Anaphylaxis – a 2019 practice parameter update and GRADE analysis

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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 Institutes of Allergy and Infectious Disease (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 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, African-American race, older age, male sex, and additional coexisting comorbid conditions. (5-9) While many cases of anaphylaxis are idiopathic, medications are the leading triggers in adults, with foods and stinging insects the most frequently implicated in children and adolescents. (1, 10, 11) Food allergy impacts 8% to 11% of children and adults in the United States (12-14), while adverse drug reactions (ADRs) affect up to 10% of the population (and 20% of hospitalized patients) with hypersensitivity reactions accounting for 10% of all ADRs. (15) While medical complexity increases for patients with prior hypersensitivity reactions to radiocontrast media (RCM), fortunately the prevalence of RCM ADRs had decreased in recent decades. (16) 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.(15)

It is well established that IgE binding and cross-linking of the high-affinity receptor FcEpsilonRI on the surface of mast cells and basophils is an important mechanism in many cases of anaphylaxis. (17) However, because some patients with anaphylaxis have low or undetectable circulating allergen-specific IgE, some models have suggested a potential role for IgG-dependent anaphylaxis. (18) Additional cell types involved in anaphylaxis may include neutrophils, monocytes, macrophages, and platelets, signaling through mediators which include complement components, CysLTs, platelet activating factor, IL-6, IL-10 and TNF-receptor 1. (19) (20)

Epinephrine is the cornerstone of anaphylaxis management but continues to be underutilized. (21-23) As a nonselective adrenergic agonist, intramuscular epinephrine works rapidly to increase peripheral vascular resistance through vasoconstriction, increase cardiac output, reverse bronchoconstriction and mucosal edema, and stabilize mast cells and basophils. (24, 25) Despite underuse of rapidly acting epinephrine as first-line treatment, fatal anaphylaxis is fortunately a rare outcome, with prevalence rates between 0.47 to 0.69 million persons (0.25%-0.33% of anaphylaxis hospitalizations or emergency department visits). (9, 26-29) Antihistamine agents are considered second line treatment for anaphylaxis, given their slow onset of action, inability to stabilize or prevent mast cell degranulation, or target additional mediators of anaphylaxis. (30) Unlike epinephrine, antihistamines will not effectively treat cardiovascular and respiratory symptoms such as hypotension or bronchospasm when used acutely as monotherapy. Although glucocorticoids are frequently used as an adjunctive therapy for anaphylaxis they should also not be administered in place of epinephrine in the treatment of acute anaphylaxis. (31, 32)

Estimates of biphasic anaphylaxis vary from less than 1% to 20% of patients; however, the ability of antihistamines and glucocorticoids to affect this outcome is unclear. (33-40) 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 JTFPP undertook a systematic review and GRADE analysis of antihistamines and glucocorticoids in anaphylaxis. Questions evaluated were (1) "What are the risk factors are associated with biphasic reactions?", and (2) "Should antihistamines or glucocorticoids be used to prevent anaphylactic reactions?"

Question 1 Key Findings and Recommendations: Based on ***very low-quality*** evidence, **we suggest extended observation in the ED for patients with resolved severe anaphylaxis to detect a biphasic reaction**. The JTFPP findings suggest biphasic anaphylaxis is associated with a more severe initial presentation of anaphylaxis (OR=2.11, 95% CI 1.23-3.61) or repeated epinephrine doses required with the initial presentation (OR 4.82, 95% CI 2.70-8.58). The estimated number needed to monitor with extended observation to be able to detect one episode of biphasic anaphylaxis before discharge 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. Prompt and adequate treatment of anaphylaxis appears central to reducing biphasic anaphylaxis risk. The implications for the clinician, based upon this systematic review and meta-analysis is that the patient presenting with severe anaphylaxis and/or requiring more aggressive treatment (e.g., more than one 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. 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.

Question 2 Key Findings and Recommendations: Based on ***very low-quality*** evidence, **we suggest against glucocorticoids or antihistamines as an intervention to prevent biphasic anaphylaxis.** As a secondary therapy, antihistamines and corticosteroids may be considerations in anaphylaxis treatment.(41) In particular, antihistamines may treat urticaria and itching to improve comfort during anaphylaxis, but if used prior to epinephrine administration could lead to a delay in first line treatment of anaphylaxis. Furthermore, glucocorticoids can also effectively prevent delayed urticaria which could confound the assessment and treatment of anaphylaxis. The JTFPP analysis did not identify significant benefit in prevention of biphasic anaphylaxis from either H1 antihistamines (OR 0.71, 95% CI 0.47-1.06), H2 antihistamines (OR 1.21, 95% CI 0.8-1.83), or glucocorticoids (OR 0.87, 95% CI 0.74-1.02). 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 one episode of biphasic anaphylaxis, with significant uncertainty in the estimate.

Based on ***very low-quality*** evidence, **we suggest administering glucocorticoids and/or antihistamines to prevent anaphylaxis or infusion related reactions when indicated for specific agents in chemotherapy protocols.** 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 hypersensitivity reactions for chemotherapy (OR 0.46, 95% CI 0.35-0.6). In contrast to chemotherapy premedication, benefit was not observed when using premedication to prevent anaphylaxis in the setting of monoclonal antibody therapy without prior reaction to the administered agent (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.

Based on ***very low-quality*** evidence, **we suggest against routinely administering glucocorticoids and/or antihistamines to prevent anaphylaxis due to iso-osmolar, non-ionic radiocontrast media agent.** The JTFPP analysis did not identify significant benefit from the use of premedication prior to the RCM to prevent anaphylaxis (RR 1.07 95% CI 0.67-1.71). The absence of benefit of premedication in patients with prior immediate hypersensitivity reactions 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.(42) Given the diversity of clinical circumstances evaluated and low confidence in the literature base, higher quality 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 support this practice.

Based on ***very low-quality*** evidence, **we suggest in favor of the administration of glucocorticoids and/or antihistamines as an intervention to prevent anaphylaxis in patients undergoing aeroallergen rush immunotherapy (RIT).** 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, one study suggested some benefit with fexofenadine pretreatment 2 hours before conventional

immunotherapy using cedar pollen or dust mite allergens.(43) 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 (e.g., 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 evidence is lacking to support this practice.

Additional Good Practice Statements

Good Practice Statement # 1: Administer epinephrine as the only 1st 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 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, the use of epinephrine auto-injectors, and referral to an allergist. Of note, there may be some circumstances where self-injectable epinephrine is deferred (i.e., resolved anaphylaxis and drug trigger with high likelihood of successful avoidance) and patient-preference sensitive decision making may play a role in some circumstances.

INTRODUCTION AND DIAGNOSIS

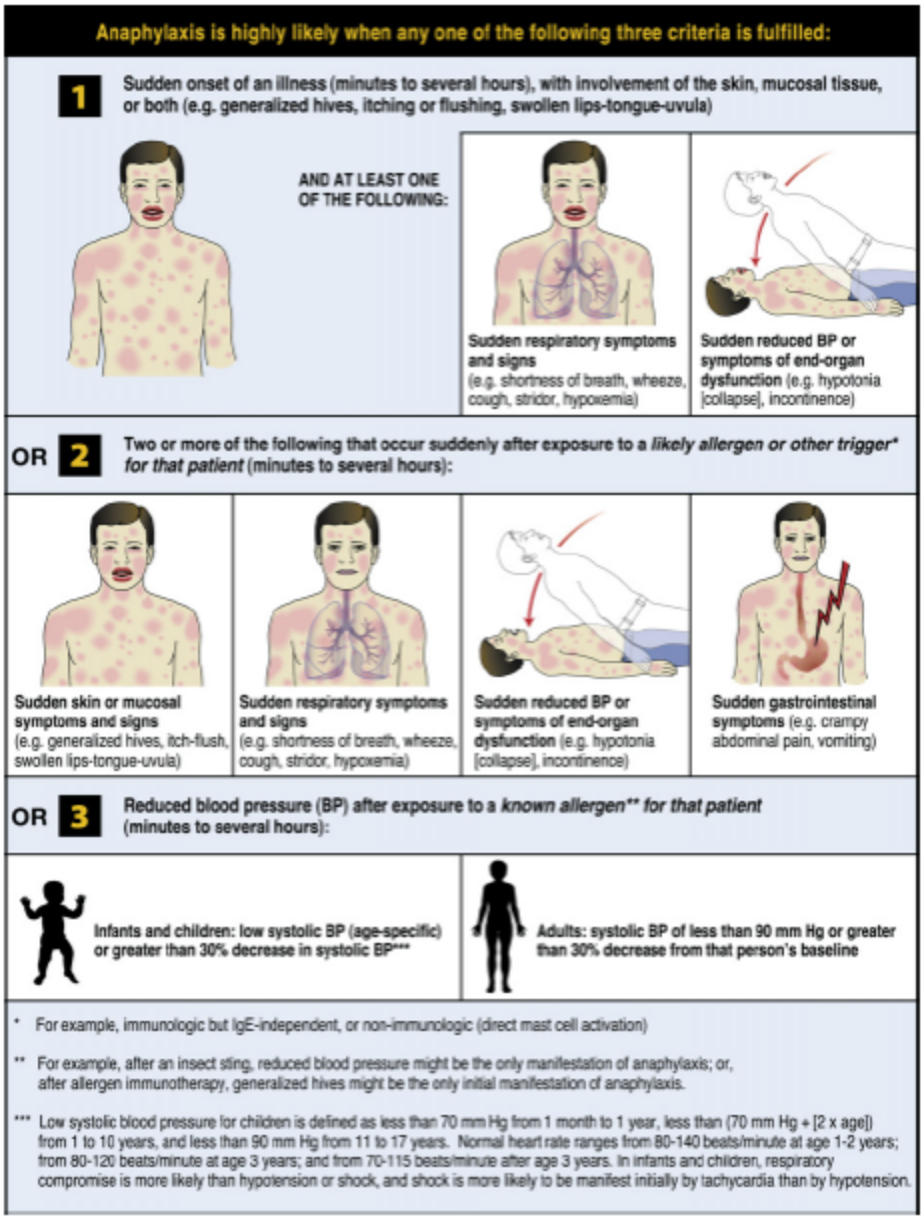
Anaphylaxis is an acute, life-threatening systemic allergic reaction associated with different mechanisms, triggers, clinical presentations, and severity.(1) The wide range of clinical manifestations and complex underlying mechanisms of anaphylaxis contribute to the difficulty in establishing a definition and diagnostic criteria for anaphylaxis. The poor sensitivity of confirmatory laboratory testing further complicates accurate diagnosis of anaphylaxis. Furthermore, the lack of established diagnostic criteria plays a major role in the under-diagnosis and inconsistent management of anaphylaxis. (44-46) In 2005, a multinational and multidisciplinary workgroup which included allergist-immunologists, emergency physicians, pediatricians, critical care specialists, internists and key stakeholders was assembled by the National Institutes of Allergy and Infectious Disease (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) to address the need for universally accepted anaphylaxis diagnostic criteria. The diagnostic criteria proposed by this workgroup were published in 2006 (47) and describe anaphylaxis as likely when one of three criteria are fulfilled: (1) acute onset of an illness (minutes to hours) with involvement of the skin, mucosal tissue, or both with either respiratory compromise or reduced blood pressure / associated symptom of end-organ dysfunction; or (2) two or more of the following that occur rapidly after exposure to a likely allergen for the patient including (a) involvement of skin-mucosal tissue, (b) respiratory compromise, (c) reduced blood pressure or associated symptoms, or (d) persistent 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 both the American Academy of Allergy, Asthma, and Immunology (AAAAI), American College of Allergy, Asthma, and Immunology (ACAAI)(48), and the World Allergy Organization (49).

The NIAID/FAAN criteria were developed to "provide the emergency responder or treating physician with a relatively simple and rapid means to make the diagnosis of anaphylaxis." The criteria (shown in Figure 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 among patients with mild presentations (for example, 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 emergency department setting, and 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 those who developed the criteria did, 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 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 may rely heavily on clinical judgment, and role of pre-emptive epinephrine prior to the development of anaphylaxis has been questioned.(50, 51) Isolated allergen associated urticaria, which may respond to antihistamines, should be distinguished from anaphylaxis for which prompt epinephrine administration is indicted. In addition, a patient presenting to the emergency department who reports symptoms meeting NIAID/FAAN diagnostic criteria that spontaneously resolved prior to arrival in the emergency department, should be diagnosed with anaphylaxis despite the fact that epinephrine administration is no longer immediately necessary in a now stable patient.

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 to 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. (52-54) Some (although not all) 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%. (33-35) 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 4-5% (range 0.18% - 14.7%) (37, 38, 40, 55, 56) No studies have systematically evaluated therapies for the late phase reaction; however, therapy for the late phase is similar to the initial phase. (57)

Figure 1 (permissions needed):



EPIDEMIOLOGY AND RISK FACTORS

Estimates of anaphylaxis vary widely, and many studies suggest that the prevalence is increasing, particularly in developed countries. The life-time prevalence of anaphylaxis has been estimated at 1.6-5.1% (1, 4, 58), with an incidence rate of 42 per 100,000 person-years. (59) Data from a European anaphylaxis registry revealed that over one quarter of cases occur in patients under 18 years of age. (60) As indicated in an international consensus on anaphylaxis (ICON) document, cardiovascular disease and asthma are well-recognized risk factors for severe

anaphylaxis (5). Additional risk factors potentially associated with fatal anaphylaxis include African-American race, older age, male sex, and additional preexisting comorbid conditions. (6-9). Atopic diseases are risk factors for anaphylaxis triggered by food, exercise and latex. (61) While one survey of Turkish beekeepers suggested some risk of atopic disease as a risk for systemic reactions in bee keepers (62), it has not been established that atopic disease increases the risk for Hymenoptera sting associated anaphylaxis.

Medications are the leading cause of adult anaphylaxis (1) while foods and stinging insect venom are the most common triggers of anaphylaxis in children and adolescents. (10, 58) In the middle-aged adult population, anaphylaxis most often ocurs at home. (1) Medications most frequently implicated in the United States are antibiotics, NSAIDs, immunomodulators, and biological agents (63). In contrast, in Portugal a review of 313 patients with a history of drug-induced anaphylaxis revealed the most common trigger to be NSAIDS, followed by antibiotics and anesthetics (64); while in an anaphylaxis registry of German-speaking countries (Germany, Austria and Switzerland) the most common trigger (when all age groups are considered) was reported to be insect venom, followed by food and drugs, respectively (65). In studies of food-induced anaphylaxis, rates ranging from as low as 1 per 100,000 to as high as 70 per 100,000 have been reported by using data from hospitalizations, emergency department visits, and medical records reviews. (66-68) When examining anaphylaxis specifically, the proportion due to foods varied between 13-65%. (66-71). The specific trigger may not be identified during the acute anaphylactic event, especially if the reaction is occurring for the first time, and may only be identified retrospectively at a follow-up evaluation. For example, one study of ED records in Florida found that only 37% of patients could pinpoint a specific trigger upon initial presentation (72). Futhermore, initial suspected culprits are often not confirmed on subequent allergy testing which suggests caution in presumption of potential triggers and supports the necessity of follow-up evaluation by an allergy specialist.(44, 73, 74)

With respect to treatment, delayed use of intramuscular epinephrine has been associated with increased risk for fatality, and several observational studies and case-report series suggest a continued disparity between the diagnosis of anaphylaxis and frequency of appropriate epinephrine treatment. (75, 76) In one study of drug-induced anaphylaxis evaluated and managed

in an emergency department, only 8% of patients received epinephrine. (76) 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 to 0.69 million persons (8, 9, 26-28). The 3 leading causes of fatal anaphylaxis are drugs (29%-58.5%) (8, 26, 77, 78), insect stings (3.3%-54%)(8, 26, 77, 78), and food (2%-6.7%) (8, 26, 78). While anaphylaxis-related hospitalizations have increased, general case fatality rates have been stable in the range of 0.25%-0.33% of hospitalizations or ED presentations for anaphylaxis (29). 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, (79) whereas antibiotics predominate in Australia (26) and France (80). A review by Pichichero et al. described the population incident risk of anaphylaxis to penicillin between 0.004% to 0.015% with a fatality rate of 0.0002% to 0.0015% (81). 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 (79, 82) Additional observational case-series have shown patients dying from food anaphylaxis often have previous food-induced allergic reactions. (26, 34, 83) Notably, respiratory arrest may occur more commonly with foods (86% of fatalities in the UK registry) with shock more common in fatalities due to iatrogenic and venom reactions. (79) It is important to note that most fatal reactions are unpredictable and statistically, occur very rarely; however, appropriate management of the underlying provoking allergy after recovery from a severe reaction may decrease the risk for a subsequent severe reaction, including fatality. (82) Referral to an allergy specialist after recovery from anaphylaxis is recommended in order to correctly identify the diagnosis, the potential cause of the reaction, and to educate the patient on the risk of future reaction and measures to reduce the risk, including a prescription for and education regarding the use of epinephrine.

BURDEN OF DISEASE

Food-induced Anaphylaxis

Prevalence

Food allergy (or presumed food allergy) is a leading cause of anaphylaxis presenting to US emergency departments, with an estimated 30,000 cases per year. (84) Food allergy (assessed through a nationally-representative internet self-report study) is estimated to affect up to 8% of children and up to 11% of adults in the United States. (12-14) Food allergens may be attributed to upwards of 50% of emergency department reported anaphylaxis cases in developed countries, including the United States. (85)

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 (86). Whereas Clark et al (87) reported stable trends in the frequency of US emergency department visits for food allergy in the period of 2001-2009 , they did find a statistically significant decline among individuals ≥ 18 years of age. In a retrospective cohort study of 37 pediatric hospitals from 2007-2012 (88), an increasing rate of food induced anaphylaxis (FIA)-related ED visits was reported but without any increase in the proportion of ED patients hospitalized or admitted to the ICU. This decrease in the proportional rate of ED visits to utilization of inpatient and ICU 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 (89). More recently, Motosue et al (90) 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. (91) 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 evaluations including diagnostic studies and regular follow-up outpatient visits. (92)

Patel et al in 2011 (92) 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 between 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 visits, 67.3% of the office visit costs, and 97.7% of the total outpatient department visit costs. US National estimates for epinephrine autoinjector 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 autoinjector and have it available when needed. (83, 93). 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 (92) with morbidity-related costs accounting for 85% of indirect costs, resulting from disease related sick days (lost productivity and wages). (92) Simulations from probabilistic sensitivity analyses have generated mean annual direct costs of $307 million and indirect costs of $203 million in the US. (92) While evidence suggests that activation of emergency medical services (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 if recurrence of symptoms occurs. (94)

Drug-induced Anaphylaxis

Adverse drug reactions (ADR) may affect up to 1⁄10th of the world's population and up to 20% of all hospitalized patients. More than 10% of all ADR are drug hypersensitivity reactions (DHR). 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. (95) The most common DHR involves antibiotics such as penicillins and cephalosporins, sulfonamides, aspirin, and other non-steroidal anti-inflammatory drugs. DHR can be severe and life threatening and are associated with significant mortality rates. Drugs may be responsible for upwards of 20% of fatalities due to anaphylaxis. The incidence of anaphylaxis due to medication triggers is increasing over time. (59) DHR have a significant socioeconomic impact related to both direct costs (management of reactions and hospitalizations) and indirect costs (missed work⁄school days; alternative drugs); however, this is overall a major gap in the literature for summarizing the economic burden of DHR. (15) A US nationwide cross-sectional telephone self-reported survey reported a prevalence of anaphylaxis in the general population of 1.6% with medications being the most common trigger (35%). (1) 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, 15)

ADR from RCM occur less frequently than prior to 1990 when patients received high-osmolar, ionic RCM. Prior ADR to RCM can contribute to burden of disease by creating medical complexity associated with premedication; however, while glucocorticoid premedication has become embedded in practice for patients with prior RCM hypersensitivity, evidence supporting the use of prophylaxis in patient receiving low or iso-osmolar, non-ionic contrast agents is lacking. ADR associated with RCM do not relate to iodine, and the term iodine allergy should not be used in the context of RCM reactions. Patients receiving RCM may experience acute or delayed reactions, with delayed reactions reported as frequently as acute reactions. (16) Four categories of reactions to RCM have been described: benign acute-onset, anaphylaxis, benign-delayed onset, and severe delayed-onset. (16) In one 2016 review of 120,822 patients receiving iopromide, iodixanol, iopamidol, ioversol, iobitridol, or iohexionol, hypersensitivity reactions were reported in 0.4% with only 1.4% of these reactions described as severe. (96) It has been suggested that most individuals with acute RCM hypersensitivity can be effectively managed by selecting an alternative RCM without premedication, but that patients should be informed that delayed reactions (mostly benign rashes within one week of exposure) are as common as acute reactions. (16).

