Mehr et al,[186] Scranton et al.[190] The pooled Peto OR was 4.82 (95% CI, 2.70-8.58). Using a fixed-effect analysis, patients who receive >1 epinephrine treatment initially are at increased risk of having a biphasic reaction. The evidence is graded very low certainty based on (1) very serious risk of bias as the studies are retrospective observational studies and included studies with limited or no follow-up and (2) serious imprecision as the studies had a low number of events.

Glucocorticoid treatment in patients ≤18 years of age. Seven retrospective observational studies (n = 1203) are included for this outcome: Alqurashi et al,[42] Calvani et al,[175] Inoue and Yamamoto,[179] Lee and Greenes,[142] Manuyakorn et al,[185] Mehr et al,[186] Vezir et al.[192] The pooled Peto OR was 1.55 (95% CI, 1.01-2.38). Using a fixed-effect analysis, patients ≤18 years of age who receive glucocorticoid treatment are at a higher risk of having a biphasic reaction than are patients ≥18 years of age who receive glucocorticoid treatment. The evidence is graded very low certainty based on (1) very serious risk of bias as the studies are retrospective observational studies, included studies with limited or no follow-up, and included limited patient selection (inpatient setting) and (2) serious imprecision as the studies had a low number of events.

Time to first epinephrine. Eight retrospective observational studies (n = 1469) are included for this outcome: Alqurashi et al,[42] Ko et al,[181] Lee et al,[182] Lee et al,[194] Lee and Greenes,[142] Lertnawapan and Maek-a-nantawat,[183] Poachanukoon and Paopairochanakorn,[189] and Scranton et al.[190] Reviewers were unable to perform an analysis for this outcome because the ,investigators provided interquartile range (IQR) and median values and therefore this outcome could not be pooled together. Three of the 8 studies showed delayed administration of epinephrine resulted in higher rates of biphasic anaphylaxis while the other 5 studies showed no statistical difference. Lee et al[194] identified 872 anaphylaxis-related visits to an ED from 2008 to 2015. There was a statistically significant association with biphasic reactions when the first dose of epinephrine was administrated >60 minutes after symptoms developed (OR, 2.29; 95% CI, 1.09-4.79). Lee and Greenes[142] also performed a retrospective

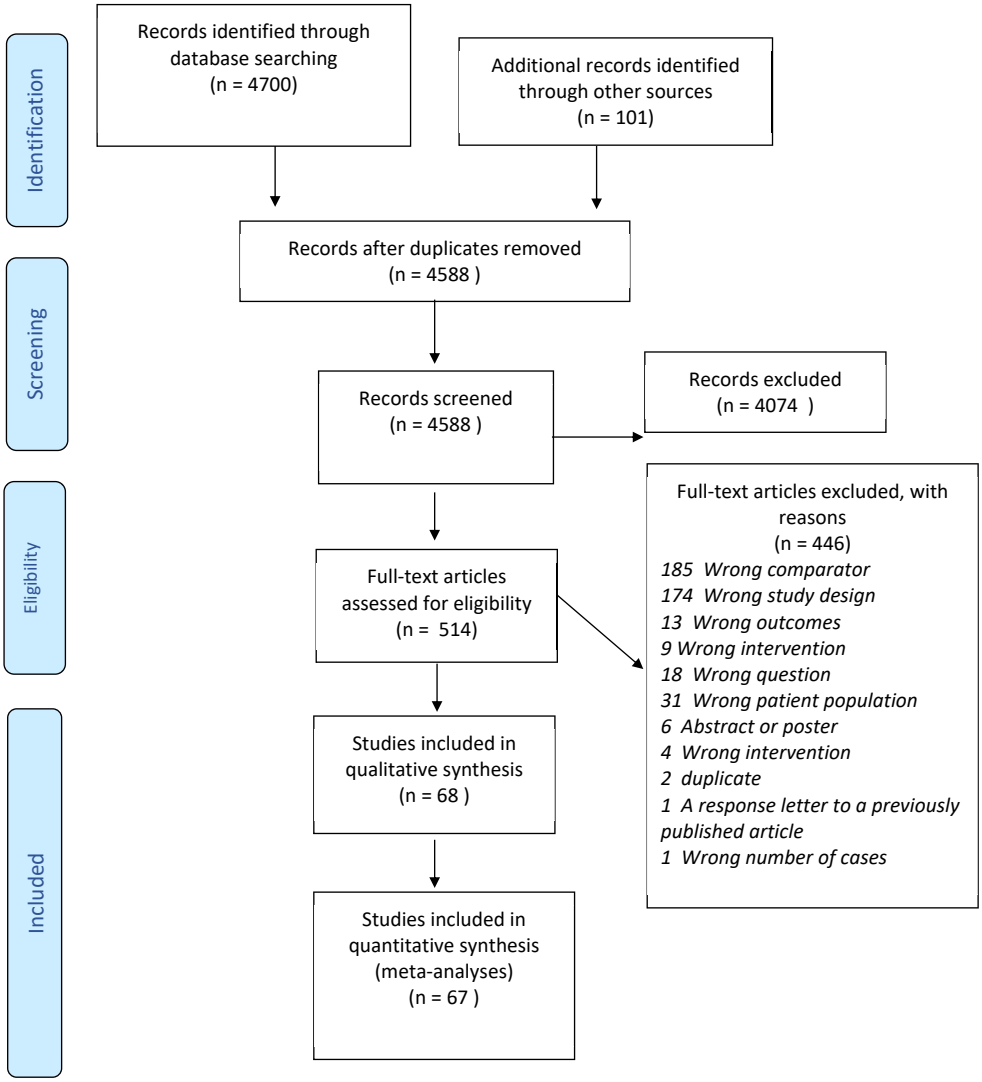


FIG 4. Topic area 2 PRISMA flow diagram.

analysis of 108 children admitted to a children's hospital. The median time from initial symptoms to initial dose of epinephrine for patients with a biphasic reaction was 190 minutes and 48 minutes for patients without a biphasic reaction ($P = .03$). Lertnawapan and Maek-a-nantawat[183] conducted an observational study on patients (n = 208) presenting to an ED with anaphylaxis. Time from symptom onset to administration of epinephrine was significantly longer in the biphasic group than in the nonbiphasic group (240 minutes [IQR, 122.5-380 minutes] vs 70 minutes [IQR, 40-135 minutes]; $P = .002$). Alqurashi et al[42] found median time from the onset of the reaction to first dose of epinephrine was not statistically different between patients with biphasic reactions (64 minutes [IQR, 25-175 minutes]) and without biphasic reactions (59 minutes [IQR, 25-105minutes]; $P = .35$). In a subgroup analysis of subjects who received epinephrine for the initial reaction, Alqurashi et al[42] identified a protective effect from early epinephrine (a time delay of epinephrine >90 minutes increased biphasic risk; $P = .01$). Ko et al[181] showed no association between the timing of epinephrine and the occurrence of biphasic reactions ($P = .52$). Median time from symptoms to epinephrine was 30 minutes (IQR, 20-60) in the nonbiphasic group and 70 minutes (IQR, 20-570) in the biphasic groups. Poachanukoon and Paopairochanakorn[189] found the median time from the onset of symptoms to the initial administration of epinephrine in the patients with biphasic reactions was longer than in the nonbiphasic group but the difference did not reach statistical significance. Median time to initial dose of epinephrine in the nonbiphasic group was 82 minutes and 263 minutes in the biphasic group. No range was given. Scranton et al[190] found no difference in mean time to epinephrine between the nonbiphasic group (8.5 ± 13.8 minutes) and the biphasic group (8.2 ± 12.8 minutes; $P = .94$). Lee et al[182] found no difference in time from first reaction onset to first epinephrine dose between the nonbiphasic group (23.0 minutes) and the biphasic group (28.5 minutes; $P = .60$).

Food trigger. Although previously found to be associated with a decreased risk for biphasic anaphylaxis,[43] the current analysis did not find a significant association of foods with

TABLE IV. Question 2 GRADE summary of findings table: Should glucocorticoids or antihistamines be used to prevent biphasic anaphylaxis?

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biphasic	Uniphasic	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Glucocorticoids to prevent biphasic anaphylaxis												
26	Observational studies	Very serious*	Serious†	Serious‡	Serious§	All plausible residual confounding would reduce the demonstrated effect	616 of 871 (70.7%)	10,270 of 14,762 (69.6%)	**OR 0.87** (0.74-1.02)	30 fewer per 1000 (from 4 more to 67 fewer)	⊕◯◯◯ Very low	Important
H1 Antihistamines to prevent biphasic anaphylaxis												
16	Observational studies	Very serious*	Serious†	Serious‡	Serious§	All plausible residual confounding would reduce the demonstrated effect	210 of 245 (85.7%)	2875 of 3304 (87.0%)	**OR 0.71** (0.47-1.06)	44 fewer per 1000 (from 6 more to 111 fewer)	⊕◯◯◯ Very low	Important
H2 Antihistamines to prevent biphasic anaphylaxis												
10	Observational studies	Very serious*	Not serious	Serious†	Serious	All plausible residual confounding would reduce the demonstrated effect	60 of 173 (34.7%)	763 of 1955 (39.0%)	**OR 1.21** (0.80-1.83)	46 more per 1000 (from 52 fewer to 149 more)	⊕◯◯◯ Very low	Important

Boldface indicates guideline group judgment in each domain.
*Risk of bias across studies related to lack of blinding, lack of randomization, potential confounding by severity of presentation, practice variation, and differential use of epinephrine.
†Significant heterogeneity across studies.
‡Endpoint included outcomes reported as surrogate to biphasic reactions included ED revisits.
§Several studies with wide ranging 95% CIs.

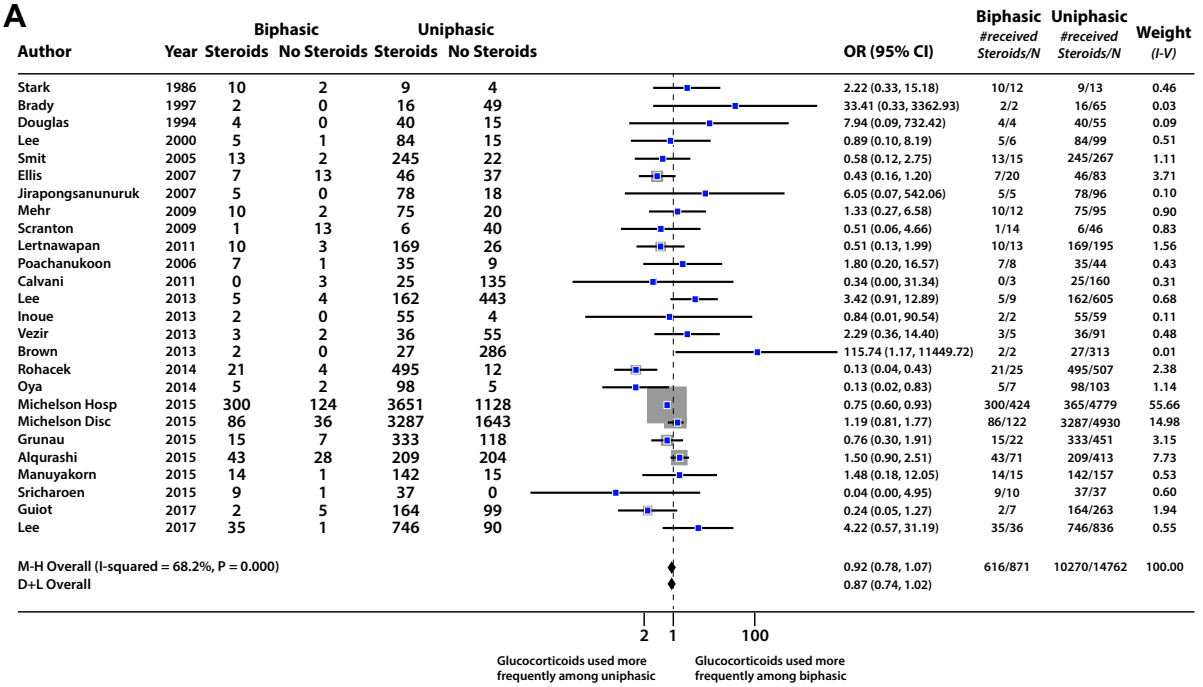
decreased risk for biphasic anaphylaxis (Peto OR, 0.89; 95% CI, 0.68-1.17).

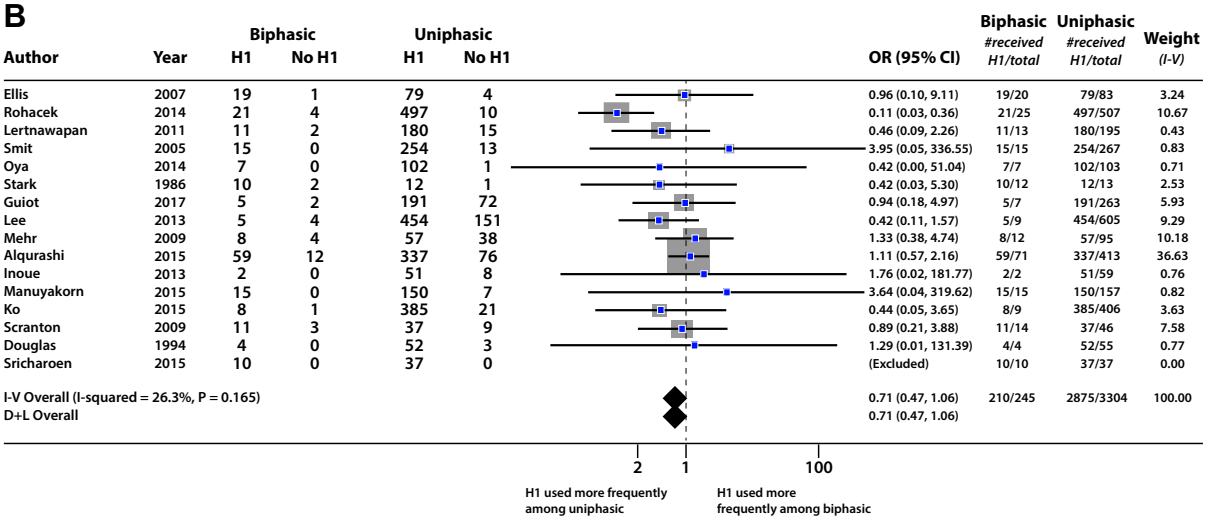
Topic area 2. Should antihistamines or glucocorticoids be used to prevent anaphylactic reactions?

Question 2. Should antihistamines and/or glucocorticoids be used to prevent biphasic anaphylaxis?
Question 3. Should antihistamine and/or glucocorticoid premedication be used to prevent index hypersensitivity/infusion reactions to chemotherapy?
Question 4. Should antihistamine and/or glucocorticoid premedication be used to prevent recurrent HSRs to RCM?
Question 5. Should antihistamine and/or glucocorticoid premedication be used to prevent HSRs to allergen immunotherapy or other agents?

- Patients: Adults and children experiencing anaphylaxis who are treated with glucocorticoids, antihistamines, or both to (1) prevent biphasic anaphylaxis, (2) prevent index anaphylaxis with chemotherapeutic, (3) prevent recurrence of anaphylaxis to nonionic low- or iso-osmolar RCM, and (4) prevent index anaphylaxis with nonchemotherapeutic agent. The analysis did not include patients with prior reactions attributed to chemotherapy or preventative treatment for children receiving chemotherapy.
- Intervention: Use of antihistamine and/or glucocorticoid.
- Comparator: Management without antihistamine and/or glucocorticoid.
- Outcome: Occurrence of (1) biphasic anaphylaxis and (2-4) anaphylaxis.

Background. A systematic review by Alqurashi and Ellis[44] found 31 observational studies that reviewed the role of glucocorticoids for the treatment of anaphylaxis, suggesting that biphasic reactions were more likely to occur in moderate to severe anaphylaxis or when anaphylaxis was not treated with timely epinephrine. The investigators concluded there was a lack of compelling evidence to support the routine use of glucocorticoids to prevent biphasic anaphylaxis.[44] Similar to the assumption that glucocorticoids provide proven benefit in acute anaphylaxis management, common practice has adopted the use of antihistamines, glucocorticoids, or both prior to chemotherapy, radiocontrast dye administration, and many other procedures or medications thought to involve risk of allergic reactions or anaphylaxis. However, the actual rigor to which these therapies have been evaluated is questionable. Paclitaxel, an antitumor agent, is an example, with HSRs to this agent reported since early clinical use. In an early report[198] of 301 patients treated, 32 patients had definite (27 patients) or possible (5 patients) HSRs and all but 1 patient had the reaction from the





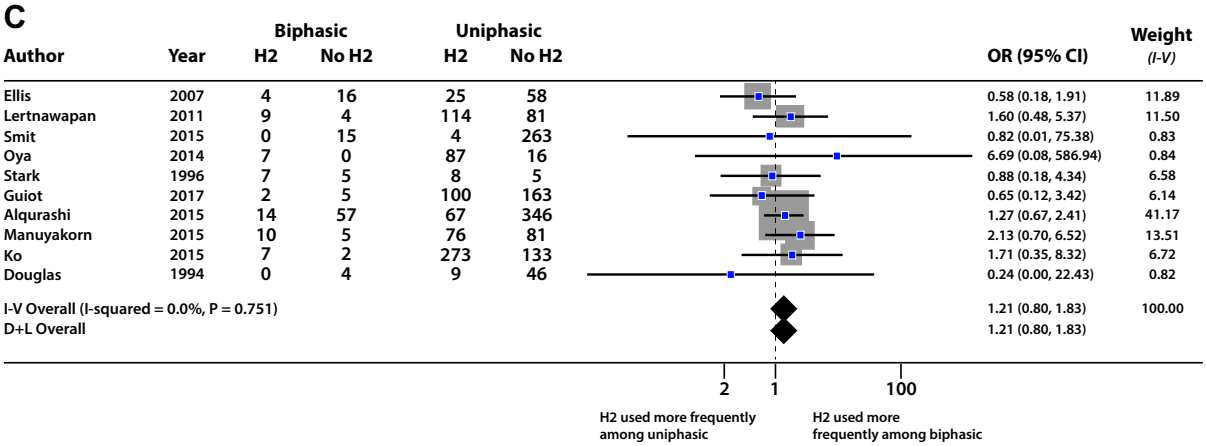


FIG 5. Should glucocorticoids or antihistamines be used to prevent biphasic anaphylaxis? **A,** Use of glucocorticoids among patients with biphasic versus uniphasic outcomes. **B,** Use of H1 antihistamines among patients with biphasic versus uniphasic outcomes. **C,** Use of H2 antihistamines among patients with biphasic versus uniphasic outcomes. *D+L*, DerSimonian-Laird; *I-V*, inverse variance; *M-H*, Mantel-Haenszel.

TABLE V. Question 3 GRADE summary of findings table: Should antihistamine and/or glucocorticoid premedication be used to prevent index hypersensitivity/infusion reactions to chemotherapy?

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Premedication	No premedication	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Rate of premedication use in subjects with or without reactions to chemotherapy												
11	Observational studies	Serious*	Serious†	Serious‡	Serious§	None	132 of 2579 (5.1%)	181 of 1430 (12.7%)	**OR 0.49** (0.37-0.66)	60 fewer per 1000 (from 76 fewer to 39 fewer)	⊕◯◯◯ Very low	Important

Boldface indicates guideline group judgment in each domain.
*Some inconsistency in protocol design could affect outcome assessments.
†Moderate heterogeneity identified in meta-analysis.
‡Studies evaluated nonselected patient populations without identified risk factors. Various protocols for premedication were evaluated. The relevance of findings to specific at risk populations is unclear.
§Several studies with wide ranging 95% CIs.

first or second exposure. Of interest, 13 patients (41%) had received premedication to prevent toxicity but nonetheless experienced HSRs. While prolongation of infusion time appears to have decreased the rate of HSRs, the addition of premedication has also become common practice in some circumstances.[198] Premedication is also used in patients with prior reactions to RCM; however, it has been suggested that the most important change in decreasing rates of HSR associated with RCM has been use of alternative low- or iso-osmolar nonionic agents.[17] Evidence supporting the use of premedication in the setting of nonionic RCM agents for high-risk patients is poorly described, and there is concern that the routine use of glucocorticoid premedication in the setting of prior HSR to RCM may cause more morbidity than benefit.[17]

Study characteristics. The search for suitable studies was completed by the JTFPP (Fig 4). Sixty-seven articles were identified for inclusion. OR were used in analysis of questions 2, 3, and 5 due to the case-control analytic strategy as biphasic and uniphasic anaphylaxis were analyzed by retrospective evaluation of therapies received before the outcome of interest. Conversely, question 4 was evaluated using the risk ratio, which is useful in the setting of a prospective analysis plan to evaluate differences in outcome between exposure and control. Of note, if the prevalence/incidence of the event is low, then the risk ratio and OR typically give very similar results. The Peto OR can be useful if there are no events or low number of events in arms evaluated, but was avoided in the topic area 2 analysis due to unbalanced arms that could lead to skewed findings using the Peto OR.[199]