Insect-venom Anaphylaxis

Hymenoptera venom allergy (HVA) describes both anaphylactic and non-anaphylactic hypersensitivity reactions to stings. Reaction types include sting-induced large local (LL) or systemic allergic reactions. A LL reaction lasts 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 2-3% of adults and up to 1% of children have had a systemic reaction to a sting, and LL reactions occur in more than 5% of adults. (97) In a review of 10 studies published between 2001-2009, Bilo et al found that 23% of 2577 cases of anaphylaxis were caused by an

insect sting.(98) Fatal anaphylaxis can result from HVA; the reported average of 40 deaths per year in the US is highly suspected to underestimate the true event rate.(51, 99) Even the first reaction can be fatal, but no screening test is available because of the very high frequency of asymptomatic sensitization (more than 20% of adults will have detectable venom-specific IgE).(100, 101) Patients often express fears of anaphylaxis because of their family history or atopic history, but HVA has not been shown (to date) to be familial and is not associated with atopy.(100)

Patients often present with concern about potential anaphylaxis after having large local or generalized cutaneous systemic reaction.(102) The morbidity of living with HVA may be underestimated.(102) 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.(103) Even people with non-anaphylactic (LL or cutaneous systemic) reactions to stings share the same concerns and can be impacted as severely as the patients with anaphylactic reactions. (102) 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.(51) Whether it is mild or severe, HVA impairs long-term quality-of-life QOL and may be a cause of substantial socioeconomic impairment.(104) HVA can impact career choices, especially in bee-keepers, groundskeepers, gardeners, and greenhouse workers.(105) HVA has important adverse consequences in terms of employment, earning capacity and leisure and sporting activities. (15) (16). For these reasons, discussion of HVA usually includes not only anaphylactic, but also mild systemic and non-anaphylactic reactions.(97)

PATHOGENESIS OF ANAPHYLAXIS

Data regarding pathophysiologic mechanisms and effector cells are limited on humans but mouse models have offered some insight.(106) It is well established that IgE binding and cross-linking of the high-affinity receptor FcEpsilonRI 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.(17) 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.(18) Furthermore, the complement system, anaphylatoxins C3a, C4a, C5a, and neutrophils (107) 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.(108) Cytokine-storm like reactions have recently been described for patients with chemotherapy induced anaphylaxis.(108)

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.(106, 109) 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.(110, 111) While histamine appears to play a significant role, other mediators have also been implicated. Therefore, pharmacologic targeting of histamine alone, e.g., 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.(112) While the positive predictive value of an elevated serum trypase is high (93%), the negative predictive value of a serum tryptase is low (17%).(2) However, several studies have reported an association between elevation of tryptase and severity of anaphylaxis from food and other causes.(113-117) In a study of prospectively recruited ED patients with anaphylaxis, mediators in addition to tryptase were found to be correlated with hypotension, a symptom of severe anaphylaxis.(19) These included histamine, IL-6, IL-10 and TNF-receptor 1.(19, 118) 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 PAF (platelet-activating factor), CysLTs, and

anaphylatoxins. PAF is a lipid-derived mediator found to be elevated in serum of patients with cold urticaria during cold challenge.(119) 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.(120) These responses are not associated with increased dermal histamine levels, (121) 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.(122) Associations have been noted with increased PAF in cases of anaphylaxis. (113) In one study increased PAF levels demonstrated the highest correlations with severe anaphylaxis (when compared to 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 symptoms only; grade 2: mild to moderate anaphylaxis; grade 3: severe anaphylaxis).(123) Data to support the role of CysLTs stem from studies showing that intradermal injection of LTB_4, LTC_4 and LTD_4 can induce wheal and flare responses (124) and aerosolized LTC_4 and LTD_4 can trigger bronchoconstriction. (125, 126) In a small study of insect sting challenges, elevated serum C3a was associated with severe anaphylaxis.(127) Additional studies suggest that specific allergens such as peanut can contribute to anaphylaxis by activating complement,(128) and tryptase can generate anaphylatoxins under specific conditions.(129) 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.(130) A prospective study of anaphylaxis cases seen in emergency departments in Australia reported delayed deterioration (defined as any worsening of the reaction while under observation in the ED) in 17% of reactions. (20) 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" timeframe for epinephrine delivery to prevent delayed deterioration has not been established.(54, 131) 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, (19, 20) lending support to the hypothesis that severity of the initial reaction may be intrinsically linked to protracted symptoms.

Optimal duration of extended observation following resolution of biphasic anaphylaxis is unknown.(54) One recent meta-analysis of twelve studies including 2,890 adult patients with anaphylaxis suggested the pooled negative predictive value (NPV) of 1-hour observation was 95%, with an NPV for biphasic anaphylaxis after $\geq$ 6 hours of observation (following resolved anaphylaxis) described to be 97.3%.(132) A recent cost-effectiveness analysis suggested costs of observation would exceed $10,000 per medically observed biphasic anaphylaxis unless the recurrence rate exceeded 17% for patients discharged after a 1-hour asymptomatic interval (Shaker et al, submitted for publication). From a healthcare sector perspective, extended observation could be cost-effective at very high rates of fatality risk reduction (76%) from an additional 5-hours of asymptomatic observation (Shaker et al, submitted for publication).

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, while antihistamines and glucocorticoids are considered solely second line therapy. As previously discussed, anaphylaxis is a clinical diagnosis that can present with any combination of symptoms affecting various organ systems (47). The clinical presentation and severity of symptoms differs between 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 into the anterolateral thigh is the first-line treatment for anaphylaxis.(47) Epinephrine is a nonselective agonist of all adrenergic receptors, which are present within every organ system affected by anaphylaxis.(24) By increasing peripheral resistance via alpha-1 receptors and increasing cardiac output via beta-1 receptors, epinephrine causes vasoconstriction, which can treat hypotension, shock, urticaria, angioedema, and upper airway mucosal edema. Epinephrine can reverse bronchoconstriction and treat lower respiratory symptoms through its effect on beta-2 adrenergic receptors. In addition, epinephrine has been shown *in vivo* to activate beta-2 adrenergic receptors on mast cells and basophils and prevent additional release of histamine and other mediators.(25) Thus, epinephrine not only treats all symptoms associated with anaphylaxis but it 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, 133, 134) This is based upon a limited number of pharmacodynamic studies in volunteers (not in anaphylaxis) which 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.(24) A small study conducted in children 4-12 years of age demonstrated a higher mean peak plasma concentration (2136 $\pm$ 351 vs. 1802 $\pm$ 214 pg/ml) and faster onset of action (8 $\pm$ 2 vs. 34 $\pm$ 14 minutes) for intramuscular compared with subcutaneous administration of epinephrine.(135) A similar study in adult males also demonstrated higher mean peak plasma concentration for intramuscular epinephrine in the thigh (9722 $\pm$ 4801 pg/ml) compared with both intramuscular administration in the deltoid (1821 $\pm$ 426 pg/ml) and subcutaneous administration in the deltoid region (2877 $\pm$ 567 pg/ml). 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 also not effective. Importantly, studies comparing intramuscular and subcutaneous injections in the thigh have not been completed. (136) Furthermore, the studies described above were conducted in healthy adults and children who were not experiencing anaphylaxis, were taken from small samples, and thus the generalizability of these findings to the clinical setting has not been

established. (133) There are also no data that have evaluated if 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. Efforts to develop alternative epinephrine delivery routes (such as sublingual and intranasal epinephrine formulations) are underway. (137-140) 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.(141) However, for patients with inadequate response to intramuscular epinephrine and intravenous saline, intravenous epinephrine can be given by continuous infusion by micro-drip, 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 using 1 mg (1 mL of 1:1,000) of epinephrine to 1,000 mL of 0.9 NL saline; starting the infusion at 2 mcg/min (2 mL/min, equivalent of 120 mL/h) and increase up to 10 mcg/min (10 mL/min, equivalent of 600 mL/h); titrating the dose continuously according to blood pressure, cardiac rate, and oxygenation. 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.(57)

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.(106) 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-practices strategy.(47) The mortality from anaphylaxis, though real, is remarkably low at less than 0.5% per episode of anaphylaxis.(142) 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 non-fatality situations where provoking conditions and treatment factors were identical to determine a relative risk).(29, 142)

Role of Antihistamines and Glucocorticoids

Antihistamines are often included as adjunctive therapy for cutaneous 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.(110) There are four histamine receptors located through 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, less sedation, yet similar onset of action.(30) Antihistamines act as an inverse agonists at histamine receptors and are effective therapy for patients with urticaria and can treat many of the cutaneous symptoms associated with anaphylaxis including pruritus, flushing, and urticaria.(143) However, data suggesting additive benefit of antihistamines to epinephrine administration during anaphylaxis is lacking. 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 (144) but peak plasma concentrations are not reached until 60-120 minutes, and an additional 60-90 minutes may be necessary for diffusion of the medication into extravascular tissues to exert maximal effect.(30, 145, 146) 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 emergency medical services, it should never be utilized in

place of timely intramuscular epinephrine administration, but it may have an adjunct role in treating urticaria after epinephrine has been administered.

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 non-selective, 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 established their benefit when combined with epinephrine and/or antihistamines.(32) Studies investigating the use of glucocorticoids for treatment of anaphylaxis have shown that their use is associated with reduced length of hospital stay but has not shown any benefit of preventing return visits to the emergency department following discharge.(147, 148)

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* vivo data have demonstrated inhibitory effects within 5 to 30 minutes through up-regulation of anti-inflammatory mediators and by decreasing mast cell mediator release on a cellular level (31, 149), 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 or not 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 & 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 workgroup used the Population, Intervention, Comparator, Outcome (PICO) evidence-based framework for formulating each question. (150) After all questions were discussed and informal preliminary searches completed, the workgroup used the modified Delphi process (151, 152) 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 workgroup for Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis.(153)

Literature Search: Design, Inclusion and Exclusion Criteria, and databases

The workgroup agreed to include cohort and observational studies, nonrandomized clinical trials, and articles with multiple case studies provided a comparator was reported (Table 1). 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 (Dohan, Qatar), web-based software platforms used by guideline writing groups (e.g., Cochrane Reviews) to streamline the production of systematic reviews. Each abstract was reviewed by two workgroup members or collaborators and categorized as relevant or irrelevant based upon the predetermined inclusion/exclusion criteria. When required, a third workgroup 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 more targeted areas including prophylaxis to prevent recurrence of anaphylaxis to nonionic low osmolar or iso-osmolar, radiocontrast media, 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 if they were appropriate for quantitative meta-analysis. In that each question used varying databases, dates, inclusion/exclusion criteria, these were discussed within the methodological review for each question.

Quality 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 workgroups and the JTFPP reviewed draft assessments, applied assessments of clinical importance for each patient-important outcome, and determined an overall quality of evidence across outcomes. The level of methodologic quality 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 (153), five areas were evaluated: inconsistency, indirectness, imprecision, risk of bias, and publication bias.

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 vs 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:

- For patients—most people in your situation would want the recommended course of action and only a small proportion would not; 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 your situation would want the recommended course of action, but many would not
- For clinicians—you should recognize that different choices will be appropriate for different patients and that you 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 Workgroup Consensus on Certainty of Evidence, Recommendations, Clinical Statement Profiles and Conclusions

To achieve consensus and resolve any differences in judgment within the workgroup 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. (151, 154, 155) The workgroup and/or JTFPP members discussed all the answers and were encouraged to modify their answers on the next round(s) of email voting and anonymous "summary of the experts" feedback until a consensus was reached.

Determination of Quality of References for a specific outcome and across critical outcomes

The quality of evidence indicates the extent to which one can be confident that an estimate of effect is correct. The GRADE system for evaluating the quality of evidence (http://gdt.guidelinedevelopment.org/app) defines the elements that guideline writing groups need to consider when evaluating the quality 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 (e.g. RCT or observation study). Methodology groups may designate a method of rating the quality of individual references to assist in this analysis. Following a determination of the quality of each individual reference, the GRADE handbook recommends that in the final analysis for each outcome of interest, the quality 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 determination of the "overall quality of evidence" supporting a recommendation, all "critical" outcomes are reviewed together, and the lowest quality grade assigned to any critical outcome of interest will determine the quality assigned for the "overall quality of evidence" to support a recommendation.

GRADE: From Certainty in 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 quality of evidence is

evaluated, the GRADE analysis continues to consider additional factors before recommending or suggesting in favor or against a certain diagnostic, therapeutic approach, or course of action: 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 workgroup 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.

QUESTION 1: In adults and children who develop anaphylaxis, what risk factors are associated with biphasic reactions?

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

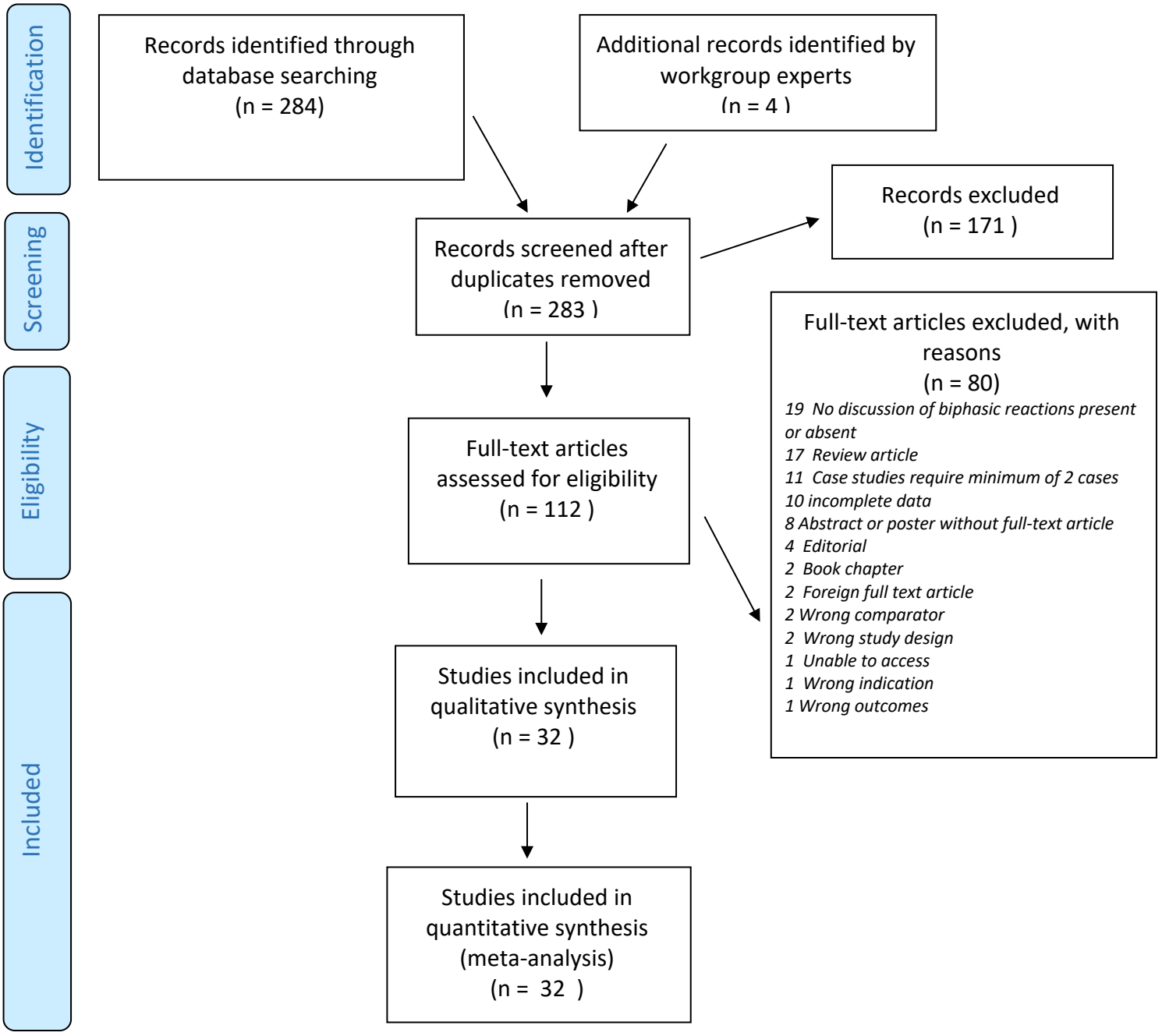
Outcome: Occurrence of biphasic anaphylaxis

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=0.048) and possibly less corticosteroid (p=0.06) treatment.(35) A systematic review by Lee et al (56) found twenty-seven observational studies 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 (Q1 PRISMA diagram)

803 Q1 PRISMA Flow Diagram



Studies Included:

Alqurashi 2015 (156); Brady 1997 (157); Brazil 1998 (158);Brown 2013 (20);Calvani 2011 (159); Cianferoni 2011 (160); Confino-Cohen 2010 (161); Douglas 1994 (162); Ellis 2007 (35); Grunau 2014 (55); Inoue 2013 (163); Jirapongsananuruk 2007 (164); Ko 2015 (165); Lee (2000); Lee 2013 (166); Lee 2017 (59); Lertnawapan 2011 (167); Manivannan 2014 (168); Manuyakorn 2015 (169); Mehr 2009 (170);Noone 2015 (171); Orhan 2011 (172); Poachanukoon 2006 (173); Rohacek 2014 (37); Sampson 1992 (34); Scranton 2009 (174); Smit 2005 (175); Sricharoen 2015 (52); Stark 1986 (33); Vezir 2013 (176); Yang 2008 (177)

Key results. Based on very low quality evidence, the following associated factors significantly increase the risk of biphasic anaphylaxis: (a) anaphylaxis caused by any drug in patients less than 18 years of age, *Peto OR* = 2.35, 94% CI [1.16, 4.76] (b) anaphylaxis caused by an unknown trigger, *Peto OR* = 1.63, 95% *CI* [1.14, 2.33] (c) anaphylaxis symptoms with cutaneous manifestations, *Peto OR* = 2.54, 95% *CI* [1.25, 5.15] (d) anaphylactic symptom of wide pulse pressures, *Peto OR* = 2.11, 95% *CI* [1.32, 3.37] (c) severe initial anaphylaxis symptoms, *Peto OR* = 2.11, 95% *CI* [1.23, 3.61] (d) anaphylaxis in patients less than 18 years of age treated with steroids, *Peto OR* = 1.55, 95% *CI* [1.01, 2.38] and (e) patients requiring more than one dose of epinephrine *Peto OR* = 4.82, 95% *CI* [2.70 to 8.58]. 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.

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., 2015; Brady Jr, Luber, Carter, Guertler, & Lindbeck, 1997; Brazil & MacNamara, 1998; Cianferoni et al., 2001; Douglas, Sukenick, Andrade, & Brown, 1994; Ellis & Day, 2007; Grunau et al., 2014; Inoue & Yamamoto, 2013; Jirapongsananuruk et al., 2007; J. M. Lee & Greenes, 2000; S. Lee, Peterson, Lohse, Hess, & Campbell, 2017;

Lertnawapan & Maek-a-nantawat, 2011; Manivannan et al., 2014; Manuyakorn et al., 2015; Mehr et al., 2009; Rohacek, Edenhofer, Bircher, & Bingisser, 2014; Smit, Cameron, & Rainer, 2005; Sricharoen, Sittichanbuncha, Wibulpolprasert, Srabongkosh, & Sawanyawisuth, 2015; Stark & Sullivan, 1986; Vezir et al., 2013; Yang et al., 2008). 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 quality based on very serious risk of bias and serious inconsistency between the included studies. Biases include (a) the use of retrospective data, (b) limited or no follow-up, (c) limited patient selection (inpatient setting), and (d) 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., 2015; Manuyakorn et al., 2015; Mehr, Liew, Tey, & Tang, 2009; Orhan et al., 2011; Vezir et al., 2013). 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 quality based on (a) very serious risk of bias as the studies were retrospective in nature with limited or no follow-up; (b) serious inconsistency as the studies had moderate heterogeneity, $I^2 = 46\%$; and (c) serious imprecision as the studies had a low number of events.

Cutaneous Symptoms. Six retrospective observational studies (*n* = 1949) are included for this outcome (Alqurashi et al., 2015; Grunau et al., 2014; Inoue & Yamamoto, 2013; J. Lee, Garrett, Brown-Whitehorn, & Spergel, 2013; Manuyakorn et al., 2015; Mehr et al., 2009). The pooled *Peto OR* was 2.54, 95% *CI* [1.25, 5.15]. Using a fixed-effect analysis, patients with cutaneous symptoms are at higher risk of having a biphasic reaction than patients without cutaneous symptoms. The evidence is graded very low quality based on very serious risk of bias and inconsistency, and serious imprecision. The biases include (a) the use of retrospective data, (b) limited or no follow-up, (c) limited patient selection (inpatient setting). The definition of cutaneous symptoms varied across studies, coupled with an $I^2 = 43\%$, inconsistency is graded as

very serious. 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 & MacNamara, 1998; Inoue & Yamamoto, 2013; S. Lee et al., 2017; Rohacek et al., 2014; Smit et al., 2005; Sricharoen et al., 2015). The pooled *Peto OR* was 0.6, 95% *CI* [0.38, 0.9]. Using a fixed-effect analysis, patients with dyspnea are at lower risk of having a biphasic reaction than patients without dyspnea. The evidence is graded very low quality based on (a) serious risk of bias as the studies are retrospective observational studies and included studies had limited or no follow-up; (b) serious inconsistency as the studies had substantial heterogeneity I^2 = 73%; (c) 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., 2015; S. Lee et al., 2017). 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 patients without a wide pulse pressure. The evidence is graded very low quality based on (a) serious risk of bias as the studies are retrospective observational studies and (b) 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., 2013; Confino-Cohen & Goldberg, 2010; J. M. Lee & Greenes, 2000; Manuyakorn et al., 2015; Vezir et al., 2013). 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 patients without severe anaphylaxis. The evidence is graded very low quality based on (a) very serious risk of bias as the studies are retrospective observational studies and included studies with limited or no follow-up; (b) serious inconsistency as the studies used different definitions for severe anaphylaxis; (c) serious imprecision as the studies had a low number of events.

Greater than One Epinephrine Treatment. Five retrospective observational studies (n = 1584) are included for this outcome (Alqurashi et al., 2015; Inoue & Yamamoto, 2013; S. Lee et al.,

2017; Mehr et al., 2009; Scranton, Gonzalez, & Waibel, 2009). The pooled *Peto OR* was 4.82, 95% *CI* [2.70 to 8.58]. Using a fixed-effect analysis, patients who receive more than one epinephrine treatment initially are at increased risk of having a biphasic reaction. The evidence is graded very low quality based on (a) very serious risk of bias as the studies are retrospective observational studies and included studies with limited or no follow-up; (b) serious imprecision as the studies had a low number of events.

Steroid Treatment In Patients ≤ 18 years of age. Seven retrospective observational studies (*n* = 1203) are included for this outcome (Alqurashi et al., 2015; Calvani et al., 2011; Inoue & Yamamoto, 2013; J. M. Lee & Greenes, 2000; Manuyakorn et al., 2015; Mehr et al., 2009; Vezir et al., 2013). 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 steroid treatment are at a higher risk of having a biphasic reaction than patients ≥ 18 years of age who receive steroid treatment. The evidence is graded very low quality based on (a) 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); (b) 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. Reviewers were unable to perform an analysis for this outcome since the authors provided interquartile range (IQR) and median values and therefore this outcome could not be pooled together. Three of the eight studies showed delayed administration of epinephrine resulted in higher rates of biphasic anaphylaxis while the other five studies showed no statistical difference. S. Lee et al. (2017) identified 872 anaphylaxis-related visits to an emergency department from 2008-2015. There was a statistically significant association with biphasic reactions when the first dose of epinephrine was administrated more than 60 minutes after symptoms developed, OR = 2.29, 95% CI [1.09, 4.79]. J. M. Lee and Greenes (2000) also performed a retrospective 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 min and 48 min for patients without a biphasic reaction (p = .03). Lertnawapan and Maek-a-nantawat (2011) conducted an observational study on patients (*n* = 208) presenting to an emergency department with anaphylaxis**.** Time from symptoms onset to administration of

epinephrine was significantly longer in the biphasic group than the no biphasic group, at 240 minutes (IQR 122.5-380) vs 70 minutes (IQR 40-135) minutes, $p = 0.002$. Alqurashi et al. (2015) 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) and without biphasic reactions (59 minutes, IQR 25-105), $p = 0.35$. Ko et al. (2015) showed no association was observed 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 no biphasic group and 70 minutes (IQR 20-570) in the biphasic groups. Poachanukoon and Paopairochanakorn (2006) 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 no biphasic group but it did not reach statistical significance. Median time to initial dose of epinephrine in the no biphasic group was 82 minutes and 263 minutes in the biphasic group. No range was given. Scranton et al. (2009) found no difference in mean time to epinephrine between the no biphasic group 8.5 minutes ± 13.8 and the biphasic group 8.2 minutes ± 12.8, $p = .94$. J. Lee et al. (2013) found no difference in time from first reaction onset to first epinephrine dose between the no biphasic 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,(56) the current analysis did not find a significant association of foods with decreased risk for biphasic anaphylaxis (Peto OR 0.89, 95% CI [0.68 , 1.17].

Table Q1

GRADE Summary of Findings Table

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With No Biphasic	With Biphasic		Risk with No Biphasic	Risk difference with Biphasic

Certainty assessment							Summary of findings				
Unknown Trigger											
4275 (21 observational studies)	very serious [a,c,d,e]	serious [f]	not serious	not serious	none	⨁◯◯◯ VERY LOW	624/4005 (15.6%)	56/270 (20.7%)	**OR 1.63** (1.14 to 2.33)	156 per 1,000	**75 more per 1,000** (18 more to 145 more)
Drug Trigger <=18 years old											
996 (5 observational studies)	very serious [a,c]	serious [f]	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	135/886 (15.2%)	18/110 (16.4%)	**OR 2.35** (1.16 to 4.76)	152 per 1,000	**145 more per 1,000** (20 more to 309 more)
Cutaneous Symptoms											
1949 (6 observational studies)	very serious [a,c,d]	very serious [f, i]	not serious	very serious [b,g]	none	⨁◯◯◯ VERY LOW	1546/1838 (84.1%)	104/111 (93.7%)	**OR 2.54** (1.25 to 5.15)	841 per 1,000	**90 more per 1,000** (28 more to 123 more)
Dyspnea Symptoms											
1841 (6 observational studies)	serious [a,c]	serious [h]	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	831/1743 (47.7%)	34/98 (34.7%)	**OR 0.60** (0.38 to 0.96)	477 per 1,000	**123 fewer per 1,000** (220 fewer to 10 fewer)

Wide Pulse Pressure											
1356 (2 observational studies)	serious [a]	not serious	not serious	serious [b]	none	⊕◯◯◯ VERY LOW	247/1249 (19.8%)	40/107 (37.4%)	**OR 2.11** (1.32 to 3.37)	198 per 1,000	**144 more per 1,000** (48 more to 256 more)
Severe Initial Symptoms											
724 (5 observational studies)	very serious [a,d]	Very serious [f, j]	not serious	serious [b]	none	⊕◯◯◯ VERY LOW	248/638 (38.9%)	44/86 (51.2%)	**OR 2.11** (1.23 to 3.61)	389 per 1,000	**184 more per 1,000** (50 more to 308 more)
> 1 dose of Epinephrine											
1584 (5 observational studies)	very serious [a,c]	very serious [h]	not serious	serious [b]	none	⊕◯◯◯ VERY LOW	130/1449 (9.0%)	34/135 (25.2%)	**OR 4.82** (2.70 to 8.58)	90 per 1,000	**232 more per 1,000** (120 more to 368 more)
Steroids <= 18 years old											
1203 (7 observational studies)	very serious [a,c,d]	not serious	not serious	serious [b]	none	⊕◯◯◯ VERY LOW	632/1089 (58.0%)	78/114 (68.4%)	**OR 1.55** (1.01 to 2.38)	580 per 1,000	**102 more per 1,000** (2 more to 187 more)

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Explanations

a. Retrospective data may introduce selection bias and increase possible confounding errors

b. Low number of events (less than 250 biphasic reactions)

c. Included study or studies with limited follow-up of 24 hours or no follow-up resulting in possible missed biphasic patients

d. Included study or studies with limited patient selection including patients from inpatient setting or from a specialty clinic

e. Included study or studies with larger exclusion of patients due to missing data

f. Moderate heterogeneity as evidence by I^2 of 30-60%

g. Wide confidence interval

h. Substantial heterogeneity as evidence by I^2 of 50-90%

i. Different definitions of cutaneous symptoms

j. Different scales for measuring severity of anaphylactic reaction

Figure Q*1a*: *Comparison: Biphasic Versus No Biphasic, Outcome: Drug Trigger*

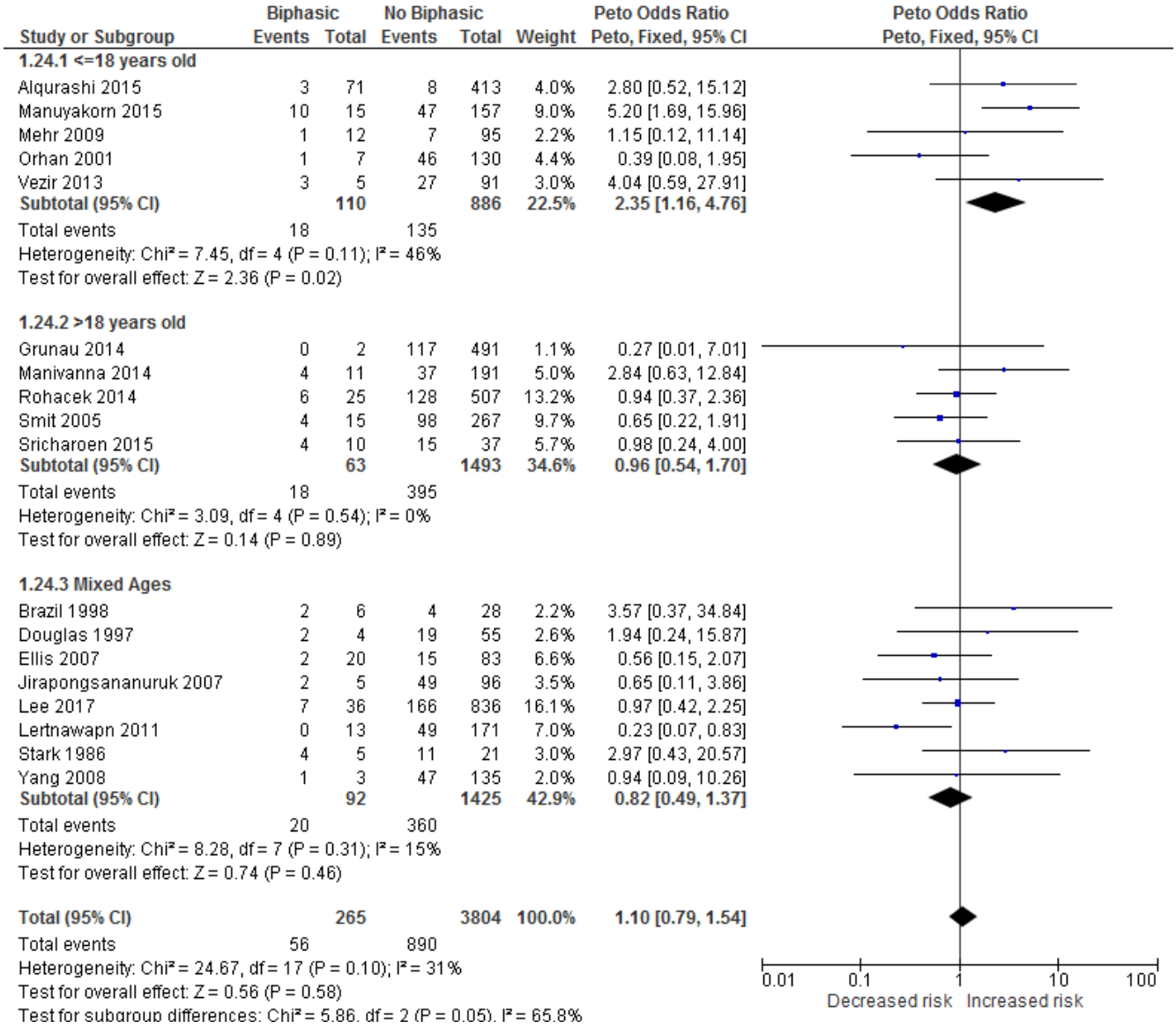

Figure Q*1b* : *Comparison: Biphasic Versus No Biphasic, Outcome: Unknown Trigger*

Study or Subgroup	Biphasic Events	Biphasic Total	No Biphasic Events	No Biphasic Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Alqurashi 2015	15	71	67	413	28.2%	1.42 [0.72, 2.77]
Brady 1997	0	2	20	65	1.4%	0.24 [0.01, 4.97]
Brazil 1998	0	6	9	28	3.3%	0.20 [0.03, 1.44]
cianferoni 2001	0	2	6	105	0.3%	0.34 [0.00, 145.92]
Douglas 1997	0	4	10	55	1.8%	0.28 [0.02, 4.11]
Ellis 2007	6	20	18	83	9.6%	1.59 [0.50, 5.00]
Grunau 2014	1	2	104	494	1.1%	5.65 [0.19, 168.54]
Inoue 2013	0	2	4	59	0.4%	0.34 [0.00, 95.37]
Jirapongsananuruk 2007	2	5	15	96	2.2%	5.61 [0.51, 61.25]
Lee 2000	0	6	16	100	2.4%	0.29 [0.03, 2.87]
Lee 2017	13	36	181	836	19.7%	2.30 [1.03, 5.14]
Lertnawapn 2011	4	13	30	171	6.0%	2.39 [0.56, 10.20]
Manivanna 2014	4	11	30	191	4.8%	4.34 [0.86, 21.95]
Manuyakorn 2015	0	15	5	157	1.3%	0.33 [0.01, 7.55]
Mehr 2009	2	12	5	95	2.2%	6.35 [0.57, 71.15]
Rohacek 2014	7	25	71	507	9.8%	3.05 [0.98, 9.49]
Smit 2005	2	15	2	267	0.7%	7845.15 [97.25, 632841.64]
Sricharoen 2015	0	10	3	37	1.6%	0.27 [0.02, 4.48]
Stark 1986	0	5	2	20	1.0%	0.27 [0.01, 9.35]
Vezir 2013	0	5	8	91	1.2%	0.32 [0.01, 8.18]
Yang 2008	0	3	18	135	1.1%	0.31 [0.01, 9.19]
Total (95% CI)		**270**		**4005**	**100.0%**	**1.63 [1.14, 2.33]**
Total events	56		624			

Heterogeneity: Chi² = 36.56, df = 20 (P = 0.01); I² = 45%
Test for overall effect: Z = 2.69 (P = 0.007)

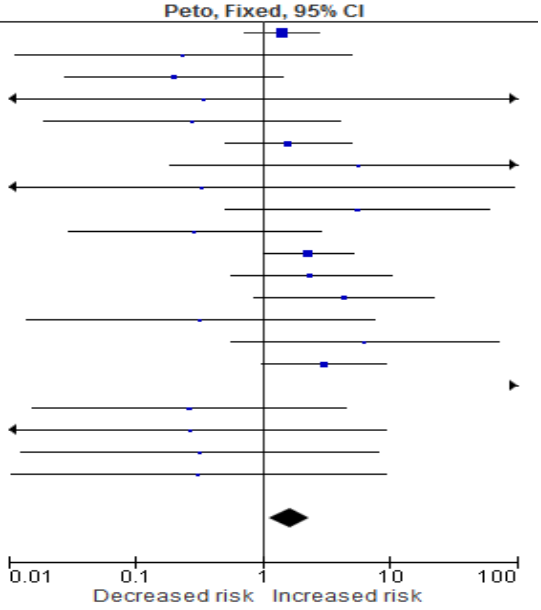

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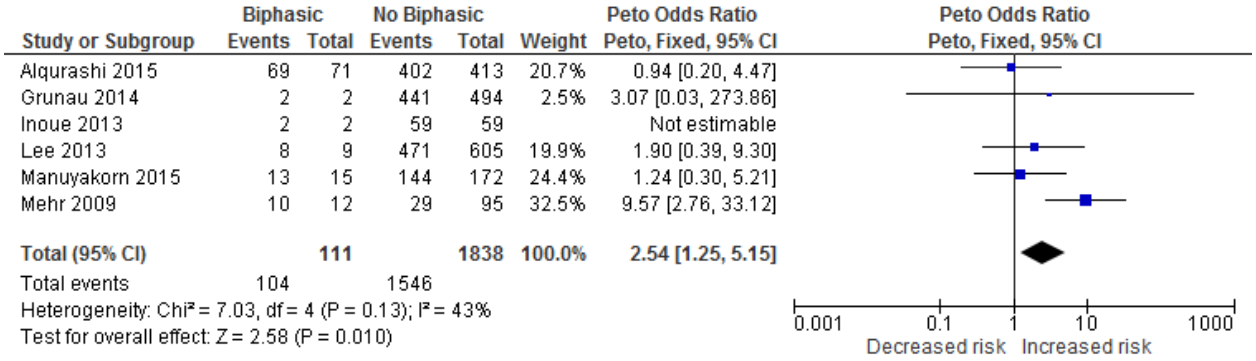
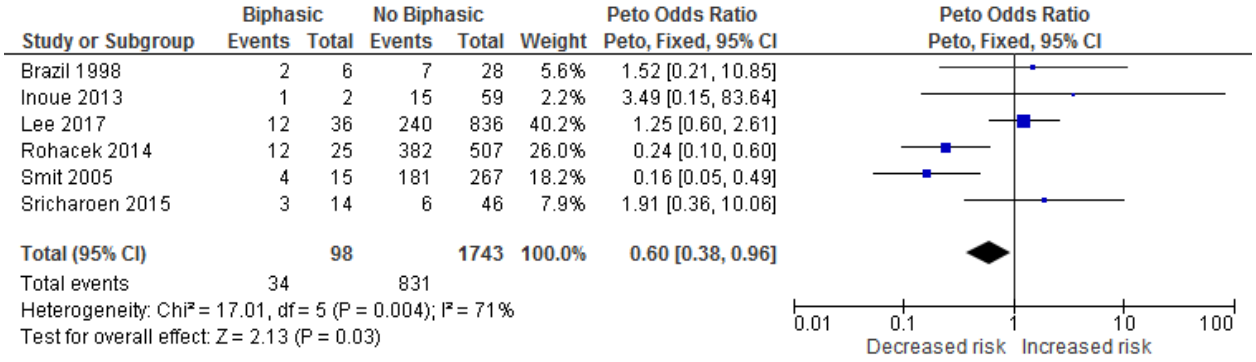
Figure Q*1c*: *Comparison: Biphasic Versus No Biphasic, Outcome: Cu*



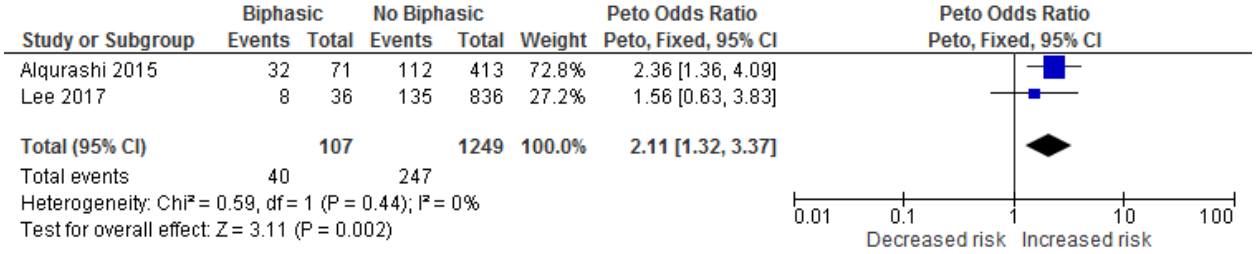
taneous Symptoms

Figure Q*1d*: *Comparison: Biphasic Versus No Biphasic,*



Outcome: Dyspnea Symptoms

Figure Q*1e*: *Comparison: Biphasic Versus No B*



iphasic, Outcome: Wide Pulse Pressure

Figure Q*1f*: *Comparison: Biphasic Versus No Biphasic, Outcome: Severe Initial Symptoms*

Study or Subgroup	Biphasic Events	Biphasic Total	No Biphasic Events	No Biphasic Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Brown 2013	22	49	72	266	66.0%	2.34 [1.20, 4.54]
Confino-Cohen 2010	0	11	11	120	5.9%	0.31 [0.03, 2.82]
Lee 2000	6	6	90	99	3.4%	3.16 [0.17, 59.06]
Manuyakorn 2015	12	15	47	62	16.6%	1.26 [0.34, 4.73]
Vezir 2013	4	5	28	91	8.1%	8.96 [1.34, 59.87]
Total (95% CI)		**86**		**638**	**100.0%**	**2.11 [1.23, 3.61]**
Total events	44		248			

Heterogeneity: Chi² = 5.88, df = 4 (P = 0.21); I² = 32%
Test for overall effect: Z = 2.70 (P = 0.007)

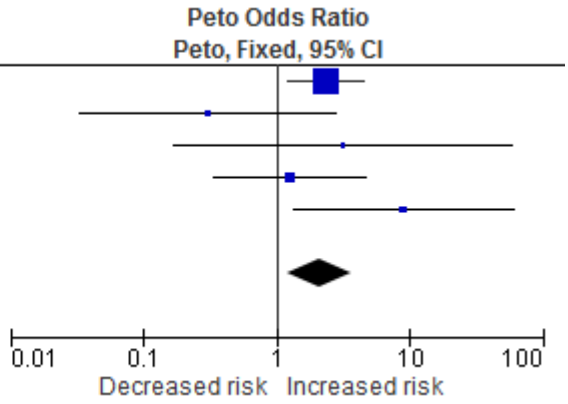


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Figure Q*1g*: *Comparison: Biphasic versus No Biphasic, Outcome: Steroids*