Topic area 2 included studies. The following studies were used in the analyses of questions 2 to 5:

Question 2: Alqurashi et al,[42] Brady et al,[173] Brown et al,[21] Calvani et al,[175] Douglas et al,[178] Ellis and Day,[39] Grunau et al,[200] Guiot et al,[201] Inoue and Yamamoto,[179] Jirapongsanuruk et al,[180] Kawano et al,[202] Ko et al,[181] Lee et al,[203] Lee and Greenes,[142] Lee et al,[182] Lertnawapan and Maek-a-nantawat,[183] Lin et al,[204] Manuyakorn et al,[185] Mehr et al,[186] Michelson et al,[166] Oya et al,[205] Poachanukoon and Paopairochanakorn,[189] Rohacek et al,[41] Scranton et al,[190] Smit et al,[191] Sricharoen et al,[55] Stark and Sullivan,[37] Vezir et al.[192]
Question 3: Chang et al,[206] Francis et al,[207] Jerzak et al,[208] Mach et al,[209] Onetto et al,[210] Rougier,[211] Seki et al,[212] Shen et al,[213] Thompson et al,[214] Trudeau et al,[215] Weiss et al.[198]
Question 4: Abe et al,[216] Katayama et al,[217] Kolbe et al,[218] Lee et al,[219] Park et al,[220] Park et al.[221]
Question 5: Augustsson et al,[222] Berchtold et al,[223] Braaton et al,[224] Brockow et al,[225] Caron et al,[226] Fan et al,[227] Gold et al,[228] Hejjaoui et al,[229] Jacobstein et al,[230] Jagdis et al,[231] Lorenz et al,[232] Mueller et al,[233] Neilson et al,[234]; Portnoy et al,[235] Reimers et al,[236] Sanders et al,[237] Schoning et al,[238] Tankersley et al,[239] Ohashi et al.[46]

Key results. *Question 2.* As shown in Table IV and Fig 5, very low-certainty evidence suggests that glucocorticoids do not provide clear benefit in terms of reducing the risk for biphasic anaphylactic reactions (OR, 0.87; 95% CI, 0.74-1.02). Prolonged hospitalization and revisits were analyzed as surrogate markers in Michelson et al,[166] in which glucocorticoids were associated with decreased length of hospital stay but not with 3-day ED revisit among hospitalized children. However, this study was limited by the poor distinction between protracted or biphasic anaphylaxis, introducing possible classification bias. Meta-regression analyses were performed to address potential confounding by differential rates of epinephrine use, with the summary estimate adjusted by accounting for whether there were differences across studies with regard to the odds of the biphasic versus the uniphasic group also receiving epinephrine at baseline. In meta-regression analyses, epinephrine use accounted for about one-half of the between study variance, with moderate variance remaining after this correction ($\tau^2 = 0.4$).

Similar to findings regarding glucocorticoid use in anaphylaxis, antihistamines also did not provide benefit in reduction of biphasic reactions (for H1 antihistamines: OR, 0.71; 95% CI, 0.47-1.06; and for H2 antihistamines: OR, 1.21; 95% CI, 0.80-1.83) (Table IV and Fig 5). Additional analyses were performed excluding Mehr et al[186] and Lee et al[182] to account for uncertainty in antihistamine preparations used without change in findings (for H1 antihistamine: OR, 0.69; 95% CI, 0.44-1.09). To address potential confounding by differential rates of epinephrine use, the summary estimate was adjusted by accounting for whether there were differences across studies with regard to the odds of the biphasic versus the uniphasic group also receiving epinephrine at baseline. In the meta-regression analysis, epinephrine use did not account for significant variation across studies. Kawano et al[202] reported findings of a retrospective cohort to evaluate the effect of antihistamine treatment to prevent

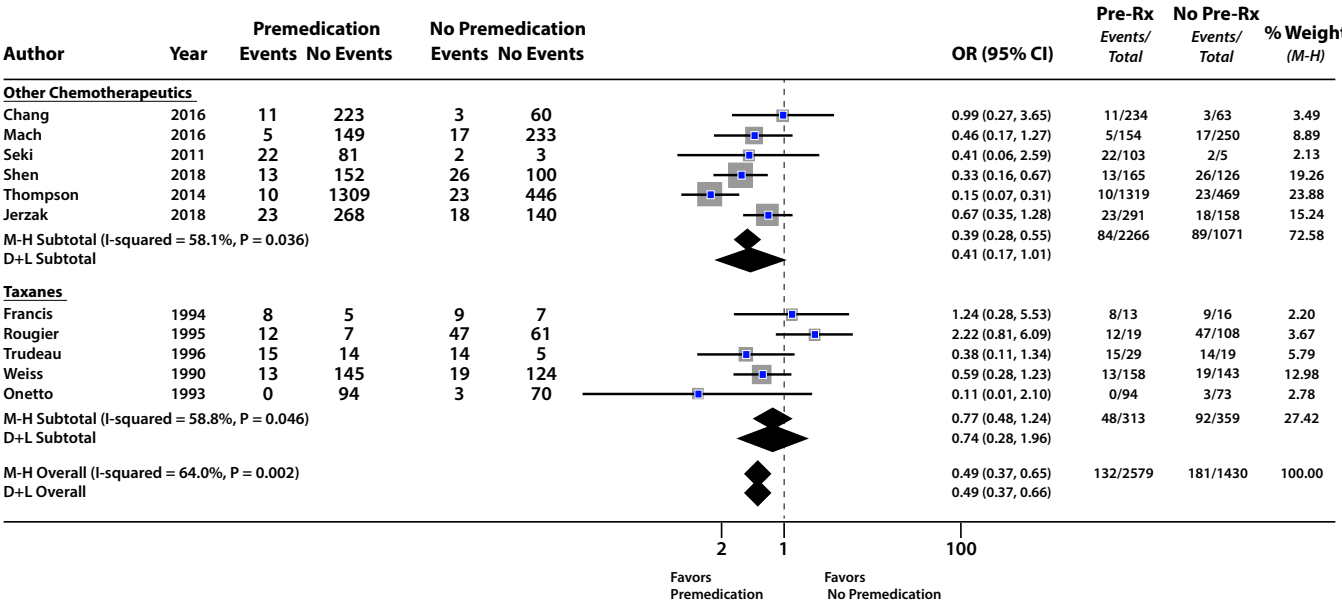


FIG 6. Should antihistamine and/or glucocorticoid premedication be used to prevent index hypersensitivity/infusion reactions to chemotherapy? Events are hypersensitivity or infusion-related reactions. Premedication is glucocorticoids and/or antihistamines.

TABLE VI. Question 4 GRADE summary of findings table: Should antihistamine and/or glucocorticoid premedication be used to prevent recurrent HSRs to RCM?

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Premedication	No premedication	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Subsequent RCM reaction with or without premedication												
6	Observational studies	Serious*	Serious†	Not serious	Serious‡	None	523 of 4277 (12.2%)	1218 of 15,851 (7.7%)	**RR 1.07** (0.67-1.71)	5 more per 1000 (from 25 fewer to 55 more)	⊕◯◯◯ Very low	Important

Boldface indicates guideline group judgment in each domain.
RR, Risk ratio.
*Due to observations study design sources of bias could affect effect estimate.
†Significant heterogeneity among studies.
‡Several studies with wide ranging 95% CIs.

progression to anaphylaxis, so this study was excluded from the final analysis. However, the inclusion of Kawano et al[202] did result in a significant OR in favor of antihistamine use (OR, 0.65; 95% CI, 0.47-0.91). The significance of Kawano et al[202] is difficult to interpret because patients were selected using an ED diagnostic code of "allergic reaction" (code 995.3 in International Classification of Diseases, Ninth Revision) and patients receiving H1 antihistamines were more likely to receive epinephrine and glucocorticoids in their report. Similarly, Lin et al[204] was excluded as the comparator in this analysis was an antihistamine, and Sricharoen et al[55] was excluded as all subjects received antihistamines.

Question 3. Premedication for chemotherapy was evaluated by outcome of HSR or infusion-related reaction (Table V and Fig 6). Specific agents evaluated included pegaspargase, docetaxel, carboplatin, oxaliplatin, and paclitaxel. Given heterogeneity of premedication, specific analysis of premedication variant strategies was not performed. Very low-certainty evidence suggests that glucocorticoid and/or antihistamine premedication does provide benefit in terms of reducing the risk for hypersensitivity or infusion-related reactions in adults receiving chemotherapy who have not previously experienced a reaction to the drug when used in the context of a chemotherapy protocol (OR, 0.49; 95% CI, 0.37-0.66) (Table V and Fig 6). The test for heterogeneity yielded a statistically significant difference between studies ($P = .002$; $I^2 = 64.0\%$). Jung et al[240] evaluated glucocorticoid premedication for rituximab in patients with B-cell malignancies, demonstrating a reduced rate of rituximab infusion–related reactions in patients pretreated with glucocorticoids (2.7%) compared with patients who did not receive premedication (13%) (OR, 0.183; 95% CI, 0.067-0.496; $P < .001$). Additional sensitivity analyses including the Jung et al[240] analysis in the overall chemotherapy meta-analysis enhanced the benefit of chemotherapy premedication identified (OR, 0.45; 95% CI, 0.34-0.6).

Question 4. Very low-certainty evidence suggests that glucocorticoid and/or antihistamine premedication does not provide benefit in terms of reducing the risk for HSRs in patients

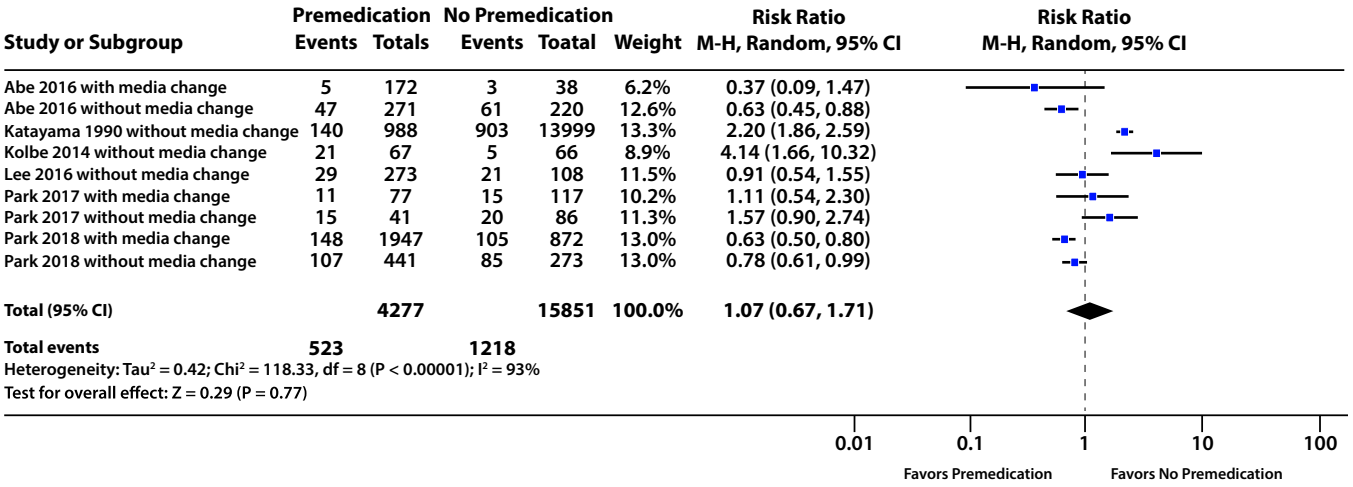


FIG 7. Should antihistamine and/or glucocorticoid premedication be used to prevent recurrent HSRs to RCM?