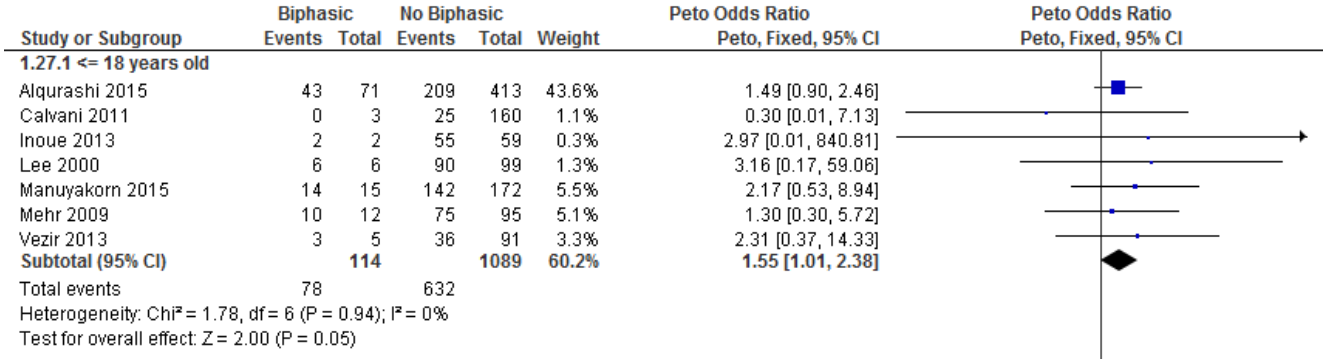


Figure Q*1h: Comparison: Biphasic versus No Biphasic, Outcome:* Greater than One Epinephrine

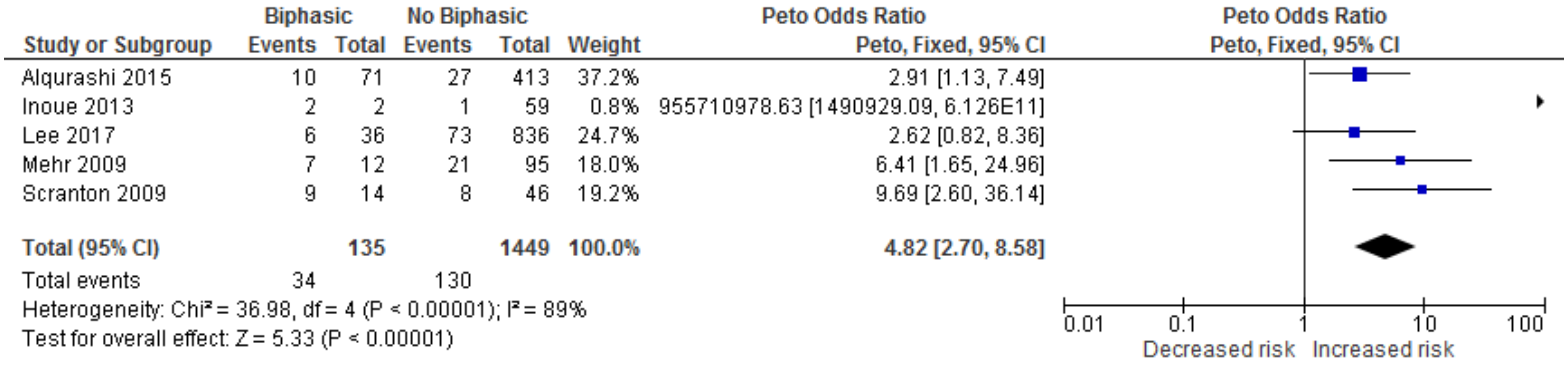
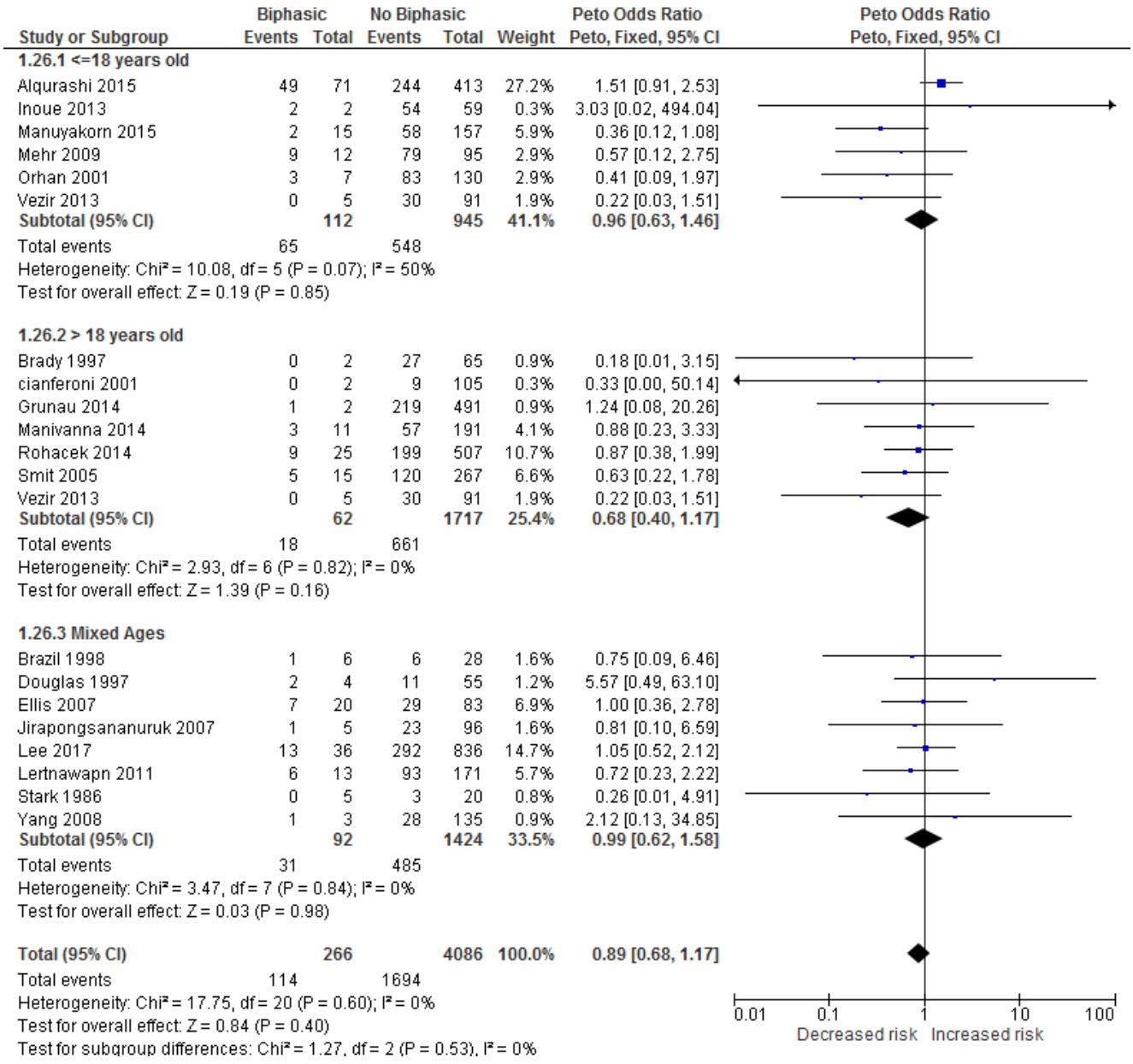


Figure Q1i: Comparison: Biphasic versus No Biphasic, Outcome: Food Trigger


Biphasic
No Biphasic
Peto Odds Ratio
Peto Odds Ratio
Study or Subgroup
Events Total Events Total Weight
Peto, Fixed, 95% CI
Peto, Fixed, 95% CI
1.26.1 <=18 years old
Alqurashi 2015 49 71 244 413 27.2% 1.51 [0.91, 2.53]
Inoue 2013 2 2 54 59 0.3% 3.03 [0.02, 494.04]
Manuyakorn 2015 2 15 58 157 5.9% 0.36 [0.12, 1.08]
Mehr 2009 9 12 79 95 2.9% 0.57 [0.12, 2.75]
Orhan 2001 3 7 83 130 2.9% 0.41 [0.09, 1.97]
Vezir 2013 0 5 30 91 1.9% 0.22 [0.03, 1.51]
Subtotal (95% CI) 112 945 41.1% 0.96 [0.63, 1.46]
Total events 65 548
Heterogeneity: Chi² = 10.08, df = 5 (P = 0.07); I² = 50%
Test for overall effect: Z = 0.19 (P = 0.85)
1.26.2 > 18 years old
Brady 1997 0 2 27 65 0.9% 0.18 [0.01, 3.15]
cianferoni 2001 0 2 9 105 0.3% 0.33 [0.00, 50.14]
Grunau 2014 1 2 219 491 0.9% 1.24 [0.08, 20.26]
Manivanna 2014 3 11 57 191 4.1% 0.88 [0.23, 3.33]
Rohacek 2014 9 25 199 507 10.7% 0.87 [0.38, 1.99]
Smit 2005 5 15 120 267 6.6% 0.63 [0.22, 1.78]
Vezir 2013 0 5 30 91 1.9% 0.22 [0.03, 1.51]
Subtotal (95% CI) 62 1717 25.4% 0.68 [0.40, 1.17]
Total events 18 661
Heterogeneity: Chi² = 2.93, df = 6 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.39 (P = 0.16)
1.26.3 Mixed Ages
Brazil 1998 1 6 6 28 1.6% 0.75 [0.09, 6.46]
Douglas 1997 2 4 11 55 1.2% 5.57 [0.49, 63.10]
Ellis 2007 7 20 29 83 6.9% 1.00 [0.36, 2.78]
Jirapongsananuruk 2007 1 5 23 96 1.6% 0.81 [0.10, 6.59]
Lee 2017 13 36 292 836 14.7% 1.05 [0.52, 2.12]
Lertnawapn 2011 6 13 93 171 5.7% 0.72 [0.23, 2.22]
Stark 1986 0 5 3 20 0.8% 0.26 [0.01, 4.91]
Yang 2008 1 3 28 135 0.9% 2.12 [0.13, 34.85]
Subtotal (95% CI) 92 1424 33.5% 0.99 [0.62, 1.58]
Total events 31 485
Heterogeneity: Chi² = 3.47, df = 7 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.98)
Total (95% CI) 266 4086 100.0% 0.89 [0.68, 1.17]
Total events 114 1694
Heterogeneity: Chi² = 17.75, df = 20 (P = 0.60); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Chi² = 1.27, df = 2 (P = 0.53), I² = 0%
0.01
0.1
1
10
100
Decreased risk
Increased risk

998

999

1000
1001
1002

EVIDENCE TO RECOMMENDATIONS: QUESTION#1

Question: In adults & children who develop anaphylaxis, what risk factors are associated with 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:	Healthcare 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 hours 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

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1004 CLINICAL STATEMENT

- Very low-quality evidence suggests extended observation is appropriate for patients with severe initial anaphylaxis. For patients with resolved non-severe anaphylaxis who are without significant co-morbidities 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-hour 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.

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1006 ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes • **Yes** ○ Varies ○ Don't 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, 58) The prevalence of fatal	There is some uncertainty as to the exact rate of biphasic anaphylaxis and evidence regarding optimal treatment for biphasic anaphylaxis is scant.

	anaphylaxis is between 0.47 to 0.69 per million persons 0.25%-0.33% of ED visits or hospitalizations.(9, 10, 27-29)	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small • **Moderate** ○ Large ○ Varies ○ Don't 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-quality evidence suggests biphasic anaphylaxis is associated with: (a) severe initial anaphylaxis symptoms, OR = 2.11, 95% CI [1.23, 3.61], (b) more than one dose of epinephrine, OR = 4.82, 95% CI [2.70 to 8.58], and (c) anaphylactic symptom of wide pulse pressures, OR = 2.11, 95% CI [1.32, 3.37]. Additional associations include: (d) anaphylaxis caused by any drug in patients	More severe anaphylaxis carries a greater risk for biphasic anaphylaxis. Additional associations are quite broad, may be confounded by anaphylaxis severity, and apply to a majority of patients with anaphylaxis, who would likely have one of the additional associated factors (drug trigger in children, idiopathic or cutaneous symptoms, or children receiving steroids).

	less than 18 years of age, OR = 2.35, 94% CI [1.16, 4.76], (e) anaphylaxis caused by an unknown trigger, OR = 1.63, 95% CI [1.14, 2.33], (f) anaphylaxis symptoms with cutaneous manifestations, OR = 2.54, 95% CI [1.25, 5.15], and (g) anaphylaxis in patients less than 18 years of age treated with steroids, OR = 1.55, 95% CI [1.01, 2.38].	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial • **Varies** ○ Don't know	For ED or hospital presentations of anaphylaxis, the case-fatality rate is estimated at 0.25% to 0.33%, including both uni- and biphasic anaphylaxis.(29) 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	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.

	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.(132) Therefore the risks and benefits need to be balanced. While harm may result from missed cases of anaphylaxis in 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?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **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-quality 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-hour to a $\geq$ 6 hour observation, the number needed to treat by extended observation to prevent one biphasic reaction following discharge is 41 (range, 18-195) for patients presenting with severe anaphylaxis and 13 (range, 7-27) for those requiring multiple doses of epinephrine.(132, 178)	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. Upon discharge, patients should be instructed to see an allergist-immunologist. (41)

Values (Value judgments) Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ 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, for patients with severe initial anaphylaxis, evidence suggests observation for 6 hours is appropriate. There is an absence of patient-preference sensitive evidence to inform physicians of the relative valuation of trade-offs when prolonged observation is compared to 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 non-severe anaphylaxis may prefer more extended observation (beyond 1-hour). 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?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison • **Probably favors the intervention** ○ Favors the intervention ○ Varies Don't know	Potential harm could result from over-reliance 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)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings	Direct and indirect costs may vary depending on how risk factors are incorporated into patient management. Prolonged emergency department observation or	Anaphylaxis patient education, referral to an allergist, and prescription of an epinephrine auto-injector at discharge are important for all patients with anaphylaxis.(41)

• **Varies** ○ Don't know	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.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low • **Low** ○ Moderate ○ High ○ No included studies	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 activity-based cost strategy can be used to estimate hourly costs from allergy clinic or emergency department observation.(179, 180)	Indirect costs involve job-related opportunity costs and may vary significantly across patient populations. Additional costs would be incurred for patients receiving overnight hospital admission for post-anaphylaxis monitoring.

Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison • **Probably favors the intervention** ○ Favors the intervention ○ Varies Don't know ○ No included studies gree.	Medical observation of patients with severe anaphylaxis for ≥ 6 hours can be a cost-effective strategy if it provides at least a 76% fatality risk reduction compared to a shorter, e.g., 1 hour, observation. (Shaker et al. Estimation of Health and Economic Benefits of Extended Observation of Resolved Anaphylaxis: A Cost Effectiveness Analysis. Submitted). However, this level of risk reduction may be unrealistic even in situations of severe anaphylaxis because the baseline risk is so small.	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?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced	The impact on equity may vary depending on how risk	All patients experiencing anaphylaxis should be closely

○ Probably no impact ○ Probably increased ○ Increased • **Varies** ○ Don't know	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.	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 preference must be taking into consideration.
Acceptability & Quality improvement opportunity Is the intervention acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes • **Yes** ○ Varies ○ Don't know	Evidence suggests that a 1-hour symptom-free observation period of non-severe anaphylaxis has a 95% NPV for biphasic anaphylaxis.(132)	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?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes • **Varies** ○ Don't know	One recent meta-analysis suggests a 95% NPV associated with a 1-hour medical observation, and a 97.3% NPV associated with an observation period of at least 6 hours.(132)	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 hours).
Intentional Vagueness		
○ No ○ Probably no ○ Probably yes • **Yes** ○ Varies Don't know	Evidence was drawn from a heterogeneous population of non-randomized clinical studies and is susceptible to methodologic bias. The optimal extended observation time following resolved anaphylaxis is poorly defined. While a ≥6 hour observation period could be suggested in higher-risk patients, uncertainty remains regarding the cost-effectiveness of such an approach in many circumstances (Shaker et al, submitted for publication)	Due to very low quality of evidence and absence of a randomized controlled trial to address this question, there remains uncertainty and potential bias. A role for patient-preference 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 Don't know	Patients with severe-anaphylaxis may reasonably choose to defer prolonged observation beyond 6-hours. (Shaker et al. Estimation of Health and Economic Benefits of Extended Observation of Resolved Anaphylaxis: A Cost Effectiveness Analysis. Submitted) 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 upon fear, anxiety, past experiences, or specific psycho-social 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 non-severe anaphylaxis should have the option for more extended observation.
Exclusions		
○ No • **Probably no** ○ Probably yes ○ Yes ○ Varies	It is important to distinguish biphasic anaphylaxis from uniphasic anaphylaxis without complete resolution (protracted anaphylaxis).	Additional factors associated with biphasic anaphylaxis would be difficult to incorporate into clinical triage strategies, such as anaphylaxis

Don't know	Specific subpopulations were not excluded.	caused by a drug trigger in children, anaphylaxis with cutaneous symptoms, and use of glucocorticoids in children. Some clinical associations identified may be confounded by anaphylaxis severity. Given the low quality 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 Don't know	We would not recommend policy level interventions to mandate specific observation times or incorporate specific risk factors to predict biphasic anaphylaxis, as the quality 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.

1007 SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM IS A PRIORITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know

	JUDGEMENT						
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		**Varies**	Don't 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	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't 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**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	**Don't know**

QUESTION 2: Should antihistamines or glucocorticoids be used to prevent anaphylactic reactions?

Patients: Adults and children experiencing anaphylaxis who are treated with glucocorticoids, antihistamines, or both to: (a) prevent biphasic anaphylaxis, (b) prevent index anaphylaxis with chemotherapeutic, (c) prevent recurrence of anaphylaxis to nonionic low osmolar or iso-osmolar, radiocontrast media, and (d) prevent index anaphylaxis with non-chemotherapeutic 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

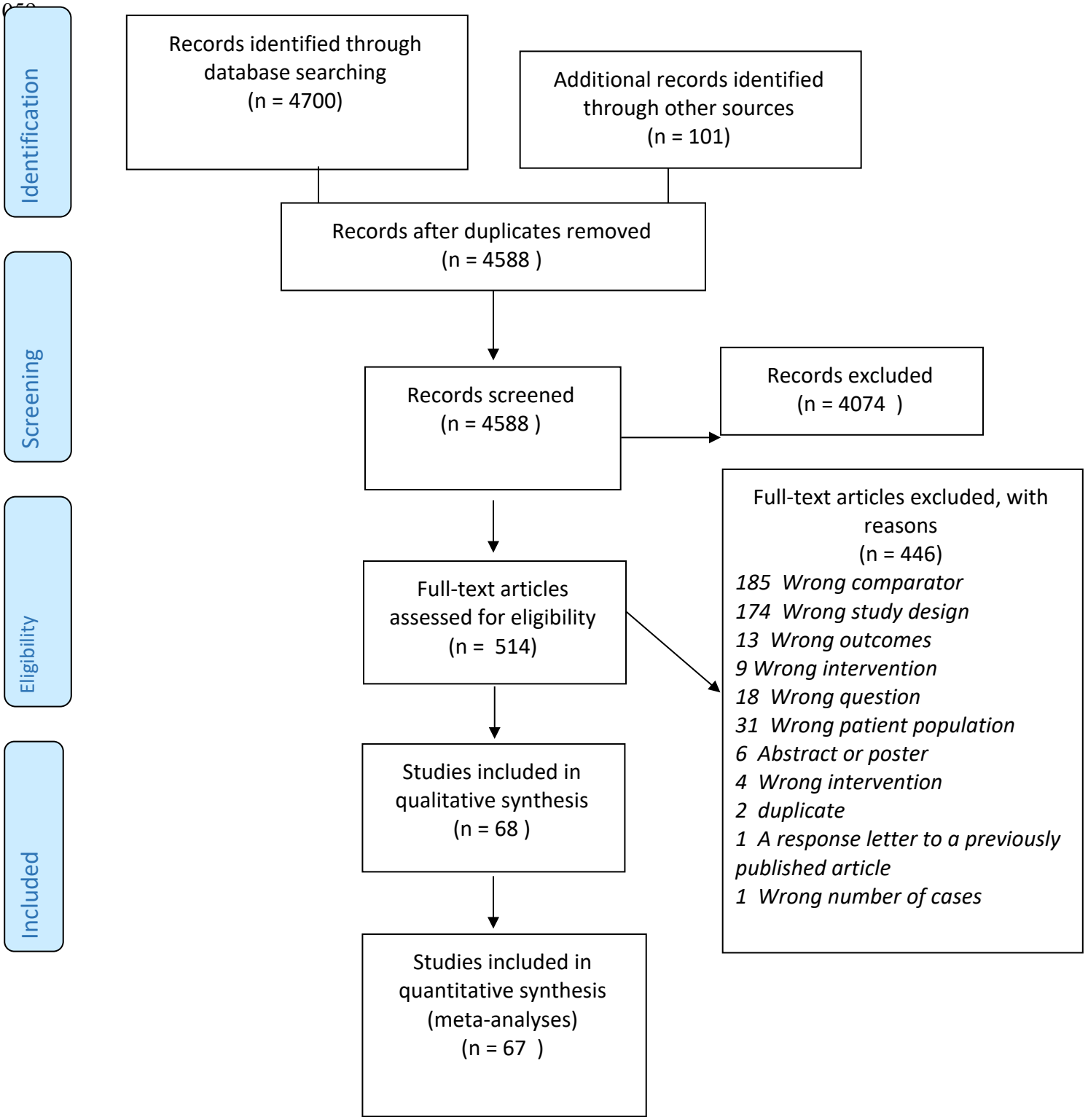
Outcome: Occurrence of (a) biphasic anaphylaxis and (b-d) anaphylaxis.

Background: A systematic review by Alqurashi et al found thirty-one 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 authors concluded there was a lack of compelling evidence to support the routine use of glucocorticoids to prevent biphasic anaphylaxis.(40) 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 has been evaluated is questionable. Taxol, an antitumor agent, is one example with hypersensitivity reaction to this agent reported since early clinical use. In one early report (181), of 301 patients treated, 32 patients had definite (27 patients) or possible (5 patients) hypersensitivity reactions (HSRs) and all but one patient had the reaction from the 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. (181). However, it has been suggested that the most important change in decreasing rates of HSR associated with RCM has been use of low or iso-osmolar non-ionic

agents. Evidence supporting the use of premedication in the setting of non-ionic RCM agents 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. (16)

Study characteristics. The search for suitable studies was completed by the JTFPP (Figure eQ2). Sixty-five articles were identified for inclusion. Odds ratios (OR) were used in analysis of Q2a and Q2b due to the case-control analytic strategy as biphasic and uniphasic anaphylaxis were analysed by retrospective evaluation of therapies received before the outcome of interest. Conversely, Q2c and Q2d were evaluated using the risk ratio (RR), 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 RR 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 Q2 analysis due to unbalanced arms which could lead to skewed findings using the Peto OR. (182)

Q2 PRISMA Flow Diagram



Included Studies:

Q2a: Adults and children treated for anaphylaxis who are treated with glucocorticoids, antihistamines, or both to: (a) prevent biphasic anaphylaxis:

Alqurashi 2015 (156); Brady 1997 (183); Brown 2013 (20); Calvani 2011 (159); Douglas 1994 (162); Ellis 2007 (35); Grunau 2015 (184); Guiot 2017 (185); Inoue 2013 (163); Jirapongsananuruk 2007 (164); Kawano 2017 (186); Ko 2015 (187); Lee 2017 (188); Lee 2000 (131); Lee 2013 (166); Lertnawapan 2011(167); Lin 2000 (189); Manuyakorn 2015 (169); Mehr 2009 (190)Michelson 2015 (148); Oya 2014 (191); Poachanukoon 2006 (173);Rohacek 2014 (37); Scranton 2009 (192); Smit 2005 (175); Sricharoen 2015 (52); Stark 1986 (33); Vezir 2013 (176)

Q2b: Adults treated for anaphylaxis who are treated with glucocorticoids, antihistamines, or both to prevent index anaphylaxis with chemotherapeutic:

Chang 2016 (193); Francis 1994 (194); Jerzak 2018 (195); Mach 2016 (196); Onetto 1993 (197); Rougier 1995 (198); Seki 2011 (199); Shen 2018 (200); Thompson 2014 (201); Trudeau 1996 (202); Weiss 1990 (181)

Q2c: Adults and children treated for anaphylaxis who are treated with glucocorticoids, antihistamines, or both to prevent recurrence of anaphylaxis to radiocontrast media:

Abe 2016 (203); Katayama 1990 (204); Kolbe 2014 (205); Lee 2016 (206); Park 2017 (207); Park 2018 (208)

Q2d: Adults and children treated for anaphylaxis who are treated with glucocorticoids, antihistamines, or both to prevent index anaphylaxis with non-chemotherapeutic agent:

Augustsson 2007 (209); Berchtold 1992 (210); Braaton 2015 (211); Brockow 1997 (212); Caron 2009 (213); Fan 1999 (214); Gold 2017 (215); Hejjaoui 1990 (216); Jacobstein 2005 (217); Jagdis 2014 (218); Lorenz 1980 (219); Mueller 2008 (220); Neilson 1996 (221); Portnoy 1994 (222); Reimers 2000 (223); Sanders 2005 (224); Schoening 1982 (225); Tankersley 2002 (226); Yoshihiro 2006 (227)

Key results (Q2a1)

As shown in Figure Q2a, very low-quality evidence suggests that glucocorticoids do not provide 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 analysed as surrogate markers in Michelson 2015 (148), in which glucocorticoids was associated with decreased length of hospital stay but not with 3-d day ED revisit among hospitalized children. However, the addition of this study was limited by the poor distinction between protracted or biphasic anaphylaxis, with the distinction between outcomes possibly representing this 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 regards to the odds of the biphasic versus the monophasic group also receiving epinephrine at baseline. In meta-regression analyses epinephrine use accounted for about half of the between study variance, with moderate variance remaining after this correction (Tau2 = 0.4).

Key results (Q2a2)

Similar to findings regarding glucocorticoid use in anaphylaxis, antihistamines also did not provide benefit in reduction of biphasic reactions (Figure Q2a2; OR 0.71, 95% CI 0.47-1.06 for H1-antihistamines and OR 1.21, 95% CI 0.8-1.83 for H2-antihistamines). Additional analyses were performed excluding Mehr 2009 (190) and Lee 2013 (228) to account for uncertainty in antihistamine preparations used without change in findings (OR 0.69, 95% CI 0.44-1.09 for H1-antihistamine). 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 regards to the odds of the biphasic versus the monophasic group also receiving epinephrine at baseline. In the meta-regression analysis epinephrine use did not account for significant variation across studies. Kawano 2017 reported findings of a retrospective cohort to evaluate the effect of antihistamine treatment to prevent progression of anaphylaxis, so was excluded from the final analysis.(186) However, the inclusion of Kawano did result in a significant OR in favor of antihistamine use (OR 0.65, 95% CI 0.47-0.91). The significance of Kawano 2017 is difficult to interpret because patients were selected using an ED diagnostic code of "allergic reaction" (ICD-9 code 995.3) and patients receiving H1 antihistamines were more likely to receive epinephrine and steroids in their report. Similarly, Lin 2000 was excluded as the comparator in

this analysis was an antihistamine. (189). Sricharoen was excluded as all subject received antihistamines.

Table Q2a1. Should Glucocorticoids be Used to Prevent Biphasic Reactions?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biphasic	Monophasic	Relative (95% CI)	Absolute (95% CI)		
Rate of Steroid Use in Biphasic Vs Monophasic Anaphylaxis												
26	observational studies	very serious [a]	serious [b]	serious [c]	serious [d]	all plausible residual confounding would reduce the demonstrated effect	616/871 (70.7%)	10270/14762 (69.6%)	**OR 0.87** (0.74 to 1.02)	**30 fewer per 1,000** (from 4 more to 67 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. 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
b. Significant heterogeneity across studies
c. Indirect outcomes reported as surrogate to biphasic reactions included emergency department revisits, hospitalizations, and length of stay - with some disparity occurring among surrogates measured.
d. Several studies with wide ranging 95% Confidence Intervals

Figure Q2a1. Use of steroids among patients with biphasic versus monophasic outcomes

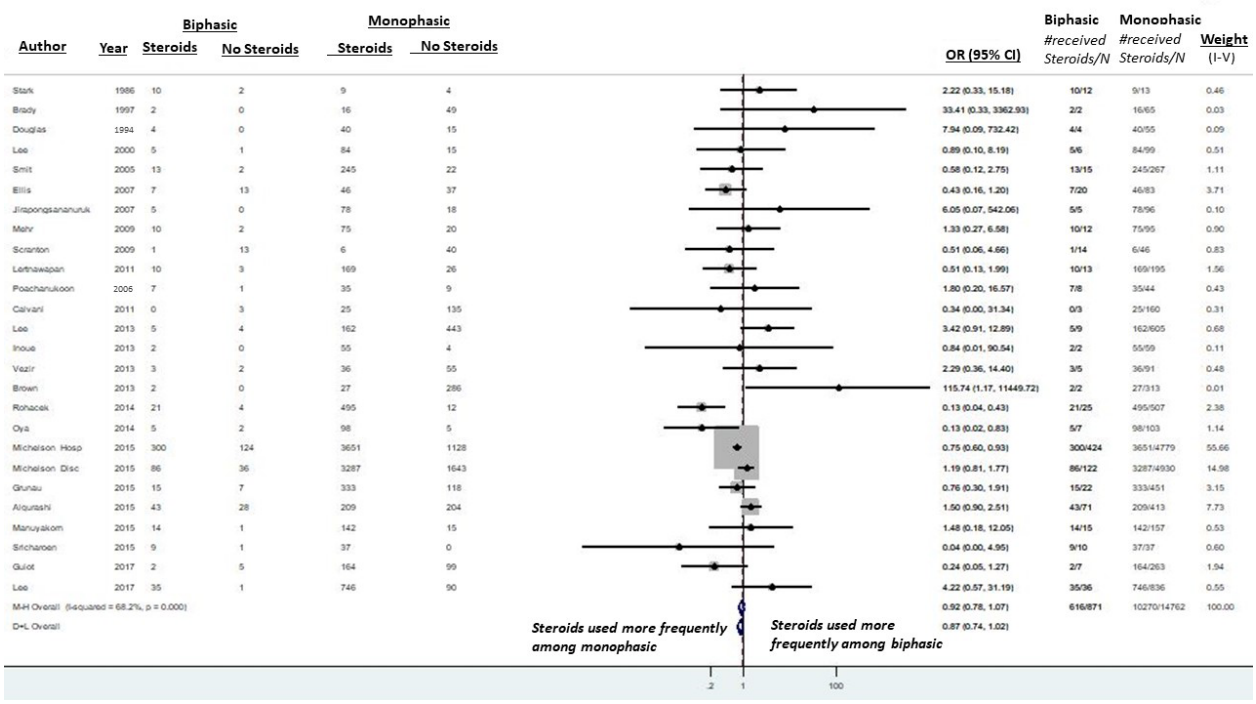


Table Q2a2. Should Antihistamines be Used to Prevent Biphasic Reactions?

H1 antihistamines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biphasic	Monophasic	Relative (95% CI)	Absolute (95% CI)		
Patients with acute allergic reactions treated with Antihistamine H1 to prevent biphasic or protracted anaphylaxis												
16	observational studies	very serious [a]	serious [b]	serious [c]	serious [d]	all plausible residual confounding would reduce the demonstrated effect	210/245 (85.7%)	2875/3304 (87.0%)	**OR 0.71** (0.47 to 1.06)	**44 fewer per 1,000** (from 6 more to 111 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. 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
b. Significant heterogeneity across studies
c. Endpoint included outcomes reported as surrogate to biphasic reactions included emergency department revisits
d. Several studies with wide ranging 95% Confidence Intervals

H2 antihistamines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biphasic	Monophasic	Relative (95% CI)	Absolute (95% CI)		
Patients with acute allergic reactions treated with Antihistamine H2 to prevent biphasic or protracted anaphylaxis												
10	observational studies	very serious [a]	not serious	serious [b]	serious [c]	all plausible residual confounding would reduce the demonstrated effect	60/173 (34.7%)	763/1955 (39.0%)	**OR 1.21** (0.80 to 1.83)	**46 more per 1,000** (from 52 fewer to 149 more)	⨁◯◯◯ VERY LOW	IMPORTANT

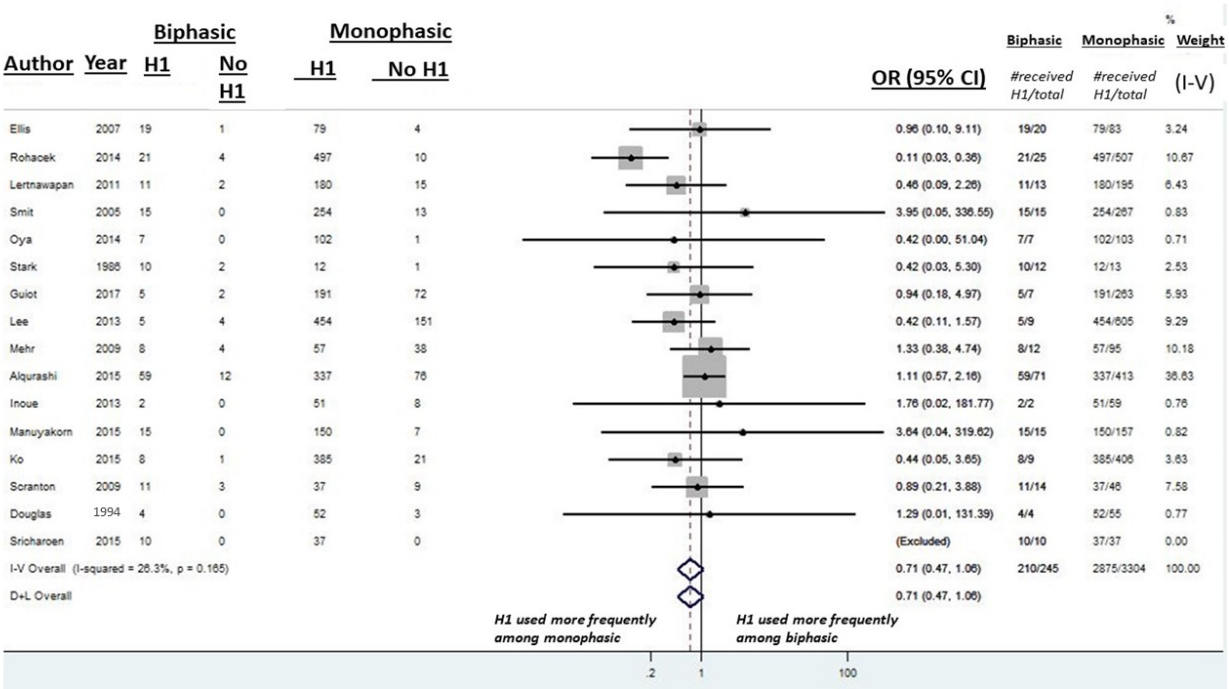
CI: Confidence interval; **OR:** Odds ratio

Explanations

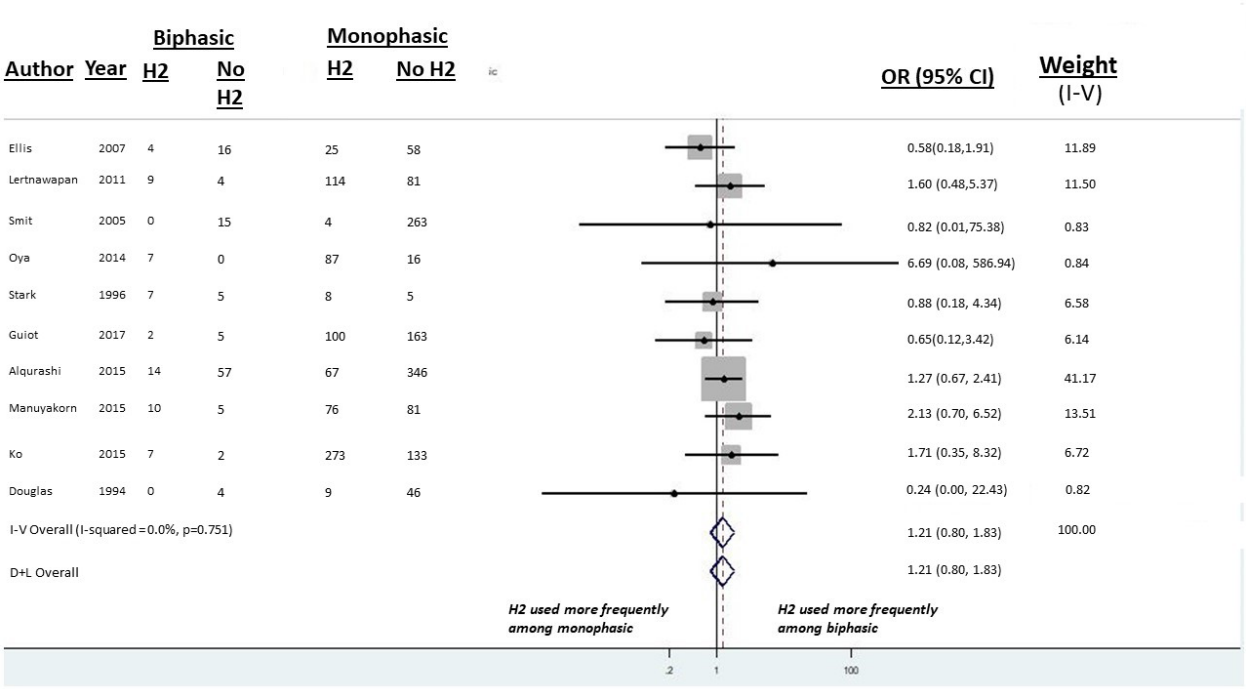
a. Risk of bias across studies related to lack of blinding, lack of randomization, potential confounding by severity of presentation, practice variation, and differential use of epinephrine
b. Endpoint included outcomes reported as surrogate to biphasic reactions included emergency department revisits
c. Several studies with wide ranging 95% Confidence Intervals

Figure Q2a2. Use of H1 and H2 blockers among patients with biphasic versus monophasic outcomes

H1 antihistamines



H2 antihistamines



Key results (Q2b)

Premedication for chemotherapy was evaluated by outcome of hypersensitivity reaction or infusion related reaction. Given heterogeneity of premedication, specific analysis of premedication variant strategies was not performed. Very low-quality 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). The test for heterogeneity yielded a statistically significant difference between studies (P=0.002; I^2 =64.0%). Additional sensitivity analyses including Jung 2014 (229), which evaluated pre-mediation for rituximab in patients with B cell malignancy, generated an OR of 0.45, 95% CI 0.34-0.6).

Table Q2b: Should Antihistamine and/or Glucocorticoid Premedication Be Used To Prevent Index Hypersensitivity/Infusion Reactions to Chemotherapy?