TABLE VII. Question 5 GRADE summary of findings table: Should antihistamine and/or glucocorticoid premedication be used to prevent HSRs to infliximab, allergen immunotherapy, or other agents?

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Premedication	No premedication	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Rate of investigator-defined allergic reactions												
19	Observational studies	Serious*	Serious†	Serious‡	Serious§	All plausible residual confounding would reduce the demonstrated effect	228 of 9473 (2.4%)	395 of 15922 (2.5%)	**RR 0.74** (0.49-1.11)	6 fewer per 1000 (from 13 fewer to 3 more)	⊕◯◯◯ Very low	Important

Boldface indicates guideline group judgment in each domain.
*Risk of bias across studies related to lack of blinding, lack of randomization, potential confounding by severity of presentation, practice variation.
†Significant heterogeneity across studies.
‡Significant degree of heterogeneity in outcomes reported.
§Several studies with wide ranging 95% CIs.

with prior RCM reactions (risk ratio, 1.07; 95% CI, 0.67-1.71) (Table VI and Fig 7). The test for heterogeneity yielded a statistically significant difference between studies ($P < .001$; $I^2 = 93\%$). Lasser et al[241] was excluded from the primary analysis because it was unclear which patients in this cohort who received nonionic contrast had experienced prior RCM HSRs; however, in sensitivity analyses including patients with overall hypersensitivity as well as more severe (grade II/III) reactions, premedication did not provide clear benefit (overall reactions: risk ratio, 0.97; 95% CI, 0.61-1.52; and grade II/III reactions: risk ratio, 1.00; 95% CI, 0.64-1.57). It is important to note that specific evaluation of patients with prior severe delayed onset allergic reactions for RCM is not well studied and was not addressed in the current analysis. Severe delayed RCM reactions have included Stevens-Johnson syndrome, toxic epidermal necrolysis, drug-related eosinophilia with systemic symptoms, and vasculitis—with fatalities reported.[242-250] For instance, although iodixanol is a low-osmolar nonionic dimer, delayed T-cell-mediated reactions have been described.[244] While skin testing with delayed readings at 48 and 72 hours may play a role in identifying non-cross-reactive agents,[244] there remains uncertainty as to whether such an approach is necessary when compared with simply choosing a non-cross-reactive RCM for presumed T-cell-mediated severe delayed onset reactions.[17] Similarly, the necessity of other measures to prevent recurrent severe delayed reactions, which have included intravenous immunoglobulin, desensitization, and cyclosporine, is unknown.[251-253] A simple approach was recently proposed by Macy[17] who reviewed RCM HSRs and described 4 non-cross-reacting RCM groups from the perspective of delayed-onset T-cell-mediated reactions (defined as groups A, B, C, and ungrouped). Group A RCM agents (which include the low-osmolar monomers iopamidol, iomeprol, ioversol, iohexol, and low-osmolar dimer iodixanol) were contrasted from group B (including the low-osmolar monomer iobitridol and low-osmolar dimer ioxaglate), group C (high-osmolar ionic monomer amidotrizoate/diatrizoate), and ungrouped agents (low-osmolar monomers iopromide, iopamidol, iothalamate). One management strategy suggested that glucocorticoid premedication begun 1 day before the procedure (and continued for 5 days) may have a role in severe delayed-onset reactions to group A RCM agents together with selection of a non-cross-reactive group (such as iopromide or iopamidol).[17] The optimal approach to patients with delayed severe RCM reactions requires further study.

Question 5. Very low-certainty evidence suggests that glucocorticoid and/or antihistamine premedication does not

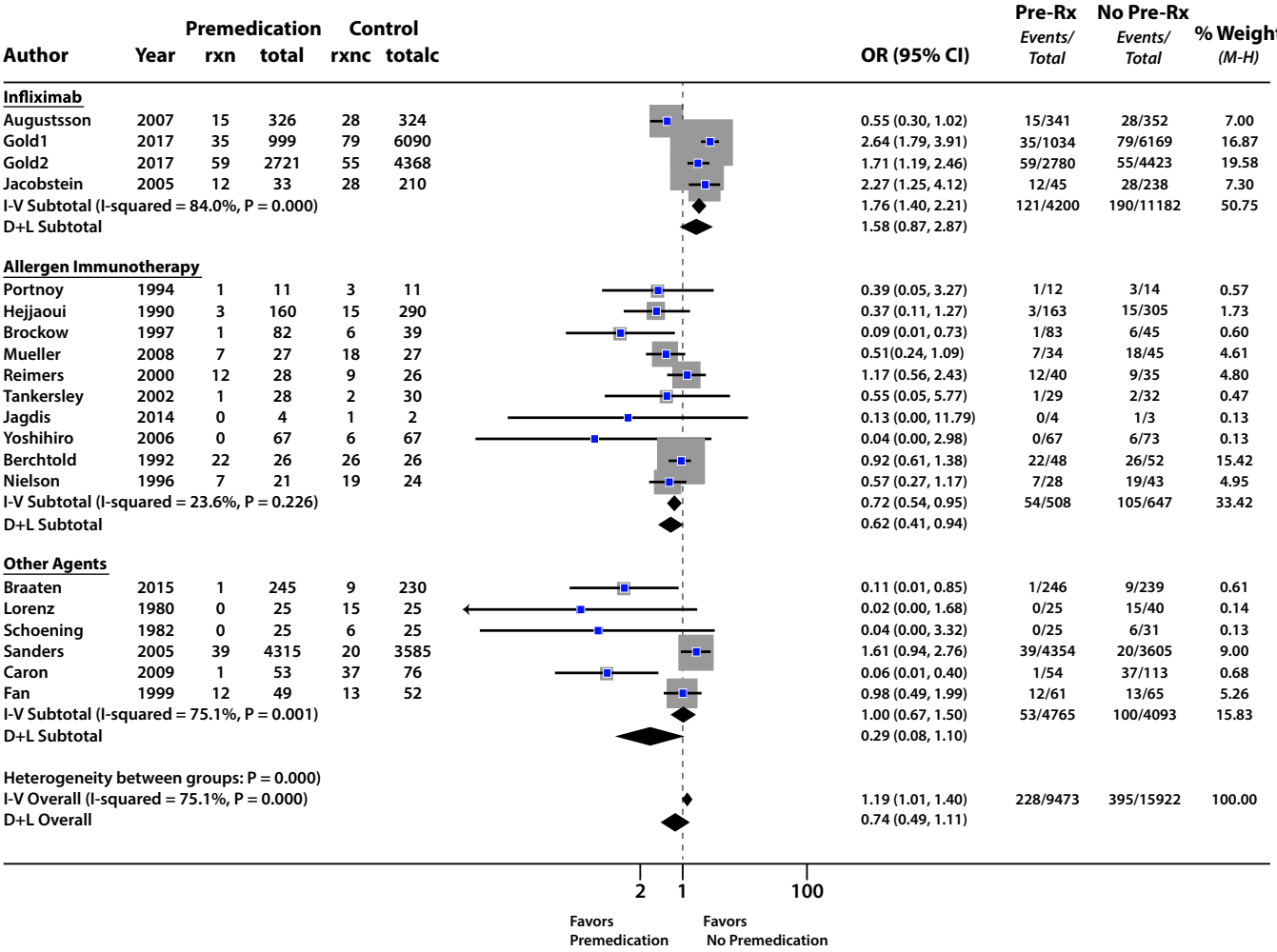


FIG 8. Should antihistamine and/or glucocorticoid premedication be used to prevent HSRs to infliximab, allergen immunotherapy, or other agents? *rxn*, Reaction with premedication; *rxnc*, reaction in controls; *totalc*, total for control.

provide benefit in terms of reducing the risk for HSRs in subjects receiving infliximab, allergen immunotherapy, or other (nonchemotherapy, non-RCM) medications (risk ratio, 0.74; 95% CI, 0.49-1.11) (Table VII and Fig 8). In contrast to infliximab, an analysis by Jung et al[240] demonstrated glucocorticoid premedication was effective in preventing rituximab infusion reactions in the context of B-cell malignancies. Additionally, the subgroup analysis of allergen immunotherapy did demonstrate a significant benefit of premedication, driven largely by studies of premedication in accelerated allergen immunotherapy schedules, which present greater risks of anaphylaxis (risk ratio, 0.62; 95% CI, 0.41-0.94). This benefit may relate to a high baseline rate of systemic reactions. For example, Portnoy et al[235] reported a double-blind placebo controlled trial of RIT in 22 allergic children 6 to 18 years of age. Systemic reactions (inclusive of isolated urticaria) were reported in 27% of subjects treated with H1 antagonists, H2 antagonists, and glucocorticoids compared with 73% of placebo subjects. One of 11 children experienced anaphylaxis in the treatment group compared with 3 of 11 in the placebo group. However, if additional consideration was given to patients receiving RIT who experienced either anaphylaxis or investigator-classified pulmonary symptoms (wheezing, shortness of breath, or chest tightness), the difference between active treatment and placebo was 18% versus 45%, respectively.[235] Additional sensitivity analysis performed using this modified definition of anaphylaxis from Portnoy et al[235] did not significantly change results. Exclusion of the RIT patients from Portnoy et al[235] and Hejjaoui et al[229] resulted in an OR of 0.65 (95% CI, 0.41-1.04) for patients in the immunotherapy subgroup.

RECOMMENDATIONS

Question 1. What risk factors should clinicians take into consideration in determining the likelihood of biphasic anaphylaxis?