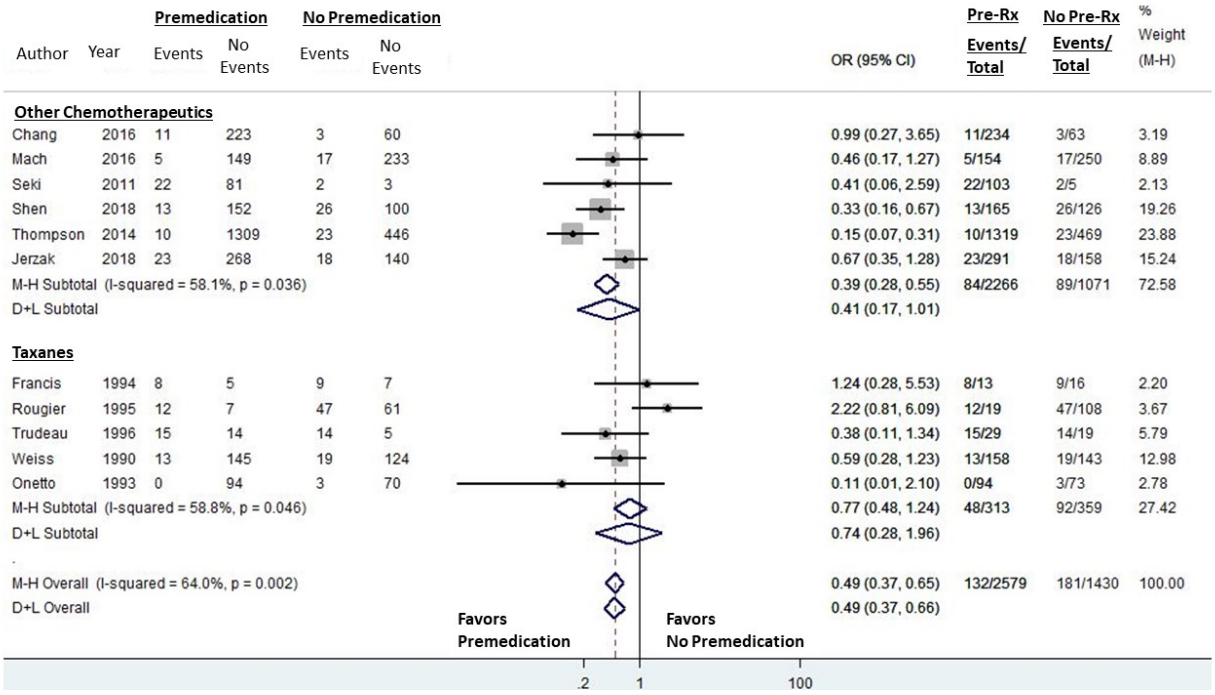
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Premedication	No Premedication	Relative (95% CI)	Absolute (95% CI)		
Rate of Premedication Use in Subjects with or without reactions to chemotherapy												
9	observational studies	serious [a]	serious [b]	serious [c]	serious [d]	none	132/2579 (5.1%)	180/1429 (12.6%)	**OR 0.49** (0.37 to 0.66)	**60 fewer per 1,000** (from 75 fewer to 39 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. some inconsistency in protocol design could affect outcome assessments
b. Moderate heterogeneity identified in meta-analysis
c. Studies evaluated non-selected patient populations without identified risk factors. Various protocols for premedication were evaluated. The relevance of findings to specific at risk populations is unclear.
d. Several studies with wide ranging 95% Confidence Intervals

Figure Q2b: Forest Plot of Chemotherapy Studies



Events = Hypersensitivity or Infusion Related Reactions; **Premedication** = Glucocorticoids and/or Antihistamines; **Odds Ratio** = Displaying the odds of hypersensitivity reactions with premedication compared to without premedication

Key results (Q2c)

Very low-quality evidence suggests that glucocorticoid and/or antihistamine premedication does not provide benefit in terms of reducing the risk for hypersensitivity reactions either patients with prior RCM reactions (RR 1.07 95% CI 0.67-1.71). The test for heterogeneity yields a statistically significant difference between studies ($P<0.001$; $I^2=93\%$). It is important to note that specific evaluation of patients with prior severe delayed onset allergic reactions tor 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 (DRESS), and vasculitis, with fatalities reported. (230-238) For instance, although iodixanol is a low-osmolar nonionic dimer delayed T-cell mediated have been described.(232) While skin testing with delayed readings at 48 and 72 hours may play a role in identifying non-cross reactive agents (232), there remains uncertainty as to whether such an approach is necessary when compared to simply choosing a non-cross reactive RCM for presumed T cell mediated severe delayed onset reactions. (42) Similarly, the necessity of other measures to prevent recurrent severe delayed reactions have included IVIG, desensitization, and cyclosporine is unknown.(239-241) A simple approach was recently proposed by Macy who reviewed RCM hypersensitivity reactions and contrasted Group A RCM agents (which include the low-osmolor monomers iopamidol, iomeprol, iversol, iohexol and low-osmolar dimer iodixanol) from Group B (including the low-osmolar monomer iobitridol and low-osmolar dimer ioxaglate), Group C (high-osmolar ionic monomer amidotrizoate/diatrizoatea), and ungrouped agents (low-osmolar monomers iopramide, iopamidol, iothalamate), suggesting that glucocorticoid premedication begun one day before the procedure (and continued for five 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).(42) The optimal approach to patients with delayed severe RCM reactions requires further study.

Table Q2c: Should Antihistamine and/or Glucocorticoid Premedication Be Used To Prevent Recurrent Hypersensitivity Reactions Radiocontrast Media?

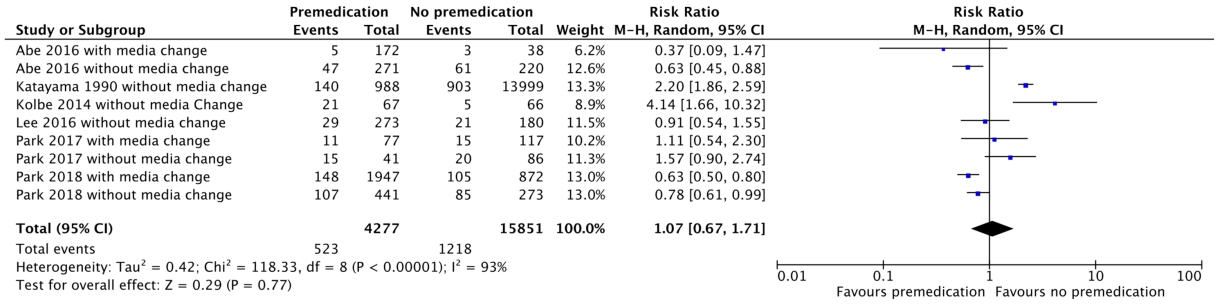
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Premedication	No Premediction	Relative (95% CI)	Absolute (95% CI)		
Subsequent RCM reaction with or without premedication												
6	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	523/4277 (12.2%)	1218/15851 (7.7%)	**RR 1.07** (0.67 to 1.71)	**5 more per 1,000** (from 25 fewer to 55 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Due to observations study design sources of bias could affect effect estimate
b. Significant heterogeneity among studies
c. Several studies with wide ranging 95% Confidence Intervals

Figure Q2c. Forest Plot: All Included Studies



Key results (Q2d)

Very low certainty evidence suggests that glucocorticoid and/or antihistamine premedication also does not provide benefit in terms of reducing the risk for hypersensitivity reactions in subjects receiving monoclonal antibodies, allergen immunotherapy, or other (non-chemotherapy, non-RCM) medications (RR 0.74, 95% CI 0.49-1.11). However, the subgroup analysis of allergen immunotherapy did demonstrate a significant benefit of premedication, driven largely by studies of premeditation in accelerated allergen immunotherapy schedules, which present greater risks of anaphylaxis (RR 0.62, 95% CI 0.41-0.94). This benefit may relate to a high baseline rate of systemic reactions. For example, Portnoy 1994 (222) reported a double-blind placebo controlled trial of rush immunotherapy in 22 allergic children aged 6 to 18 years of age. Systemic reactions

(inclusive of isolated urticaria) were reported in 27% of subjects treated with H1 antagonist, H2 antagonists, and glucocorticoids compared with 73% of placebo subjects. One of 11 children experienced anaphylaxis in the treatment group compared to 3/11 in the placebo group. However, if additional consideration was given to patients receiving rush immunotherapy 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% vs 45%, respectively. (222) Additional sensitivity analysis performed using this modified definition of anaphylaxis from Portnoy 1994 and did not significantly change results. Exclusion of the RIT patients from Portnoy 1994 and Hejjaoui 1990 resulted in an OR of 0.65 (95% CI, 0.41-1.04) for patients in the immunotherapy subgroup.

Table Q2d: Should Antihistamine and/or Glucocorticoid Premedication Be Used To Prevent Hypersensitivity Reactions to Monoclonal Antibodies, Allergen Immunotherapy, or Other Agents?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allergic Reaction	No Reaction	Relative (95% CI)	Absolute (95% CI)		
Rate of investigator defined allergic reactions												
16	observational studies	serious [a]	serious [b]	serious [c]	serious [d]	all plausible residual confounding would reduce the demonstrated effect	224/9298 (2.4%)	377/15603 (2.4%)	**RR 0.74** (0.49 to 1.11)	**6 fewer per 1,000** (from 12 fewer to 3 more)	⨁◯◯◯ VERY LOW	IMPORTANT

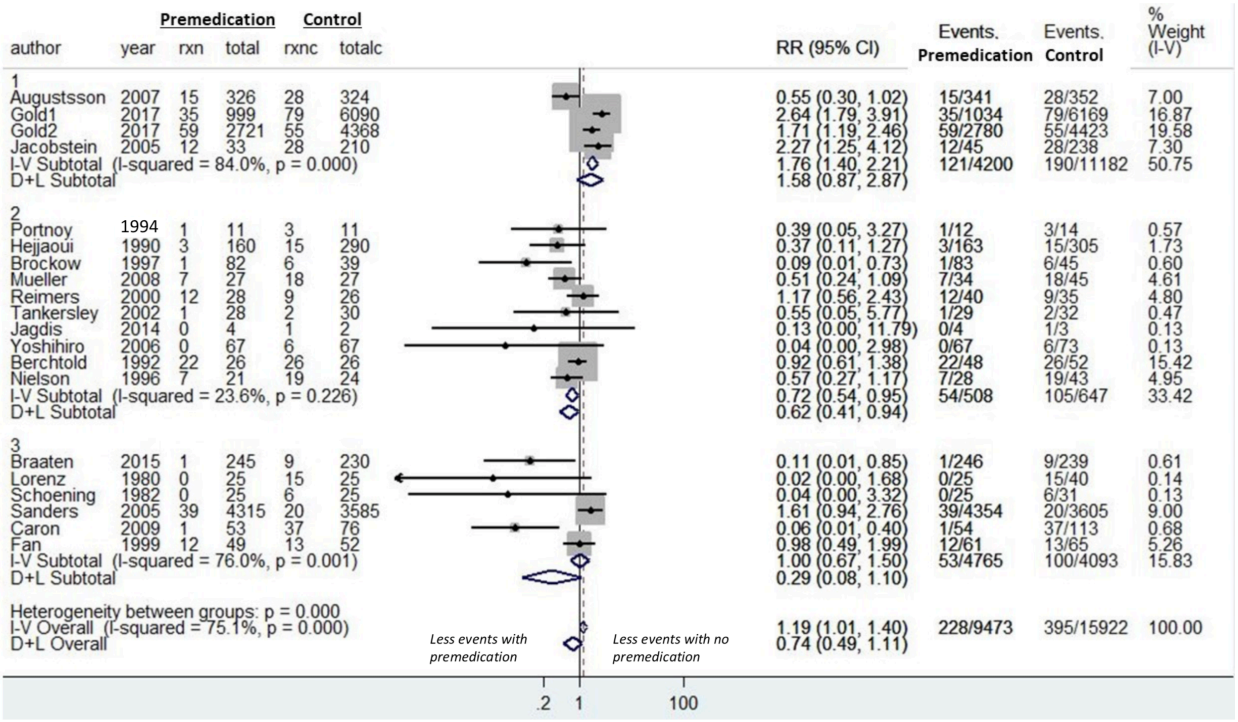
CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Risk of bias across studies related to lack of blinding, lack of randomization, potential confounding by severity of presentation, practice variation
b. Significant heterogeneity across studies
c. Significant degree of heterogeneity in outcomes reported
d. Several studies with wide ranging 95% Confidence Intervals

Figure Q2d Use of premedication among patients with at risk for allergic reactions

1283



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EVIDENCE TO RECOMMENDATIONS: QUESTION #2

Question: In adults and children, should antihistamines or corticosteroids be used to prevent anaphylactic reactions?	
POPULATION:	Adults and children with anaphylaxis
INTERVENTION:	Use of antihistamines and/or corticosteroids to prevent anaphylactic reactions
COMPARISON:	Not using antihistamines and/or corticosteroids for the purpose of preventing anaphylaxis
MAIN OUTCOMES:	Prevention of anaphylaxis
SETTING:	Emergency Department, out-patient, medical office, community

PERSPECTIVE:	Clinicians and patients want to know if anaphylaxis can be prevented with antihistamines and/or corticosteroids.
BACKGROUND:	Clinicians frequently recommend antihistamines and/or corticosteroids to prevent anaphylaxis. Based on practice experience with RCM premedication, premedication is often used for chemotherapy, monoclonal antibody infusions, and allergen immunotherapy. However, the benefit of antihistamines and/or corticosteroids premedication for RCM, as well as each of these other settings, is uncertain. In addition, there is uncertainty if antihistamines and/or corticosteroids prevent biphasic anaphylaxis recurrence following resolved anaphylaxis of any cause.
CONFLICT OF INTERESTS:	None

1287 CLINICAL STATEMENT

	Very low-certainty evidence suggests that treatment with corticosteroids, 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 monoclonal antibody without a prior history of anaphylaxis, or in patients with a history of anaphylaxis to RCM receiving an alternative low or iso-osmolar non-ionic RCM agent.

1288

1289 ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes • **Yes** ○ Varies ○ Don't 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. The prevalence of fatal anaphylaxis is between 0.47 to 0.69 per million persons and 0.25%-0.33% of ED visits or hospitalizations.(9, 27, 29) Anaphylaxis prevention strategies have used antihistamines and corticosteroids 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,	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.

	allergen immunotherapy, and others)	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial • **Small** ○ Moderate ○ Large ○ Varies ○ Don't know	The JTFPP analysis did find a non-significant trend to prevention of biphasic anaphylaxis with corticosteroids (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 0.8-1.83). Premedication did show benefit with rush allergen immunotherapy (RIT), with a NNT of 19 (range 12 to 119) at an anaphylaxis patient expected event rate (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 0.46, 95% CI 0.35,0.6), but not monoclonal antibody (RR 1.58,	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

	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 monoclonal antibody therapy. Within the confidence limits, in the setting of alterative low osmolar or iso-osmolar RCM in patients with prior RCM reactions, the NNT would be 36 under the most optimistic scenario of premedication benefit.	only manifestation of an allergic response.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large • **Moderate** ○ Small ○ Trivial ○ Varies ○ Don't know	Corticosteroids and first-generation antihistamines may have adverse effects, particularly in certain more vulnerable populations, which may include sedation and confusion, particularly in the elderly.(242-246) Side-effects of these therapies may confound recognition, assessment, and/or	Additional medical complexity of these treatments may create obstacles to efficient healthcare delivery.

	treatment of anaphylaxis. It is unlikely that antihistamines and corticosteroids 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?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **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 corticosteroids 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?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **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 corticosteroids and/or antihistamines; however, with the degree of uncertainty identified in the JTFPP analysis, value-judgements 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 corticosteroid or antihistamine therapy in some circumstances.	Patients may choose to defer more complex treatment protocols that involve corticosteroids 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?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison • **Probably favors the comparison** ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies Don't know	Sedation from 1st generation antihistamines could be mitigated with the use of a 2nd generation antihistamine. In patients without comorbidities, the rare use of oral or intravenous corticosteroids carries a low, overall risk, especially in comparison to anaphylaxis. While rare severe adverse events may occur from 1st generation antihistamine or glucocorticoid (e.g., 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 corticosteroids 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 corticosteroids and/or antihistamines is the risk for delay in treatment with epinephrine.

Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs • **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't 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 20-30 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)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High • **No included studies**	There is uncertainty in the evidence of required resources as randomized controlled trials of corticosteroid and antihistamine premedication are sparse. While treatment protocols of corticosteroids and antihistamines to prevent biphasic anaphylaxis and prevention of monoclonal antibody anaphylaxis may vary, strategies for RCM pre-medication are more standardized.(42) Portnoy et al began pre-treatment one day prior to RIT.(222)	There is some uncertainty as to whether more or fewer resources would be required for observation, given that the current use of antihistamines and corticosteroids 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?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison	If observation time is unaffected, there would be a minimal reduction in cost from omitting treatment with antihistamines and corticosteroids to prevent biphasic anaphylaxis. However, if	Cost-effectiveness would likely be sensitive to rates of anaphylaxis, hospitalization, and fatality risk reduction.

○ Probably favors the intervention ○ Favors the intervention ○ Varies Don't know • **No included studies**	observation time was increased due to the withholding of these medications, there could be increased overall costs. 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 corticosteroid premedication are small, and with benefit evident in at least one RCT the premedication approach is likely cost-effective.(222) In addition, one small study suggested benefit from antihistamine premedication before conventional immunotherapy.(43) in the outpatient setting—as these medications are low cost.	
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced • **Probably no impact** ○ Probably increased	Increased medical complexity may increase disparities in health equity. In rural settings, access to 24-hour pharmacies may limit	Oral antihistamines and oral corticosteroids are relatively inexpensive, so it is possible in some

○ Increased ○ Varies ○ Don't know	immediate availability of antihistamine and corticosteroid 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 are is uncertain. Patients with poor health literacy may be at risk for incorrect dosing of home regimens as preventative anaphylaxis strategies become more complicated.	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 corticosteroids, the effect on health equity could be more pronounced. As such, elimination of routine use of antihistamines and corticosteroids to prevent biphasic anaphylaxis could improve health equity
Acceptability & Quality Improvement Opportunity Is the intervention acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes	Antihistamines and corticosteroids are common medications used to treat and prevent allergic reactions. While these treatments should not	The practice of treating patients experiencing anaphylaxis with antihistamines and

• **Varies** ○ Don't know	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 corticosteroids 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	corticosteroids 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.

	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 non-anaphylactic 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 upon the underlying patient expected event rate for anaphylaxis from a specific trigger.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes • **Varies** ○ Don't know	Use of antihistamines and corticosteroids by ED physicians to both treat and prevent anaphylaxis is widespread. The very 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 corticosteroids prior to monoclonal antibody treatment and in patents with prior RCM anaphylaxis receiving an	Additional high-quality evidence is needed to better inform practice as to the role of antihistamines and corticosteroids for the purpose of preventing anaphylaxis.

	alternative low or iso-osmolar agent. Patients receiving RIT may consider treatment with antihistamines and corticosteroids. While further study is needed, one study suggests possible benefit from antihistamine premedication before conventional aeroallergen immunotherapy.(43)	
Intentional Vagueness		
Yes	Due to low quality of evidence and absence of a randomized controlled trials in most settings evaluated, there remains uncertainty in the role of antihistamines and corticosteroids in the prevention of anaphylaxis.	Additional high-quality evidence is needed to better inform practice.
Role of Patient Preference		
Probably yes	Patients may feel "safer" with the use of antihistamines and/or corticosteroids, but this preference is likely to be highly influenced by counseling and education they receive from healthcare providers. The patient will need education and re-education on the signs and symptoms of anaphylaxis and on the use of epinephrine as the only first-line medication for the	Shared decision making would be appropriate in some circumstances given the absence of clear benefit in prevention of anaphylaxis with antihistamines and corticosteroids in many settings. Patient-preference sensitive care could address unwarranted

	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 corticosteroids as second-line medications following epinephrine administration. Antihistamines and corticosteroids may provide some role in treating the urticaria and pruritus occurring during anaphylaxis.	practice variation to prevent biphasic anaphylaxis, monoclonal antibody anaphylaxis, and RCM anaphylaxis prevention.
Exclusions		
Yes	Given the low quality 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 quality of evidence relating to this question is very low.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM IS A PRIORITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't 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 BENEFIT S. 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	Don't know

	JUDGEMENT						
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't 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	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

RECOMMENDATIONS:

QUESTION #1

We suggest extended observation in the ED for patients with resolved severe anaphylaxis to detect a biphasic reaction

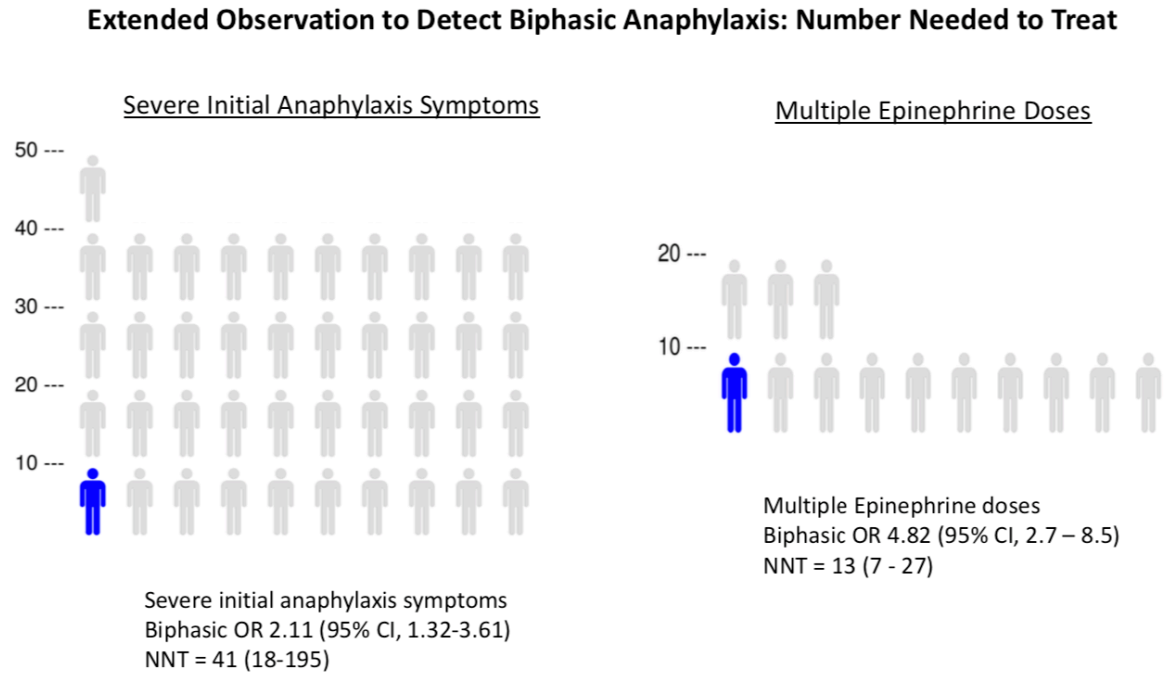
Recommendation: Conditional

Certainty of evidence: Very low

Technical statement: The JTFPP findings suggest biphasic anaphylaxis is associated with a more severe initial presentation of anaphylaxis (OR=2.11, 95% CI 1.23-3.61) or repeated epinephrine doses required with the initial presentation (OR 4.82, 95% CI 2.70-8.58). 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. A recent meta-analysis of observation times suggested 1-hour observation was associated with a 95% negative predictive value (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.(132) Based on this analysis, the incremental patient expected biphasic event rate (PEER) between asymptomatic 1-hour and $\geq$ 6-hour observation is 2.3%. Therefore, the number needed to treat (NNT) with extended observation to be able to detect one episode of biphasic anaphylaxis before discharge (Figure Q1rec) 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.(178) For patients at high risk for biphasic anaphylaxis or those with a higher risk of anaphylaxis fatality (e.g., serious medical co-morbidities), more prolonged monitoring can be cost-effective. In a recent analysis 6-hour observation was cost-effective only if it was able to provide a high-degree of protection against anaphylaxis fatality (24% fatality relative risk for extended vs 1-hour observation), and otherwise this more prolonged observation time was not cost-effective or providing superior value. (*Shaker et al. Estimation of Health and Economic Benefits of Extended Observation of Resolved Anaphylaxis: A Cost Effectiveness Analysis. Submitted).* 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 non-severe 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. Such lower risk patients would be characterized as having a very small risk of biphasic anaphylaxis (<5%) following discharge associated with a less than 50% fatality risk reduction from extended observation. Therefore, the JTFPP suggests than in in patients with a severe initial presentation of anaphylaxis (for example, those with hypotension, wide pulse pressures, multiple doses of epinephrine, or other markers of severity) extended observation be considered following resolution of the index episodes without recurrence. 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.(54) In some circumstances a role may exist for shared decision making tools around the duration of prolonged ED observation.