Recommendation 1. We suggest that a clinician incorporate severity of anaphylaxis presentation and/or the administration of >1 dose of epinephrine for the treatment of initial anaphylaxis as a guide to determining a patient's risk for developing biphasic anaphylaxis. Conditional recommendation. Certainty rating of evidence: very low.

Technical statement. The JTFPP findings suggest biphasic anaphylaxis is associated with a more severe initial presentation

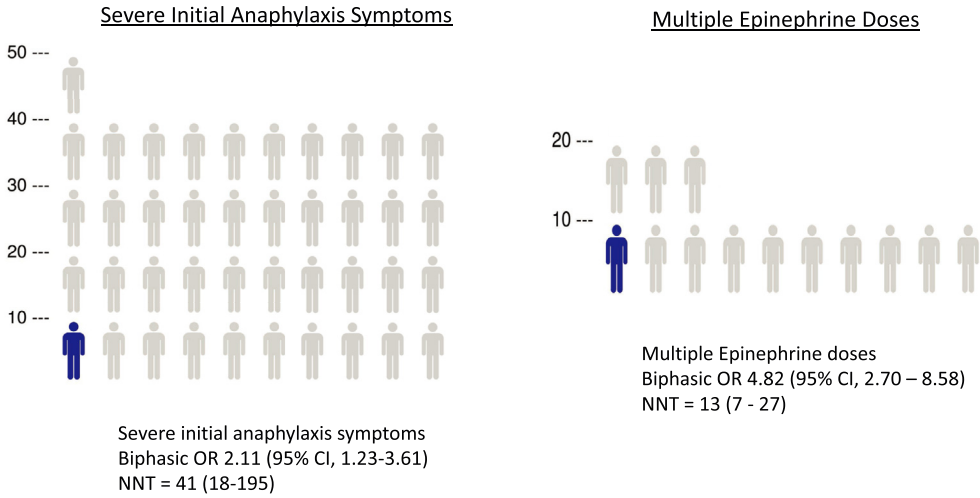


FIG 9. Extended observation to detect biphasic anaphylaxis: number needed to observe.

of anaphylaxis (OR, 2.11; 95% CI, 1.23-3.61) or repeated epinephrine doses (ie, >1 epinephrine dose) required with the initial presentation (OR, 4.82; 95% CI, 2.70-8.58). Additional risk factors identified included wide pulse pressure (OR, 2.11; 95% CI, 1.32-3.37), unknown anaphylaxis trigger (OR, 1.63; 95% CI, 1.14-2.33), cutaneous signs and symptoms (OR, 2.54; 95% CI, 1.25-5.15), and drug trigger in children (OR, 2.35; 95% CI, 1.16-4.76). While dyspnea on presentation was associated with a decreased risk for anaphylaxis, overall confidence in this estimate was low (OR, 0.6; 95% CI, 0.38-0.96).

Recommendation 2. We suggest in favor of extended clinical observation in a setting capable of managing anaphylaxis (to detect biphasic anaphylaxis) for patients with resolved severe anaphylaxis and/or the need for more than one dose of epinephrine. Strength of recommendation: conditional. Certainty of evidence: Very low.

Technical comment. At present, evidence is lacking to clearly demonstrate the period of universal extended observation that may be required or cost-effective in all patients with severe anaphylaxis or those who require multiple doses of epinephrine (Tables II and III). A recent meta-analysis of observation times suggested 1-hour observation was associated with a 95% NPV of biphasic anaphylaxis, while a 6-hour or longer observation period was associated with a 97.3% NPV of biphasic anaphylaxis occurring after discharge.[57] Based on this analysis, the incremental biphasic PEER between asymptomatic 1-hour and ≥6-hour observation is 2.3%. Therefore, the NNT with extended observation to be able to detect 1 episode of biphasic anaphylaxis before discharge (Fig 9) would be 41 (range, 18 to 195) for patients with a more severe initial presentation of anaphylaxis and 13 (range, 7 to 27) for patients with multiple epinephrine doses.[195] For patients at high risk for biphasic anaphylaxis or those with a higher risk of anaphylaxis fatality (eg, serious medical comorbidities), more prolonged monitoring can be cost-effective.[58] In a recent analysis, 6-hour observation was cost-effective if it was able to provide a high degree of protection against anaphylaxis fatality (24% fatality relative risk for extended vs 1-hour observation).[58] Patients with comorbidities such as severe respiratory or cardiac disease and corresponding higher risks for poor anaphylaxis outcomes may therefore benefit from more extended observation. Conversely, in patients presenting with nonsevere anaphylaxis and promptly responding to a single dose of epinephrine without recurrence, evidence suggests that a 1-hour observation may be reasonable in the context of appropriate patient education.[57,58] Such lower-risk patients would be characterized as having a very small risk of biphasic anaphylaxis (<5%) following discharge associated with a <50% fatality risk reduction from extended observation.[58] Therefore, the JTFPP suggests that in patients with a severe initial presentation of anaphylaxis (eg, those with hypotension, wide pulse pressures, multiple doses of epinephrine, or other markers of severity), extended observation should be considered following resolution of the index episodes without recurrence. At present, evidence is lacking to clearly demonstrate the exact period of universal extended observation that may be required or cost-effective in all patients with severe anaphylaxis or those who require multiple doses of epinephrine.[36,58] In some circumstances a role may exist for shared decision-making tools around the duration of prolonged ED observation.

The JTFPP analysis found additional factors associated with risk of biphasic anaphylaxis that would be difficult to incorporate into clinical triage strategies, such as anaphylaxis caused by a drug trigger in children, anaphylaxis with cutaneous signs and symptoms, and use of glucocorticoids in children. Some of these associations may be confounded by anaphylaxis severity and practice variation, with very low certainty of evidence challenging the applicability of these factors to patient care until they can be further substantiated. For instance, it is highly unlikely that administration of >1 dose of epinephrine or glucocorticoids contributed to biphasic reactions, but very likely that these were indicative of a more significant anaphylactic reaction. It is possible that medication-induced anaphylaxis in children may be a risk factor for biphasic anaphylaxis, but it is not possible to determine whether this is due to having more severe anaphylaxis or whether medication, as a trigger, is an independent risk factor for biphasic anaphylaxis in children. In regard to the association of idiopathic anaphylaxis, follow-up for post-ED identification of a specific trigger was not explored; therefore, the significance of this factor is uncertain. While wide pulse pressures may be considered a marker for severe anaphylaxis, the clinician may also consider extended observation for patients with an unknown anaphylaxis trigger and children with a drug trigger.

TABLE VIII. Evidence to recommendations: Topic area 2

Evaluation and use of supplemental glucocorticoid and/or antihistamine premedication for anaphylaxis prevention	
Population:	Adults and children with anaphylaxis.
Intervention:	Use of antihistamines and/or glucocorticoids to prevent anaphylactic reactions.
Comparison:	Not using antihistamines and/or glucocorticoids for the purpose of preventing anaphylaxis.
Main outcomes:	Prevention of anaphylaxis.
Setting:	ED, outpatient, medical office, community.
Perspective:	Clinicians and patients want to know whether anaphylaxis can be prevented with antihistamines and/or glucocorticoids.
Background:	Clinicians frequently recommend antihistamines and/or glucocorticoids to prevent anaphylaxis. Premedication is often used for chemotherapy, monoclonal antibody infusions, and allergen immunotherapy. However, the benefit of antihistamines and/or glucocorticoids premedication for RCM, as well as each of these other settings, is uncertain. In addition, there is uncertainty whether antihistamines and/or glucocorticoids prevent biphasic anaphylaxis recurrence following resolved anaphylaxis of any cause.
Conflict of interests:	None.

Clinical statement
Very low-certainty evidence suggests that treatment with glucocorticoids, antihistamines, or both as part of initial anaphylaxis management does not provide clear added benefit in preventing biphasic anaphylaxis in patients with resolved anaphylaxis. While a premedication strategy may provide benefit in patients receiving rush aeroallergen immunotherapy and patients receiving some forms of protocol chemotherapy, evidence is lacking to support clear benefit in patients receiving a infliximab without a prior history of anaphylaxis, or in patients with a history of anaphylaxis to RCM receiving an alternative low- or iso-osmolar nonionic RCM agent.

Assessment

Judgment	**Research evidence**	**Additional considerations**
Problem: Is the problem a priority?		
No Probably no Probably yes **Yes** Varies Do not know	The lifetime prevalence of anaphylaxis is estimated between 1.6% and 5.1%, and biphasic anaphylaxis may occur in up to 20% of patients.[1,4] Medications are a leading trigger of anaphylaxis in adults. The prevalence of fatal anaphylaxis is between 0.47 to 0.69 per million persons and 0.25% to 0.33% of ED visits or hospitalizations.[9,29,31] Anaphylaxis prevention strategies have used antihistamines and glucocorticoids to prevent subsequent biphasic anaphylaxis in patients with resolved initial anaphylaxis, as well as premedication strategies in instances where the risk of anaphylaxis has been thought to be significant (chemotherapy, monoclonal therapy, RCM use, allergen immunotherapy, and others).	There is some uncertainty as to the exact rate of biphasic anaphylaxis and evidence regarding optimal treatment for biphasic anaphylaxis is scant. There is variation in the patient event rate of anaphylaxis in particular clinical settings.
Desirable effects: How substantial are the desirable anticipated effects?		
Trivial **Small** Moderate Large Varies Do not know	The JTFPP analysis did find a nonsignificant trend to prevention of biphasic anaphylaxis with glucocorticoids (OR, 0.87; 95% CI, 0.74-1.02) and H1 antihistamines (OR, 0.71; 95% CI, 0.47-1.06), but not for H2 antihistamines H2 antihistamines (OR, 1.21; 95% CI, 0.80-1.83). Premedication did show benefit with rush allergen immunotherapy, with a NNT of 19 (range, 12-119) at an anaphylaxis PEER of 14% from the immunotherapy analysis that included RIT. The JTFPP analysis also showed reduction in anaphylaxis and infusion reaction events with premedication for some chemotherapy agents (OR, 0.49; 95% CI, 0.37-0.66), but not infliximab (RR, 1.58; 95% CI, 0.87-2.87), or RCM (RR, 1.07; 95% CI, 0.67-1.71). However, under the best possible circumstances within these confidence limits, the NNT to prevent anaphylaxis by the administration of premedication would be 13 for chemotherapy and 385 for infliximab therapy. Within the confidence limits, in the setting of alternative low- or iso-osmolar RCM in patients with prior RCM reactions, the NNT would be 36 under the most optimistic scenario of premedication benefit.	Certainty of evidence is very low and findings are imprecise. However, it is possible that benefit could be evident in some circumstances. Based on the understanding of antihistamine and glucocorticoid mechanism of action, these therapies could decrease symptoms associated with anaphylaxis, such as urticaria. While this affect could confound the diagnosis of anaphylaxis, it may also provide some benefit in averting unnecessary care for patients who do not experience progression beyond urticaria as the only manifestation of an allergic response.
Undesirable effects: How substantial are the undesirable anticipated effects?		
Large **Moderate** Small Trivial	Glucocorticoids and first-generation antihistamines may have adverse effects, particularly in certain more vulnerable populations, which may include sedation and confusion, particularly in the elderly.[254-258] Side effects of these therapies may confound recognition, assessment, and/or treatment of	Additional medical complexity of these treatments may create obstacles to efficient health care delivery.

(Continued)

TABLE VIII. *(Continued)*

Assessment		
Judgment	**Research evidence**	**Additional considerations**
Varies Do not know	anaphylaxis. It is unlikely that antihistamines and glucocorticoids increase anaphylaxis risk; however, within the JTF analysis the precision of estimate included the possibility of increased biphasic anaphylaxis. This effect could be confounded by severity of anaphylaxis. Reliance on antihistamines could also result in delay in epinephrine use.	
Certainty of evidence (intentional vagueness): What is the overall certainty of the evidence of effects?		
Very low Low Moderate High No included studies	Due to very low certainty of evidence and absence of a randomized controlled trial to address this question, there remains uncertainty and potential bias in the assessment of benefit or harms from glucocorticoids and/or antihistamines to prevent anaphylaxis.	The evidence base is of low certainty and a randomized controlled trial in regard to premedication may be warranted.
Values (value judgments): Is there important uncertainty about or variability in how much people value the main outcomes?		
Important uncertainty or variability Possibly important uncertainty or variability Probably no important uncertainty or variability No important uncertainty or variability	With greater certainty of benefit, patients would likely accept a greater rate of adverse effects from glucocorticoids and/or antihistamines; however, with the degree of uncertainty identified in the JTFPP analysis, value judgments may be made by patients and providers in a more personalized context. Patients with comorbidities such as diabetes and poorly controlled hypertension may choose to defer glucocorticoids or antihistamine therapy in some circumstances.	Patients may choose to defer more complex treatment protocols that involve glucocorticoids and/or antihistamines if the addition of these agents creates obstacles to care until there is greater certainty of benefit.
Balance of effects (benefit-harm assessment): Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Favors the comparison **Probably favors the comparison** Does not favor either the intervention or the comparison Probably favors the intervention Favors the intervention Varies Do not know	Sedation from first-generation antihistamines could be mitigated with the use of a second-generation antihistamine. In patients without comorbidities, the rare use of oral or intravenous glucocorticoids carries a low, overall risk, especially in comparison to anaphylaxis. While rare severe adverse events may occur from first-generation antihistamine or glucocorticoid (eg, fatal automobile accidents and aseptic necrosis of the hip), the likelihood of such events after single course of therapy would be very low. While under the best-case scenario, benefit from glucocorticoids and antihistamines could be evident with a NNT of 20 to 30 patients in some settings, all patients receiving therapy experience increased risk of adverse effects, medical complexity, and cost.	While this analysis is focused on anaphylaxis prevention, the greatest harm of glucocorticoids and/or antihistamines is the risk for delay in treatment with epinephrine.
Resources required: How large are the resource requirements (costs)?		
Large costs **Moderate costs** Negligible costs and savings Moderate savings Large savings Varies Do not know	Costs on a societal level could be moderate, particularly if sedating antihistamines are used and lead to job-related opportunity costs or sedation-related traffic accidents. Indirect costs include time delays, opportunity costs, sedation, traffic accidents, management of hyperglycemia, and other adverse effects of therapy. However, in the best-case scenario costs of anaphylaxis could be prevented for every 20 to 30 patients treated in some settings.	If extended observation times are associated with additional treatment, or if parenteral treatments are administered, costs would be greater.
Certainty of evidence of required resources: What is the certainty of the evidence of resource requirements (costs)?		
Very low Low Moderate High **No included studies**	There is uncertainty in the evidence of required resources as randomized controlled trials of glucocorticoid and antihistamine premedication are sparse. While treatment protocols of glucocorticoids and antihistamines to prevent biphasic anaphylaxis and prevention of monoclonal antibody anaphylaxis may vary, strategies for RCM premedication are more standardized.[17] Portnoy et al[235] began pretreatment 1 d prior to RIT.	There is some uncertainty as to whether more or fewer resources would be required for observation, given that the current use of antihistamines and glucocorticoids may provide a false sense of security that the patient has a significantly lower risk of anaphylaxis
Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
Favors the comparison Probably favors the comparison Does not favor either the intervention	If observation time is unaffected, there would be a minimal reduction in cost from omitting treatment with antihistamines and glucocorticoids to prevent biphasic anaphylaxis. However, if observation time was increased due to the withholding of these medications, there could be increased overall costs.	Cost-effectiveness would likely be sensitive to rates of anaphylaxis, hospitalization, and fatality risk reduction.

(Continued)

TABLE VIII. *(Continued)*

	Assessment	
Judgment	**Research evidence**	**Additional considerations**
or the comparison Probably favors the intervention Favors the intervention Varies Do not know **No included studies**	Lower costs would be expected with opportunity cost-savings from decreased medical complexity in premedication regimens; however, costs could be offset by increased rates of anaphylaxis. In the setting of RIT, costs of antihistamine and glucocorticoid premedication are small, and with benefit evident in at least 1 RCT the premedication approach is likely cost-effective.[235] In addition, 1 small study suggested benefit from antihistamine premedication before conventional immunotherapy.[46]	
Equity: What would be the impact on health equity?		
Reduced Probably reduced **Probably no impact** Probably increased Increased Varies Do not know	Increased medical complexity may increase disparities in health equity. In rural settings, access to 24-h pharmacies may limit immediate availability of antihistamine and glucocorticoid treatments if an outpatient course is prescribed following resolution of anaphylaxis. In addition, as the complexity of care increases by the use of premedication regimens, the degree to which delivery of care shifts from primary to subspecialty is uncertain. Patients with poor health literacy may be at risk for incorrect dosing of home regimens as preventative anaphylaxis strategies become more complicated.	Oral antihistamines and oral glucocorticoids are relatively inexpensive, so it is possible in some circumstances health equity impact could be minimal. However, if patients are treated for anaphylaxis at home for complete symptom resolution and further extended observation is driven by the practice of administering antihistamines and glucocorticoids, the effect on health equity could be more pronounced. As such, elimination of routine use of antihistamines and glucocorticoids to prevent biphasic anaphylaxis could improve health equity.
Acceptability and quality improvement opportunity: Is the intervention acceptable to key stakeholders?		
No Probably no Probably yes Yes **Varies** Do not know	Antihistamines and glucocorticoids are common medications used to treat and prevent allergic reactions. While these treatments should not interfere with prompt administration of epinephrine in anaphylaxis treatment, they are often administered as first-line drugs with a wait-and-see approach before epinephrine is administered. It has been shown that epinephrine is often omitted in the ED setting while antihistamines and glucocorticoids are administered for a diagnosis of anaphylaxis. Therefore, the administration of epinephrine for all patients with anaphylaxis and the withholding of antihistamines and corticosteroids for some patients will not be acceptable to all professional stakeholders. Many patients are very willing to take an antihistamine but delay self-administration of epinephrine even when they know they are having severe anaphylaxis. This guideline will likely do little to change patient behavior. Conveying the message to professionals and patients that these agents should be considered as adjunct therapies to decrease symptoms associated with anaphylaxis, such as urticaria, and not a primary treatment for anaphylaxis will require continued educational efforts. When antihistamines and corticosteroids are used with the intent of anaphylaxis prevention, evidence generally suggests that the likelihood of benefit is low and uncertain in most settings. However, as in situations of anaphylaxis treatment, antihistamines and corticosteroids may decrease risks of symptoms associated with anaphylaxis, such as urticaria. While the administration of these agents may delay recognition of anaphylaxis, they may also prevent unnecessary escalation of treatment for nonanaphylactic allergic symptoms. Evidence suggests benefit of corticosteroids and antihistamines in RIT to prevent anaphylaxis. Given that a similar mechanism of action by corticosteroids and antihistamines could also occur in anaphylaxis prevention in other situations, the beneficial use of these agents may be identified in future therapeutic trials. The NNT to prevent anaphylaxis will depend on the underlying patient expected event rate for anaphylaxis from a specific trigger.	The practice of treating patients experiencing anaphylaxis with antihistamines and glucocorticoids is fairly embedded into common practice styles. Stakeholders may weigh the risks of biphasic anaphylaxis more heavily than the risks of these medications and be uncomfortable with the risk benefit of denying adjunct treatment.
Feasibility: Is the intervention feasible to implement?		
No Probably no	Use of antihistamines and glucocorticoids by ED physicians to both treat and prevent anaphylaxis is widespread. The very	Additional high-certainty evidence is needed to better inform

(Continued)

TABLE VIII. *(Continued)*

Assessment		
Judgment	**Research evidence**	**Additional considerations**
Probably yes Yes **Varies** Do not know	low-certainty evidence from this meta-analysis and the current placement of these drugs as adjunctive agents (in addition to epinephrine) for the treatment of anaphylaxis makes practice change challenging. Likewise, office-based clinicians and patients are comfortable using an antihistamine for both the prevention and treatment of an allergic reactions. Given the evidence provided in this analysis, clinicians may consider withholding glucocorticoids prior to infliximab treatment and in patents with prior RCM anaphylaxis receiving an alternative low- or iso-osmolar agent. Patients receiving RIT may consider treatment with antihistamines and glucocorticoids While further study is needed, 1 study suggests possible benefit from antihistamine premedication before conventional aeroallergen immunotherapy.[46]	practice as to the role of antihistamines and glucocorticoids for the purpose of preventing anaphylaxis.
Intentional vagueness		
Yes	Due to low certainty of evidence and absence of a randomized controlled trials in most settings evaluated, there remains uncertainty in the role of antihistamines and glucocorticoids in the prevention of anaphylaxis.	Additional high-certainty evidence is needed to better inform practice.
Role of patient preference		
Probably yes	Patients may feel "safer" with the use of antihistamines and/or glucocorticoids, but this preference is likely to be highly influenced by counseling and education they receive from health care providers. The patient will need education and reeducation on the signs and symptoms of anaphylaxis and on the use of epinephrine as the only first-line medication for the treatment of anaphylaxis. Providers cannot allow the patient to "prefer" an antihistamine over epinephrine for the treatment of anaphylaxis. Patient preference may be a consideration in the use of antihistamines and glucocorticoids as second-line medications following epinephrine administration. Antihistamines and glucocorticoids may provide some role in treating the urticaria and pruritus occurring during anaphylaxis.	Shared decision making would be appropriate in some circumstances given the absence of clear benefit in prevention of anaphylaxis with antihistamines and glucocorticoids in many settings. Patient-preference sensitive care could address unwarranted practice variation to prevent biphasic anaphylaxis, monoclonal antibody anaphylaxis, and RCM anaphylaxis prevention.
Exclusions		
Yes	Given the low certainty of evidence, it is not possible to completely exclude subpopulations that may experience more pronounced benefit from a particular intervention to prevent anaphylaxis. The meta-analysis evaluated the role of antihistamine and/or glucocorticoid in prevention (not treatment) of anaphylaxis. In addition, children receiving chemotherapy, patients receiving chemotherapy desensitization, and patients with delayed RCM reactions were not included in the meta-analysis.	
Policy level		
No	We would not recommend policy-level interventions to either mandate or limit the use of supplemental therapy in anaphylaxis as the certainty of evidence relating to this question is very low.	