Figure Q1R



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 symptoms, and use of glucocorticoids in children. Some of these associations may be confounded by anaphylaxis severity and practice variation, with very low quality 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 more than one dose of epinephrine or corticosteroids 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 if this is due to having more severe anaphylaxis or if 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. There was no signal that any medication used for treatment of initial anaphylaxis reduced the risk of biphasic anaphylaxis. However, while the timing of epinephrine administration following the

onset of symptoms of anaphylaxis in relationship to the subsequent development of biphasic anaphylaxis was not part the meta-analysis, 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 pre-emptive epinephrine before symptom onset is generally not a cost-effective strategy.(247)

Prompt and adequate treatment of anaphylaxis appears central to reducing biphasic anaphylaxis risk. The implications for the clinician, based upon this systematic review and meta-analysis is that the patient presenting with severe anaphylaxis and/or requiring more aggressive treatment (e.g., more than one 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

We suggest against glucocorticoids or antihistamines as an intervention to prevent biphasic anaphylaxis

Certainty of evidence: Very low
Strength of recommendation: Conditional

Technical comment: As a secondary therapy, antihistamines and corticosteroids may be considerations in anaphylaxis treatment.(41) In particular, antihistamines may treat urticaria and itching to improve comfort during anaphylaxis, but if used prior to epinephrine administration could lead to a delay in first line treatment of anaphylaxis. Furthermore, glucocorticoids can also effectively prevent delayed urticaria which could confound the assessment and treatment of anaphylaxis. The JTFPP analysis did not identify significant benefit in prevention of biphasic anaphylaxis from either H1 antihistamines (OR 0.71, 95% CI 0.47-1.06), H2 antihistamines (OR

1.21, 95% CI 0.8-1.83), or glucocorticoids (OR 0.87, 95% CI 0.74-1.02). Evaluation of the number of patients needed to treat (NNT) to potentially reduce biphasic anaphylaxis rates is useful:(178)

H1 antihistamines: At a biphasic anaphylaxis patient expected event rate (PEER) of 5%, the number needed to treat (NNT) for H1 antihistamines is 72 to prevent one episode of biphasic anaphylaxis. At a biphasic anaphylaxis PEER of 20%, the NNT (to prevent one case of biphasic anaphylaxis) for H1 antihistamines is 20. However, neither of these values was certain and confidence in the benefit of treatment is low, with an association of increased biphasic anaphylaxis rates within the confidence estimate.

H2 antihistamines: At a biphasic anaphylaxis PEER of 5% and 20%, H2 antihistamine use was 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 was uncertain.

Glucocorticoids: At a biphasic anaphylaxis PEER of 5%, the number needed to treat (NNT) for glucocorticoids is 161 to prevent one case of biphasic anaphylaxis (and 47 at a biphasic anaphylaxis PEER of 20%). Again, neither of these values was 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 be needed to further inform this practice. 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.(41) The use of antihistamines may be associated with side-effects that could confound assessment of anaphylaxis, such as altered level of consciousness with 1st 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 vs. no benefit from supplemental therapies.

We suggest administering glucocorticoids and/or antihistamines to prevent anaphylaxis or infusion related reaction when indicated for specific agents in chemotherapy protocols.

Certainty of evidence: Very low

Strength of recommendation: Conditional

Technical Comment: The JTFPP analysis did not identify a significant change in rates of anaphylaxis from premedication with glucocorticoids and/or antihistamines before chemotherapy or monoclonal antibody treatment. The use of premedication was associated with a non-signficant increased rate of hypersensitivity reactions for chemotherapy (OR 1.34, 95% CI 0.69-2.61) and monoclonal antibody therapy (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 experience anaphylaxis from these agents was not evaluated. Evaluation of the number of patients needed to treat (NNT) to produce benefit (positive number) or harm (negative number), as discussed below, is useful:

Chemotherapy Predication: At an anaphylaxis PEER of 12.9%, premedication was associated with a decreased risk of anaphylaxis. The NNT was 15 (range, 13 – 19).

Monoclonal Antibody Premedication: At an anaphylaxis PEER of 2%, premedication was not associated with a decreased risk of anaphylaxis. However, the degree of certainty that therapy did not provide any possibility of benefit was uncertain.

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 a monoclonal antibody, it would be reasonable to discontinue the premedication following tolerance of the 1st or 2nd course of treatment.

We suggest against routinely administering glucocorticoids and/or antihistamines to prevent anaphylaxis due to iso-osmolar, non-ionic radiocontrast media agent

Certainty of evidence: Very low
Strength of recommendation: Conditional

Technical Comment: The JTFPP analysis did not identify significant benefit from the use of premedication prior to the RCM to prevent anaphylaxis (RR 1.07 95% CI 0.67-1.71). The absence of benefit of premedication in patients with prior immediate hypersensitivity reactions 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.(42) Risk of bias, inconsistency, imprecision, and indirectness attenuate the confidence in this guidance.

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

Given the diversity of clinical circumstances evaluated and low confidence in the literature base, higher quality 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 or use of beta-blockers, prior severe anaphylaxis), although evidence is lacking to 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.

We suggest in favor of the administration of glucocorticoids and/or antihistamines as an intervention to prevent anaphylaxis in patients undergoing aeroallergen rush immunotherapy (RIT)

Certainty of evidence: Very low

Strength of recommendation: Conditional

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, RR 0.62, 95% CI 0.41- 0.94). In the study by Portnoy et al, patients received H1 and H2 antagonists and oral corticosteroids for 3 days, beginning one day before the 2-day rush immunotherapy protocol.(222) The evidence base for premedication before conventional aeroallergen immunotherapy is limited; however, one study by Ohashi Yoshirio et. al. suggested some benefit with fexofenadine pretreatment 2 hours before conventional immunotherapy using cedar pollen or dust mite allergens.(43) The evaluation of the number of patients needed to treat (NNT) to prevent one episode of anaphylaxis is useful:

RIT Premedication: The NNT to prevent one 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. However, none of these values was certain and confidence in the benefit of treatment is low, with an association of increased anaphylaxis rates within the confidence estimate.

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 (e.g., in situations associated with higher rates of systemic reactions). Given the diversity of clinical circumstances evaluated and low confidence in the literature base, higher quality 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 evidence is lacking to support this practice.

Additional Good Practice Statements

Good Practice Statement # 1: Administer epinephrine as the only 1st 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 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, the use of epinephrine auto-injectors, and referral to an allergist. Of note, there may be some circumstances where self-injectable epinephrine is deferred (i.e., resolved anaphylaxis and drug trigger with high likelihood of successful avoidance) and patient-preference sensitive decision making may play a role in some circumstances.

Limitations

Unfortunately, the quality of evidence around supplemental therapies in anaphylaxis management is very low. While early epinephrine is recommended by the JTF when anaphylaxis is recognized in any setting, whether or not clinicians should 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. It is important to distinguish biphasic anaphylaxis (with an interval period of clear resolution) from protracted anaphylaxis

Our analysis is similar to results obtained by Ellis et al in which corticosteroids demonstrated a non-significant inverse trend with biphasic anaphylaxis (35); however caution is warranted in interpretation of these findings – particularly given the opposite association of corticosteroids 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 if these agents prevent biphasic anaphylaxis. The role of glucocorticoid and/or antihistamine premedication in more high-risk settings (such as rush immunotherapy) may be significant, and until additional evidence better informs practice, premedication may be appropriate is circumstance where a high risk of anaphylaxis exists. The absence of benefit of premedication in patients with prior immediate hypersensitivity reactions to RCM who are receiving a different low or iso-osmolar agent is consistent with prior literature. (42); 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. 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. (248) The JTF 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.

Conclusion

Anaphylaxis is a multi-system allergic emergency. Early recognition and prompt administration of intramuscular epinephrine remain the cornerstone of management. 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 is very low quality and when evaluated on the whole does not offer clear support for this practice. 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 these therapies prevent anaphylaxis in patients with a history of RCM anaphylaxis or in adult patients receiving monoclonal antibody without prior anaphylaxis.

Future Directions

At present it is unclear 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 RCM agent or in patients receiving monoclonal antibody who have not previously experienced drug hypersensitivity. However, because the evidence synthesis contained in this report is derived from low-quality, non-randomized trials, further research evaluating common practices in anaphylaxis treatment and prevention is urgently needed. Evaluation of premedication in children receiving chemotherapy and the use of premedication in subjects treated with chemotherapy desensitization would also provide valuable insight, in addition to understanding the role of premedication in patients in situations with very high risks of anaphylaxis.

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APPENDIX

eQ1

Studies <u>Not</u> Included in this Review with Exclusion Rationale (in Alphabetical Order)

Authors (YYYY)	Reason for exclusion
Civelek et al. (2016)	Characteristics of biphasic reactions not described
Grunau et al. (2015)	Population used in previous study
Jarvinen et al. (2009)	Characteristics of biphasic reactions not described
S. Lee et al. (2014)	Included study already includes this patient population
Liew et al. (2013)	Characteristics of biphasic reactions not described
Nagano et al. (2013)	Not in English
Penney et al. (2015)	Characteristics of biphasic reactions not described
Popa et al. (1984)	Case series with no control group to compare
Srivastava et al. (2014)	Characteristics of biphasic reactions not described
Topal et al. (2013)	No biphasic patients

Method Used for Appraisal and Synthesis

The Cochrane Collaborative computer program, Review Manager (Higgins & Green, 2011)[a] was used to synthesize the 32 included studies. GRADEpro GDT (Guideline Development Tool) is the tool used to create the Summary of Findings Tables for this analysis.

[a]Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cohcrane Collaboration, 2011.
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Table eQ1-1

Summary of Outcomes

Outcome	Studies	Participants	Sensitivity (95% CI)	Specificity (95% CI)	Effect Estimate (Peto Odds Ratio, 95% CI)
History					
History of Allergy	7	2589	64% (56, 72)	48% (47, 51)	1.05 [0.71, 1.57]
History of Anaphylaxis	7	2555	76% (69, 82)	79% (78, 81)	1.26 [0.88, 1.80]
History of Asthma	10	3121	34% (28, 41)	67% (65, 68)	1.06 [0.76, 1.49]
Triggers					
Food Trigger	20	4352	65% (58, 72)	59% (57, 60)	0.89 [0.68, 1.17]
Food Trigger <=18 years of age	6	1057	58% (48, 67)	42% (39, 45)	0.95 [0.63, 1.46]
Food Trigger >18 years of age	7	1779	29% (18, 42)	62% (59, 64)	0.68 [0.40, 1.17]
Food Trigger Mixed Age	8	1516	34% (24, 44)	66% (63, 68)	0.99 [0.62, 1.58]
Drug Trigger	18	4069	21% (16, 27)	77% (75, 78)	1.10 [0.79, 1.54]
Drug Trigger <=18 years of age	5	996	16% (10, 25)	85% (82, 87)	2.35 [1.16, 4.76]*
Drug Trigger >18 years of age	5	1556	29% (18, 41)	74% (71, 76)	0.96 [0.54, 1.70]
Drug Trigger Mixed Age	8	1517	21% (16, 27)	77% (75, 78)	0.82 [0.49, 1.37]
Insect/Venom Trigger	13	2852	9% (5, 13)	86% (85, 88)	0.72 [0.45, 1.16]
Unknown Trigger[a]	21	4275	21% (16, 26)	84% (83, 85)	1.63 [1.14, 2.33]*
Symptoms					
Cutaneous Symptoms[b]	6	1949	94% (87, 97)	16% (14, 18)	2.54 [1.25, 5.15]*
Itching Symptoms	7	1888	60% (50, 70)	46% (43, 48)	1.44 [0.95, 2.16]
Hive	9	2536	54% (45, 63)	47% (45, 49)	1.11 [0.73, 1.67]
Respiratory Symptoms	8	1956	78% (70, 85)	47% (45, 49)	1.24 [0.75, 2.04]
Wheezing Symptoms	7	2707	25% (17, 34)	75% (73, 76)	0.95 [0.60, 1.52]
Dyspnea Symptoms[c]	6	1841	33% (25, 43)	53% (50, 55)	0.60 [0.38, 0.96]*
Hypotension Symptoms	10	2783	13% (7, 19)	85% (84, 86)	1.39 [0.81, 2.39]
Hypotension <=18 years of age	2	591	5% (1, 12)	97% (96, 99)	3.28 [0.71, 15.12]
Hypotension >18 years of age	3	994	14% (5, 27)	77% (75, 80)	0.87 [0.33, 2.28]

Hypotension Mixed Age	5	1198	23% (14, 36)	86% (84, 88)	1.50 [0.73, 3.09]
GI Symptoms	9	2399	34% (26, 42)	72% (70, 74)	0.74 [0.51, 1.08]
Wide Pulse Pressure[d]	2	1356	37% (28, 47)	80% (78, 82)	2.11 [1.32, 3.37]*
Severe Initial Symptoms[e]	5	724	51% (40, 62)	60% (57, 65)	2.11 [1.23, 3.61]*
Treatment					
Steroids <=18 years of age	7	1203	68% (59, 77)	42% (39, 45)	1.55 [1.01, 2.38]*
Bronchodilator	13	3819	28% (23, 35)	71% (69, 73)	1.10 [0.81, 1.49]
Epinephrine	21	4643	80% (75, 84)	28% (27, 30)	1.19 [0.89, 1.59]
Epinephrine <=18 years of age	7	1188	68% (59, 77)	42% (39, 45)	1.31 (0.84, 2.05]
Epinephrine >18 years of age	8	2087	88% (79, 95)	21% (19, 23)	1.16 [0.64, 2.08]
Epinephrine Mixed Age	6	1368	87% (78, 93)	28% (25, 30)	1.08 [0.66, 1.76]
>1 Epinephrine[f]	5	1584	25% (18, 33)	91% (89, 93)	4.82 [2.70, 8.58]*
Epinephrine prior to ED Visit	2	398	32% (23, 42)	55% (49, 60)	0.99 [0.58, 1.70]

Notes

*Significant OR

[a]Retrospective data, Included studies with no reported follow up or follow up limited to 24hours, moderate heterogeneity I^2=45

[b]Retrospective data, definition of cutaneous was not standard, included studies with no reported follow up or limited to 24hours, low number of events, moderate heterogeneity I^2=43%

[c]Retrospective data, substantial heterogeneity I^2=71%, low number of events

[d]Retrospective data, low number of events

[e]Retrospective data, low number of events, follow up not reported or limited to 24hours, different definitions of severity

[f]Retrospective data, low number of events, follow up not reported or limited to 24hours, substantial heterogeneity I^2= 89%

AUTHOR	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting	Overall
(Alqurashi, Stiell et al. 2015)	Moderate	Low	Low	Low	Moderate	Low	Moderate
(Brazil and MacNamara 1998)	Moderate	Low	Moderate	High	High	Low	High
(Confino-Cohen and Goldberg 2010)	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Moderate
(Ellis and Day 2007)	Low	High	Low	Low	Moderate	Low	Moderate
(Grunau, Li et al. 2014)	Moderate	Low	Low	Low	Moderate	Low	Moderate
(Inoue and Yamamoto 2013)	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
(Jirapongsananuruk, Bunsawansong et al. 2007)	High	High	Low	Moderate	Moderate	Low	High
(Ko, Kim et al. 2015)	Moderate	Low	Low	Low	Moderate	Low	Moderate
(Lee and Greenes 2000)	High	Moderate	Low	Low	Moderate	Low	High
(Lertnawapan and Maek-a-nantawat 2011)	Moderate	Low	Moderate	Low	Moderate	Low	Moderate
(Manivannan, Hess et al. 2014)	Moderate	Low	Low	Low	Moderate	Low	Moderate
(Manuyakorn, Benjaponpitak et al. 2015)	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate
(Mehr, Liew et al. 2009)	High	Moderate	Low	Low	Moderate	Low	Moderate
(Noone, Ross et al. 2015)	High	Moderate	High	Moderate	Moderate	Low	High
(Orhan, Canitez et al. 2011)	High	High	Low	Low	Moderate	Low	High
(Rohacek, Edenhofer et al. 2014)	Moderate	Low	Low	Low	Moderate	Low	Moderate
(Smit, Cameron et al. 2005)	Moderate	Low	Low	Low	Moderate	Low	Moderate
(Sricharoen, Sittichanbuncha et al. 2015)	High	High	Low	Low	Moderate	Low	High
(Stark and Sullivan 1986)	High	Low	Moderate	Moderate	Moderate	Low	High
(Vezir, Erkocoglu et al. 2013)	Moderate	Moderate	Low	Moderate	Moderate	Low	Moderate
(Brady Jr, Luber et al. 1997)	Moderate	Low	Low	Low	Moderate	Low	Moderate

(Calvani, Cardinale et al. 2011)	High	Moderate	Moderate	Low	Moderate	Low	High
(Cianferoni, Novembre et al. 2001)	High	High	Moderate	Low	Moderate	Low	High
(Sampson, Mendelson et al. 1992)	High	High	Moderate	Moderate	Moderate	High	High
(Yang, Lee et al. 2008)	High	High	Moderate	Low	Moderate	Low	High
(Poachanukoon and Paopairochanakorn 2006)	Moderate	Moderate	Moderate	Low	Moderate	Low	Moderate
(Brown, Stone et al. 2013)	Low	Moderate	Low	Low	Low	Low	Moderate
(Douglas, Sukenick et al. 1994)	Moderate	High	Low	Low	Moderate	Moderate	High
(Scranton, Gonzalez et al. 2009)	Moderate	Moderate	Low	Low	Low	Low	Moderate
(Lee, Peterson et al. 2017)	Moderate	Low	Low	Low	Low	Low	Moderate
(Lee, Garrett et al. 2013)	Moderate	Moderate	Moderate	Low	Moderate	Low	Moderate

Table eQ1-2
Risk of Bias (Quality in Prognosis Studies)

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2353 **Included Studies:**

Author	Year	Outcome	Definition of outcome	Timing of Measurement	Comment	Cochrane Risk of Bias Assessment
Rohacek	2014	Comparison tx across two groups	Appearance of any sxs such as rash, pruritus, mucosal swelling, resp, GI, circ. Compromise, after complete resolution of the primary reaction)	10 days	Significantly greater use of H1 antihistamines and glucocorticoids steroids used in monophasic reactions	Moderate
Oya	2014	Comparison tx across two groups	Uniphasic response followed by an asymptomatic period of 1hr or more, and then	Up to 8 days	Significantly greater use of glucocorticoids steroids used in monophasic reactions	Moderate

			subsequent return of symptoms without further exposure to an antigen			
Guiot	2017	Comparison tx across two groups	Emergency Department Revisit	7 days	Rate of steroid use between groups not significantly different	Moderate
Ellis	2007	Comparison tx across two groups	Second reaction had to meet the same definition as the initial anaphylaxis definition (recurrence of urticaria or another rash was not sufficient)	No later than 72hrs after ED visit and no less than 48hrs	Rate of steroid use between groups not significantly different	Moderate
Lertnawapan	2011	Comparison tx across two groups	Cases of anaphylaxis meeting NIAID criteria	Mean length of stay was 1.2 days	Delay in epinephrine administration increased risk for biphasic reaction; however, use of glucocorticoids was not a significant risk factor	Moderate