Boldface indicates guideline group judgment in each domain.

Incorporating cutaneous signs and symptoms into a clinical decision for extended observation may be limited by the common occurrence of cutaneous signs and symptoms in patients presenting with anaphylaxis. There was no signal that any medication other than epinephrine used for treatment of initial anaphylaxis reduced the risk of biphasic anaphylaxis. Notably, there does appear to be a trend to lower rates of biphasic reactions with earlier epinephrine administration following development of anaphylaxis. While early epinephrine in the setting of anaphylaxis is important, evidence suggests preemptive epinephrine before symptom onset is generally not a cost-effective strategy.[54]

Prompt and adequate treatment of anaphylaxis appears central to reducing biphasic anaphylaxis risk. The implications for the clinician, based on this systematic review and meta-analysis, is that the patient presenting with severe anaphylaxis and/or requiring more aggressive treatment (eg, >1 dose of epinephrine), following complete resolution of symptoms, may benefit from

longer observation time for a potential biphasic reaction. While the possibility of biphasic anaphylaxis should be emphasized in this higher-risk group, it is important to educate all patients on the chance of a biphasic reaction as well as avoiding known triggers, identifying symptoms of anaphylaxis, the use of auto-injector epinephrine for the treatment of anaphylaxis, and timely follow-up with an allergist.

Question 2. Should antihistamines or glucocorticoids be used to prevent biphasic anaphylaxis?

Recommendation. We suggest against administering glucocorticoids or antihistamines as an intervention to prevent biphasic anaphylaxis. Strength of recommendation: conditional. Certainty of evidence: very low.

Technical comment. As a secondary therapy, antihistamines and glucocorticoids may be considerations in anaphylaxis treatment.[45] In particular, antihistamines may treat urticaria and itching to improve comfort during anaphylaxis, but if used prior to epinephrine administration, they could lead to a delay in first-line treatment of anaphylaxis. The JTFPP analysis did not identify significant benefit in prevention of biphasic anaphylaxis from H1 antihistamines (OR, 0.71; 95% CI, 0.47-1.06), H2 antihistamines (OR, 1.21; 95% CI, 0.80-1.83), or glucocorticoids (OR, 0.87; 95% CI, 0.74-1.02). An interaction was identified between age and glucocorticoid use, with glucocorticoids actually increasing risk for biphasic anaphylaxis in children (OR, 1.55; 95% CI, 1.01-2.38); however, confounding effect of severity could not be excluded. Evaluation of the NNT of patients to potentially reduce biphasic anaphylaxis rates is useful.[195]

At a biphasic anaphylaxis PEER of 5%, the NNT for H1 antihistamines is 72 to prevent 1 episode of biphasic anaphylaxis. At a biphasic anaphylaxis PEER of 20%, the NNT (to prevent 1 case of biphasic anaphylaxis) for H1 antihistamines is 20. However, neither of these values is certain, and confidence in the benefit of treatment is low, with an association of increased biphasic anaphylaxis rates within the confidence estimate.

At biphasic anaphylaxis PEERs of 5% and 20%, H2 antihistamine use is not associated with a decreased risk of biphasic anaphylaxis. However, the degree of certainty that H2 antihistamine therapy did not provide any possibility of benefit is uncertain.

At a biphasic anaphylaxis PEER of 5%, the NNT for glucocorticoids is 161 to prevent 1 case of biphasic anaphylaxis (and 47 at a biphasic anaphylaxis PEER of 20%). Again, neither of these values is certain, and confidence in the benefit of treatment is low, with an association of increased biphasic anaphylaxis rates within the confidence estimate.

Certainty of evidence is very low, and additional well-designed controlled trials are needed to further inform this practice (Tables VIII and IX). However, the JTFPP strongly recommends that secondary therapies never interfere with early epinephrine treatment, as this is the primary medication for the treatment of anaphylaxis.[45] The use of antihistamines may be associated with side effects that could confound assessment of anaphylaxis, such as altered level of consciousness with first-generation antihistamines. Harms from high-dose glucocorticoids may also outweigh benefits; however, due to the very low certainty of evidence (risk of bias, inconsistency, and imprecision), there remains uncertainty in the assessment of benefit versus no benefit from supplemental therapies.

Question 3. Should antihistamine and/or glucocorticoid premedication be used to prevent index hypersensitivity/infusion reactions to chemotherapy?

Recommendation. We suggest in favor of administering glucocorticoids and/or antihistamines to prevent anaphylaxis or infusion-related reaction when indicated for specific agents in chemotherapy protocols. Strength of recommendation: conditional. Certainty of evidence: very low.

Technical comment. The JTFPP analysis did identify a significant change in rates of anaphylaxis and/or infusion reactions for some chemotherapy protocols. The use of premedication was associated with a decreased rate of HSRs for chemotherapy (OR, 0.49; 95% CI, 0.37-0.66). In contrast to chemotherapy premedication, benefit was not observed when using premedication to prevent anaphylaxis in the setting of infliximab therapy without prior reaction to the administered agent (risk ratio, 1.58; 95% CI, 0.87-2.87). We did not evaluate premedication in the context of desensitization to chemotherapy agents and to monoclonal antibodies. Furthermore, the use of premedication in patients who had previously experienced anaphylaxis from these agents was not evaluated.

At an anaphylaxis PEER of 12.9%, chemotherapy premedication is associated with a decreased risk of anaphylaxis. The NNT is 16 (range, 13-25).

At an anaphylaxis PEER of 2%, infliximab premedication is not associated with a decreased risk of anaphylaxis. However, the degree of certainty that therapy did not provide any possibility of benefit was very low. It is not possible to exclude some potential benefit from the use of glucocorticoids and/or antihistamines to prevent anaphylaxis, and additional well-designed controlled trials are needed to further inform this practice. A clinician may reasonably defer premedication use for the intention of preventing anaphylaxis. If standard practice dictates the use of premedication prior to the administration of infliximab, it would be reasonable to discontinue the premedication following tolerance of the first or second course of treatment.

Question 4. Should antihistamine and/or glucocorticoid premedication be used to prevent recurrent HSRs to RCM?

Recommendation. We suggest against routinely administering glucocorticoids and/or antihistamines to prevent anaphylaxis in patients with prior radiocontrast HSRs when readministration of a low- or iso-osmolar, nonionic RCM agent is required. Strength of recommendation: conditional. Certainty of evidence: very low.

Technical comment. The JTFPP analysis did not identify significant benefit from the use of premedication prior to the RCM to prevent anaphylaxis (risk ratio, 1.07; 95% CI, 0.67-1.71). The absence of benefit of premedication in patients with prior immediate HSRs to RCM who are receiving a different low- or iso-osmolar agent is consistent with prior literature; however, it is important to distinguish the immediate index reaction associated with RCM from a severe, delayed, cutaneous T-cell-mediated reaction, where premedication may add value to management.[17]

TABLE IX. Topic area 2 summary of judgments

	Judgment						
Problem is a priority	No	Probably no	Probably yes	**Yes**	Varies	Do not know	
Desirable effects	Trivial	**Small**	Moderate	Large	Varies	Do not know	
Undesirable effects	Large	**Moderate**	Small	Trivial	Varies	Do not know	
Certainty of evidence	**Very low**	Low	Moderate	High	No included studies		
Values	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects, benefits, harms, and burdens	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Do not know
Resources required	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Do not know
Certainty of evidence of required resources	Very low	Low	Moderate	High	**No included studies**		
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Do not know
Acceptability	No	Probably no	Probably yes	Yes	**Varies**	Do not know	
Feasibility	No	Probably no	Probably yes	Yes	**Varies**	Do not know	

Boldface indicates guideline group judgment in each domain.

Risk of bias, inconsistency, imprecision, and indirectness attenuate the confidence in this guidance.

At a PEER of 8.7%, RCM premedication is not associated with a decreased risk of anaphylaxis. However, the degree of certainty that therapy did not provide any possibility of benefit is low.

Given the diversity of clinical circumstances evaluated and low confidence in the literature base, higher certainty evidence is needed to better inform practice, and future recommendations could potentially change as a result of new information (Tables VIII and IX).[254-258] As such, clinicians may reasonably consider premedication in clinical circumstances associated with a high level of perceived risk of anaphylaxis or comorbidities associated with greater anaphylaxis fatality risk (such as underlying cardiovascular disease or use of beta-blockers, prior severe anaphylaxis), although evidence is lacking to clearly support this practice. Additional well-designed controlled trials are be needed to further clarify the need for premedication prior to alternative low- or iso-osmolar RCM use in patients with prior anaphylaxis to prevent recurrence. This analysis evaluated patients with both mild and severe RCM reactions, but we were unable to stratify prophylaxis by severity of index reaction. Our analysis evaluated only low- and iso-osmolar nonionic radiocontrast agents and as such does not apply to patients receiving high-osmolar contrast agents for whom prophylaxis may be appropriate.[259]

Question 5. Should antihistamine and/or glucocorticoid premedication be used to prevent HSRs to allergen immunotherapy or other agents?

Recommendation. We suggest the administration of glucocorticoids and/or antihistamines as an intervention to prevent anaphylaxis in patients undergoing aeroallergen RIT. Strength of recommendation: conditional. Certainty of evidence: very low.

Technical comment. Evidence suggests that in the setting of aeroallergen RIT, premedication may provide value in reducing systemic reactions and anaphylaxis (immunotherapy analysis including RIT: risk ratio, 0.62; 95% CI, 0.41-0.94). In the study by Portnoy et al,[235] patients received H1 and H2 antagonists and oral glucocorticoids for 3 days, beginning 1 day before the 2-day RIT protocol. The evidence base for premedication before conventional aeroallergen immunotherapy is limited; however, a study by Ohashi et al[46] suggested some benefit with fexofenadine pretreatment 2 hours before conventional immunotherapy using cedar pollen or dust mite allergens. The evaluation of the NNT of patients to prevent 1 episode of anaphylaxis is useful.

The NNT to prevent 1 case of anaphylaxis with RIT premedication at a 4.5% rate of anaphylaxis is 58, based on the immunotherapy analysis including RIT studies. At a 9% rate of anaphylaxis, the NNT of premedication for RIT is 29. Assuming a patient expected anaphylaxis event rate of 14%, the premedication NNT is 19.

The JTFPP is unable to exclude the possibility that specific situations and subpopulations may exist where premedication could provide benefit to immunotherapy in those with concomitant risk factors (eg, in situations associated with higher rates of systemic reactions). Given the diversity of clinical circumstances evaluated and low confidence in the literature base, higher certainty evidence is needed to better inform practice, and future recommendations could potentially change as a result of new information. As such, clinicians may reasonably consider immunotherapy premedication in other clinical circumstances associated with a high level of perceived risk of anaphylaxis or comorbidities associated with greater anaphylaxis fatality risk

(such as underlying cardiovascular disease or use of beta-blockers), although high-certainty evidence is lacking to support this practice.

Additional good practice statements

GRADE provides a framework to evaluate evidence certainty and translate evidence to recommendations; however, some aspects of clinical practice are difficult to rigorously evaluate due to ethical and practical limitations. Despite these limitations, the JTFPP beleives the following good practice statements are important and associated with optimal patient outcomes:

Good practice statement 1. Administer epinephrine as the first-line pharmacotherapy for uniphasic and/or biphasic anaphylaxis.

Good practice statement 2. Do not delay the administration of epinephrine for anaphylaxis, as doing so may be associated with higher morbidity and mortality.

Good practice statement 3. After diagnosis and treatment of anaphylaxis, all patients should be kept under observation in a setting capable of managing anaphylaxis until symptoms have fully resolved.

Good practice statement 4. All patients with anaphylaxis should receive education on anaphylaxis, including avoidance of identified triggers, presenting signs and symptoms, biphasic anaphylaxis, treatment with epinephrine, and the use of epinephrine auto-injectors, and they should be referred to an allergist. Of note, there may be some circumstances where self-injectable epinephrine is deferred (ie, resolved anaphylaxis and drug trigger with high likelihood of successful avoidance) and shared decision making may play a role in some circumstances.

LIMITATIONS

Unfortunately, the certainty of evidence around supplemental therapies in anaphylaxis management is very low. While early epinephrine is recommended by the JTFPP when anaphylaxis is recognized in any setting, whether clinicians should (or should not) also administer antihistamines and/or glucocorticoids is a question that has not been subjected to rigorous methodologic evaluation.

All patients with anaphylaxis should be educated regarding the risk for biphasic reactions, and self-injectable epinephrine should be available at discharge for prompt treatment if this occurs. Patients who experience greater severity of anaphylaxis are at greater risk for biphasic reaction, but the absolute risk of biphasic reactions in this population is less clear. While >1 dose of epinephrine was identified as a risk factor for biphasic anaphylaxis, we did not specifically evaluate this risk factor in the context of repeated subtherapeutic epinephrine dosing. The JTFPP recommends epinephrine be given promptly in appropriate doses when anaphylaxis is recognized. It is important to distinguish biphasic anaphylaxis (with an interval period of clear resolution) from protracted anaphylaxis. In circumstances where prescribed self-injectable epinephrine is not immediately available on discharge (eg, limited pharmacy hours or affordability), clinical judgment regarding risk of biphasic or recurrent anaphylaxis, access to subsequent emergency care, and shared decision making will be required to determine discharge decisions.

Our analysis is similar to results obtained by Ellis and Day[39] in which glucocorticoids demonstrated a nonsignificant inverse trend with biphasic anaphylaxis; however, caution is warranted in interpretation of these findings—particularly given the opposite association of glucocorticoids with biphasic anaphylaxis in children (which may be confounded by severity of index anaphylaxis and practice variation). Ultimately a randomized controlled trial of supplemental glucocorticoids and antihistamines in patients adequately treated with epinephrine with resolved anaphylaxis is needed to determine whether these agents prevent biphasic anaphylaxis.

We did not find clear evidence to support the role of glucocorticoids and/or antihistamines to prevent biphasic anaphylaxis. Clear evidence is also lacking to support a role for glucocorticoids and/or antihistamines in acute anaphylaxis, although the Cross-Canada Anaphylaxis registry recently suggested supplemental antihistamines may provide benefit when used with epinephrine.[164] In the same study,[164] supplemental use of glucocorticoids with epinephrine resulted in worse outcome.

The absence of benefit of premedication in patients with prior immediate HSRs to RCM who are receiving a different low- or iso-osmolar agent is consistent with prior literature;[17,259,260] however, it is important to distinguish the immediate index reaction associated with RCM from a severe, delayed, cutaneous T-cell-mediated reaction, where premedication may add value to management. Patients receiving RCM may experience acute or delayed reactions.[17] Four categories of reactions to RCM have been described: benign acute onset, anaphylaxis, benign delayed onset, and severe delayed onset.[17] In a 2017 review[261] of 120,822 patients receiving low- or iso-osmolar agents (iopromide, iodixanol, iopamidol, ioversol, iobitridol, or iohexol), HSRs were reported in 0.4% with only 1.4% of these reactions described as severe. The JTFPP agrees with the suggestion that most individuals with acute RCM hypersensitivity can be effectively managed by selecting an alternative low- or iso-osmolar RCM without premedication;[17] however, some controversy exists around the management of patients with prior RCM reactions.[17,259,260,262] The American College of Radiology's *ACR Manual on Contrast Media Version 10.3*[262] emphasizes that no premedication strategy is a substitute for anaphylaxis preparedness, breakthrough reactions occur, and changing to an alternative low- or iso-osmolar contrast agent may provide a greater effect size than premedication alone. While premedication before high-osmolar agents has been shown to reduce immediate reactions of all severity in average-risk patients and mild immediate adverse effects in average-risk patients receiving low-osmolar agents, protection from premedication against moderate to severe reactions in high-risk patients receiving low-osmolar agents is unproven by high-certainty evidence, with estimates suggesting the NNT to prevent a fatal reaction in a high risk patient to be 50,000 (at a cost of $131,211,400 per death prevented).[259,262,263] The *ACR Manual*[262] suggests the utility of premedication in high-risk patients receiving low-osmolar contrast is uncertain and may be accompanied by direct and indirect harms, but that it may be considered in outpatients with prior allergic-like or unknown-type contrast reactions and in similar inpatients where the use of premedication does not adversely delay care or treatment decisions. The *ACR Manual*[262] also suggests that regardless of patient status, a history of a severe contrast reaction be considered a relative contraindication to the future use of the same class of media

and premedication be considered (if feasible) if there are no alternatives. High-quality studies are needed to better inform the practice of RCM premedication in high-risk patients, and future studies should distinguish among immediate and delayed, cutaneous and noncutaneous, mild and severe reactions and should stratify premedication by anaphylactic, hemodynamic, and chemotactic reaction types.

The role of glucocorticoid and/or antihistamine premedication in more high-risk settings (such as RIT) may be significant, and until additional evidence better informs practice, premedication may be appropriate in circumstances where a high risk of anaphylaxis exists. The lack of benefit from infliximab premedication in patients without prior infusion reactions is consistent with a recent meta-analysis.[264]

Large heterogeneity in analyses and limitations in study design attenuate the confidence in this evidence synthesis. We did not evaluate premedication in the context of desensitization to chemotherapy and monoclonal antibodies.[265] The JTFPP continues to recommend prompt treatment of anaphylaxis with epinephrine and highlight that the addition of glucocorticoids and antihistamines should never delay or substitute for this primary management.

FUTURE DIRECTIONS

At present, high-certainty evidence is lacking to determine whether antihistamines and/or glucocorticoids provide benefit as supplemental therapies in anaphylaxis management in patients promptly and appropriately treated with epinephrine. In addition, it seems unlikely that antihistamine and/or glucocorticoid premedication is likely to offer clear benefit in the prevention of RCM anaphylaxis in patients with a history of immediate RCM hypersensitivity receiving an alternative low- or iso-osmolar RCM agent or in patients receiving infliximab who have not previously experienced an infliximab HSR. However, because the evidence synthesis contained in this practice parameter is derived from low-certainty, nonrandomized trials, additional research evaluating common practices in anaphylaxis treatment and prevention is urgently needed. Further studies are needed to evaluate the use of premedication in children receiving chemotherapy and the use of premedication in subjects undergoing chemotherapy desensitization. In some situations involving anaphylaxis prevention and management, shared decision making, taking into account patients' preferences and values, should be utilized, particularly when determining the length of medical observation following resolved anaphylaxis. In anaphylaxis, as in many other medical conditions, shared decision making, which entails patients (and their families) being fully informed of pros and cons of receiving a diagnostic or therapeutic intervention and participating in the medical decision making process, is appropriate in the context of desirable outcomes being closely balanced with undesirable outcomes, which in our guideline is reflected by the navigational signal to the clinician of a conditional (or "weak") recommendation.

CONCLUSIONS

Anaphylaxis is a multisystem allergic emergency. Early recognition and prompt administration of intramuscular epinephrine remain the cornerstone of management. Risk factors for biphasic reactions include severe anaphylaxis and/or the need for >1 dose of epinephrine. Additional biphasic anaphylaxis risk factors include wide pulse pressures, unknown anaphylaxis trigger, cutaneous signs and symptoms, and drug trigger in children. Although treatment of anaphylaxis in the United States also traditionally has included use of antihistamines and glucocorticoids, data demonstrating the benefit of these additional approaches are very low certainty and when evaluated on the whole do not offer clear support for this practice to prevent biphasic anaphylaxis. Supplemental therapies such as glucocorticoids and antihistamines should never delay the rapid administration of epinephrine as soon as anaphylaxis is recognized. Consistent with the lack of clear benefit of antihistamines and/or glucocorticoids in prevention of biphasic anaphylaxis, current evidence is poor that routine use of these therapies prevents anaphylaxis in patients with a history of RCM HSRs (vs using a low- or iso-osmolar contrast without premedication, preferably an alternative agent) or in patients receiving infliximab without prior anaphylaxis; however, some circumstances do exist where premedication with antihistamines and/or glucocorticoids is warranted (eg, RIT and some forms of chemotherapy). As such, while prompt recognition and administration of epinephrine remains paramount in anaphylaxis management, clinical judgment is an irreplaceable key factor to optimize high-quality care.

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