Smit	2005	Comparison tx across two groups	Symptoms of anaphylaxis included hypotension, severe cutaneous manifestation, respiratory or airway compromise, cardiovascular compromise, syncope, or loss of consciousness. Biphasic reactions included any reaction occurring after initial treatment and complete resolution of symptoms.	Median inpatient stay was 1.45 days (range 0.33-21.57); ED Observation 10.6hrs (range 1.4-99). All patients followed for 5days.	Rate of steroid use between groups not significantly different.	Moderate
Stark	1986	Comparison tx across two groups	Anaphylaxis based on symptoms including acute hypotension, laryngeal	Up to 8 days.	Two deaths reported in biphasic/protracted group.	Moderate

			edema, lower respiratory obstruction with flushing, urticaria, angioedema or evidence of specific IgE			
Michelson	2015	Comparison tx across two groups	Prolonged length of stay used surrogate marker of biphasic anaphylaxis.	≥ 2 days	Glucocorticoids inversely associated with prolonged length of stay. Prolonged length of stay associated with increasing age, complex chronic conditions, previous diagnosis of asthma, bronchodilator use, oxygen use, and ICU admission	Moderate
			Emergency Department Revisit	3 days	Glucocorticoids not significantly associated with odds of ED revisit.	Moderate

Lee	2000	Comparison tx across two groups	Biphasic reactions were defined as worsening of symptoms requiring any new therapy after resolution of anaphylaxis had occurred	Median length of stay 19 hrs (range 6 hr-143 hrs)	Rate of steroid use between groups not significantly different. Two deaths reported. Biphasic reactions associated with median time to epinephrine use of 190 minutes vs 48 minutes for those without biphasic reactions.	Moderate
Mehr	2009	Comparison tx across two groups	Anaphylaxis defined as multisystem allergic reaction with clinical features including respiratory and/or cardiovascular involvement per NIAID guidelines. Biphasic reaction defined as an initial anaphylactic	$\geq$ 6 hours	Rate of steroid use between groups not significantly different. Biphasic reactions associated with > 1 dose of epinephrine and fluid bolus. One death reported.	Moderate

			reaction with a period of resolution for > 1 hr during which there were no new symptoms or treatment administered followed by a 2nd phase anaphylactic or non-anaphylactic allergic reaction, not caused by antigen re-exposure			
Poachanukoon	2006	Comparison tx across two groups	Anaphylaxis defined as symptoms of generalized mediator release including flushing; pruritus / parathesias of lips, axilla, hands, or feet		Rate of steroid use between groups not significantly different between groups. Median time to initial dose of epinephrine was 82 minutes in monophasic group and 263 minutes in biphasic group	Moderate

			generalized pruritus; urticaria or angioedema; conjunctivitis or chemosis, including at least one symptom involving the oral and gastrointestinal, respiratory, or cardiovascular symptoms.			
Lee	2013	Comparison tx across two groups	Biphasic reaction defined as recurrence of sxs after resolution of initial anaphylactic reaction	48hrs	Rate of steroid use between groups not significantly different between groups	Moderate
Granau	2015	Comparison tx across two groups	Emergency department revisits in subjects meeting criteria for anaphylaxis by World	7 days	Re-analysis performed based on Emergency department revisits in patients meeting criteria for anaphylaxis	Moderate

			Allergy Organization definition			

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Author	Year	Outcome	Context	Definition of outcome	Comment	Risk of Bias
Alqurashi	2015	Comparison tx across two groups	Pediatric patients seen in the ED for anaphylaxis	NIAID criteria for anaphylaxis	Biphasic reactions associated with higher odds of steroids, H1 antihistamines, H2 antihistamines, and epinephrine	Moderate
Calvani	2011	Comparison tx across two groups	Pediatric patients with allergic reactions seen as outpatients in Italy across 29 pediatric clinics	NIAID criteria for anaphylaxis	Steroids used more often in monophasic reactions	High
Inoue	2013	Comparison tx across two groups	Children with anaphylaxis seen in an ED or allergy clinic with food challenge in Japan	NIAID criteria for anaphylaxis	Steroids, H1 antihistamines, and epinephrine used more frequently in biphasic reactions	Moderate

Manuyakorn	2015	Comparison tx across two groups	Children with anaphylaxis at a tertiary care hospital in Thailand	NIAID criteria for anaphylaxis	Steroids, H1 antihistamines, and H2 antihistamines used more frequently with biphasic reactions; epinephrine used less frequently	Moderate
Vezir	2013	Comparison tx across two groups	Children seen with anaphylaxis in Turkey	Anaphylaxis (European definition)	Steroids used more frequently with biphasic reactions	Moderate
Brady	1997	Comparison tx across two groups	Adult patients treated for anaphylaxis	Multisystem reactions involving >= 2 systems	Steroids used more frequently in biphasic reactions; H1 antihistamines used less frequently	Moderate
Scranton	2009	Comparison tx across two groups	Patients treated with epinephrine after a systemic allergic reaction to immunotherapy in Texas	Systemic allergic reaction to allergen immunotherapy	Steroids and antihistamines used less frequently in biphasic reactions	Moderate

Sricharoen	2015	Comparison tx across two groups	Patients with anaphylaxis seen in an emergency department in Thailand	Patients meeting World Allergy Organization anaphylaxis criteria	Steroid use slightly lower in biphasic; antihistamine use no different; epinephrine use slightly higher in biphasic reactions	High
Brown	2013	Comparison tx across two group	Patents seen in the ED in Australia	Urticaria with or without additional organ system involvement.	Steroid use higher in biphasic reactions	Moderate
Douglas	1994	Comparison tx across two groups	Adult and pediatric patients with urticaria or anaphylaxis	Symptoms of allergic reaction including: urticaria, laryngeal symptoms, hypotension, or respiratory arrest	Steroids, H1 antihistamines, and H2 antihistamines used more frequently with biphasic reactions; H2 antihistamines used less frequently	High

Jirapongsananuruk	2007	Comparison tx across two groups	Patients admitted for anaphylaxis in Thailand	Patients meeting World Allergy Organization anaphylaxis criteria	Steroids used more frequently with biphasic reactions	High
Lee	2017	Comparison tx across two groups	Patients with anaphylaxis seen in and ED	NIAID criteria for anaphylaxis	Steroids and epinephrine used more frequently with biphasic reactions	Moderate

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METHODOLOGICAL NOTES:

Methodological decision re: the analysis of the findings from Michelson and Grunau et al.

a. Studies were conducted in a prospective manner whereby they evaluated a cohort of patients presenting with allergy/anaphylaxis, divided them up by exposure/non-exposure (i.e. steroid vs no steroid) and then assessed the subjects for the development of several outcomes including a biphasic reaction.
b. Data was analyzed by comparing the frequency of steroid use among patients who experienced a biphasic vs those who experienced a monophasic reactions, because the majority of studies included in our review analyzed findings in this manner. Of note, a summary estimate of these two studies in isolation suggested that there was no significant difference in the incidence of biphasic events between patients prescribed steroids and those not prescribed steroids. Overall with Grunau and both Michelson Subgroups OR was 0.86 (95%CI: 0.71 – 1.04). When the analysis was limited to only patients seen in the ED and discharged (i.e. Grunau and Michelson Discharged Subgroup) the OR was 1.26 (95%CI: 0.85 – 1.85)

Measurement of Treatment Effect and Data Synthesis

- Analysis was performed using an odds ratio because the included studies approximated case-control methodology. The population was asses as either having the outcome (biphasic reaction (or equivalent such as ED revisit) or not (i.e. monophasic reaction) and then comparing steroid usage prior to the development of the outcome. (Cochrane Handbook 9.4.4.1)
- In the primary analysis, data was pooled using the Mantel-Haenszel (MH) fixed effect method. This method tends to be preferred by the Cochrane because it uses a weighting scheme that is specific to the effect measure (e.g. odds ratio). The MH method also tends to be more efficient when there are few events or studies are small (Cochrane Handbook 9.4.4.1).
- Meaningful heterogeneity was seen during the primary analysis, so the analysis using a random effects model. In order to conduct the confirmatory analysis, the Cochrane's recommended DerSimonian and Laird (DL) method was used This DL method makes use of inverse-variance (IV) whereby the model adjusts study weight according to the extent of heterogeneity reflected in the different effect estimates reported by included studies (Cochrane Handbook 9.4.3.1). The standard errors of the effect measures are modified to account for degree of heterogeneity across the included studies (i.e. Tau^2) (Cochrane Handbook 9.4.3.1).The random effects model is considered to be a more conservative approach in the event of substantial and meaningful heterogeneity because the random effect method will result in wider confidence intervals than reported using the Mantel-Haenszel fixed effect method (Cochrane Handbook 9.4.3.3).

Assessment of heterogeneity

- Heterogeneity across included studies was assessed by performing a chi-squared test and calculating a corresponding Cochran Q statistic and p-value. A p-value <0.10 was considered to be statistically significant. In addition, inconsistency was calculated across included studies and an I^2 >50% was considered to be reflective of substantial and meaningful heterogeneity (Cochrane Handbook 9.5.2). Finally, because

there is some evidence that the Breslow-Day test for homogeneity of odds ratios may be more appropriate to use in the case of unequal sample sizes, this test was used in addition to the Cochran Q statistic during the primary analysis in order to evaluate whether there were notable differences depending on the approach taken to the analysis. (Bagheri, Z. et al)

References:

1. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Collaboration 5.1.0 [updated March 2011]. Higgins JPT, Green S (editors). https://handbook-5-1.cochrane.org/front_page.htm
2. Bagheri, Z., Ayatollahi, S. M. T., & Jafari, P. (2011). Comparison of three tests of homogeneity of odds ratios in multicenter trials with unequal sample sizes within and among centers. *BMC Medical Research Methodology*, *11*, 58. http://doi.org/10.1186/1471-2288-11-58.)

Q2a2 Included Studies and Methodologic Notes

H1-antihistamine

Author	Year	Outcome	Definition of outcome	Timing of Measurement	Comment	Cochrane Risk of Bias Assessment
Ellis	2007	Comparison tx across two groups	Second reaction had to meet the same definition as the initial anaphylaxis definition (recurrence of urticaria or another rash	No later than 72hrs after ED visit and no less than 48hrs	Rate of anti-histamine H1 use between groups not significantly different	Moderate

			was not sufficient)			
Lertnawapan	2011	Comparison tx across two groups	Cases of anaphylaxis meeting NIAID criteria	Mean length of stay was 1.2 days	Delay in epinephrine administration increased risk for biphasic reaction; however, use of glucocorticoids/antihistamines was not a significant risk factor	Moderate
Smit	2005	Comparison tx across two groups	Symptoms of anaphylaxis included hypotension, severe cutaneous manifestation, respiratory or airway compromise, cardiovascular compromise, syncope, or loss of consciousness. Biphasic reactions included any reaction	Median inpatient stay was 1.45 days (range 0.33-21.57); ED Observation 10.6hrs (range 1.4-99). All patients followed for 5days.	Rate of steroid and antihistamine use between groups not significantly different.	Moderate

			occurring after initial treatment and complete resolution of symptoms.			
Oya	2014	Comparison tx across two groups	Uniphasic response followed by an asymptomatic period of 1hr or more, and then subsequent return of symptoms without further exposure to an antigen	Up to 8 days	Significantly greater use of glucocorticoids steroids used in uniphasic reactions; no significant difference in antihistamine H1 use	Moderate
Stark	1986	Comparison tx across two groups (*protracted and biphasic vs uniphasic	Anaphylaxis based on symptoms including acute hypotension, laryngeal edema, lower respiratory obstruction with flushing,	Up to 8 days.	Two deaths reported in biphasic/protracted group.	Moderate

			urticaria, angioedema or evidence of specific IgE			
Guiot	2017	Comparison tx across two groups	Emergency Department Revisit	7 days	Rate of steroid use between groups not significantly different	Moderate
Rohacke	2014	Comparison tx across two groups	Appearance of any sxs such as rash, pruritus, mucosal swelling, resp, GI, circ. Compromise, after complete resolution of the primary reaction)	10 days	Significantly greater use of H1 antihistamines and glucocorticoids steroids used in uniphasic reactions	Moderate

Mehr	2009	Comparison tx across two groups	Anaphylaxis defined as multisystem allergic reaction with clinical features including respiratory and/or cardiovascular involvement per NIAID guidelines. Biphasic reaction defined as an initial anaphylactic reaction with a period of resolution for > 1 hr during which there were no new symptoms or treatment administered followed by a 2nd phase anaphylactic or non-	≥ 6 hours	Rate of steroid use between groups not significantly different. Biphasic reactions associated with > 1 dose of epinephrine and fluid bolus. One death reported.	Moderate

			anaphylactic allergic reaction, not caused by antigen re-exposure			
Lee	2013	Comparison tx across two groups	Biphasic reaction defined as recurrence of sxs after resolution of initial anaphylactic reaction	48hrs	Rate of steroid and antihistamine use between groups not significantly different between groups	Moderate

Kawano	2017	Comparison tx across two groups	Progression to anaphylaxis from undifferentiated allergic reaction	7 days	Different study question with significant potential bias and indirectness of surrogate marker. As study design relates to prevention of anaphylaxis is patients presenting with allergic reactions. Antihistamine use associated with greater odds of epinephrine and steroid use.	Moderate

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2408 **H2-antihistamine**

Author	Year	Outcome	Definition of outcome	Timing of Measurement	Comment	Cochrane Risk of Bias Assessment
Ellis	2007	Comparison tx across two groups	Second reaction had to meet the same definition as the initial anaphylaxis definition (recurrence of urticaria or	No later than 72hrs after ED visit and no less than 48hrs	Rate of anti-histamine H1 use between groups not significantly different	Moderate

			another rash was not sufficient)			
Lertnawapan	2011	Comparison tx across two groups	Cases of anaphylaxis meeting NIAID criteria	Mean length of stay was 1.2 days	Delay in epinephrine administration increased risk for biphasic reaction; however, use of glucocorticoids/antihistamines was not a significant risk factor	Moderate
Smit	2005	Comparison tx across two groups	Symptoms of anaphylaxis included hypotension, severe cutaneous manifestation, respiratory or airway compromise, cardiovascular compromise, syncope, or loss of consciousness. Biphasic reactions included any reaction	Median inpatient stay was 1.45 days (range 0.33-21.57); ED Observation 10.6hrs (range 1.4-99). All patients followed for 5days.	Rate of steroid and antihistamine use between groups not significantly different.	Moderate

			occurring after initial treatment and complete resolution of symptoms.			
Oya	2014	Comparison tx across two groups	Uniphasic response followed by an asymptomatic period of 1hr or more, and then subsequent return of symptoms without further exposure to an antigen	Up to 8 days	Significantly greater use of glucocorticoids steroids used in uniphasic reactions; no significant difference in antihistamine H1 use	Moderate
Stark	1986	Comparison tx across two groups (*protracted and biphasic vs uniphasic	Anaphylaxis based on symptoms including acute hypotension, laryngeal edema, lower	Up to 8 days.	Two deaths reported in biphasic/protracted group.	Moderate

			respiratory obstruction with flushing, urticaria, angioedema or evidence of specific IgE			
Guiot	2017	Comparison tx across two groups	Emergency Department Revisit	7 days	Rate of steroid use between groups not significantly different	Moderate
Lin	2000	Comparison tx across two groups	Resolution of "acute allergic syndrome" within 2 hours of H1 blocker vs H1+H2 blocker	2 hours	Different study question with significant potential bias and indirectness of surrogate outcome	Low

Additional Studies

Author	Year	Outcome	Context	Definition of outcome	Comment	Risk of Bias
Alqurashi	2015	Comparison tx across two groups	Pediatric patients seen in the ED for anaphylaxis	NIAID criteria for anaphylaxis	Biphasic reactions associated with higher odds of steroids, H1 antihistamines, H2	Moderate

					antihistamines, and epinephrine	
Inoue	2013	Comparison tx across two groups	Children with anaphylaxis seen in an ED or allergy clinic with food challenge in Japan	NIAID criteria for anaphylaxis	Steroids, H1 antihistamines, and epinephrine used more frequently in biphasic reactions	Moderate
Manuyakorn	2015	Comparison tx across two groups	Children with anaphylaxis at a tertiary care hospital in Thailand	NIAID criteria for anaphylaxis	Steroids, H1 antihistamines, and H2 antihistamines used more frequently with biphasic reactions; epinephrine used less frequently	Moderate
Brady	1997	Comparison tx across two group	Adult patients treated for anaphylaxis	Multisystem reactions involving >= 2 systems	Steroids used more frequently in biphasic reactions; H1 antihistamines used less frequently	Moderate
Ko	2015	Comparison tx across two groups	Adult patients with anaphylaxis seen in an ED in Korea treated with steroids	Patients meeting World Allergy Organization anaphylaxis criteria	H1 antihistamines used less frequently in biphasic reactions but H2 antihistamines used more frequently	Moderate

Scranton	2009	Comparison tx across two groups	Patients treated with epinephrine after a systemic allergic reaction to immunotherapy in Texas	Systemic allergic reaction to allergen immunotherapy	Steroids and antihistamines used less frequently in biphasic reactions	Moderate
Sricharoen	2015	Comparison tx across two groups	Patients with anaphylaxis seen in an emergency department in Thailand	Patients meeting World Allergy Organization anaphylaxis criteria	Steroid use slightly lower in biphasic; antihistamine use no different; epinephrine use slightly higher in biphasic reactions	High

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2413 **METHODOLOGICAL NOTES:**

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2415 *Measurement of Treatment Effect and Data Synthesis*

- Findings were pooled using an odds ratio because the included analyses approximated case-control studies. Data was analyzed by outcome (biphasic reaction or equivalent such as ED revisit) or comparator (i.e. monophasic reaction) with comparison of H1/H2 usage prior to the development of the outcome. (Cochrane Handbook 9.4.4.1)
- In the primary analysis the data were pooled together using the Inverse Variance (IV) fixed effect method. Meaningful heterogeneity was not encountered.

Zero Cell Correction

- A zero cell correction was used for studies that reported zero cells (i.e. either no patients provided with H1 or all patients received H1). As discussed in the Cochrane Handbook (16.9.2), it is common for meta-analytic software correct for zero counts by adding a fixed value (typically 0.5) to all zero cells. The zero-cell correction is required less often in the case of the Mantel-Haenszel method because the Mantel-Haenszel method only applies the correction if the same cell is zero in all the included studies. While there are benefits to applying a "fixed correction method" to a meta-analysis, there are also risks including the possibility that it may bias estimates towards no difference or overestimate variance of study estimates. There is also concern for bias in one direction if the sizes of the study arms are unequal. The Peto Method avoids these problems because it doesn't require a zero cell correction (only exception is if no events occur in all arms of all studies). However, the Peto Method was not appropriate for our analysis because the Peto Method is at risk for bias if the study arms are highly unbalanced which was the case in this analysis. To minimize introducing additional bias into our current study, we applied a more conservative correction factor of 0.2.

Assessment of heterogeneity

- Heterogeneity across included studies was assessed by performing a chi-squared test and calculating a corresponding Cochran Q statistic and p-value. A p-value <0.10 was considered to be statistically significant. In addition, inconsistency was calculated across included studies and considered an I^2 >50% to be reflective of substantial and meaningful heterogeneity (Cochrane Handbook 9.5.2).

References:

1. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Collaboration 5.1.0 [updated March 2011]. Higgins JPT, Green S (editors). https://handbook-5-1.cochrane.org/front_page.htm
2. Bagheri, Z., Ayatollahi, S. M. T., & Jafari, P. (2011). Comparison of three tests of homogeneity of odds ratios in multicenter trials with unequal sample sizes within and among centers. *BMC Medical Research Methodology*, *11*, 58. http://doi.org/10.1186/1471-2288-11-58.)

Q2b Included Studies and Methodologic Notes

Scholars responsible for analyzing the literature

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Table eQ2b: Characteristics of Included Studies

Author, Year	Study Design	Sample Size	Cancer Type	Median*/ Mean Age (Years)	Chemotherapeutic	Premedication	Comparison	Duration (follow-up)	Risk of Bias
Chang et al., 2016	Retrospective cohort	139	Lymphoblastic leukemia	37*	Pegasparagase	Acetaminophen, diphenhydramine and/or glucocorticoid	No premedication	May 2008 - July 2014	Low
Francis et al., 1994	Randomized clinical trial	29	Non-small cell lung cancer	63*	Docetaxel	Diphenhydramine	No premedication	June 1992 - February 1993	Low
Rougier, 1995	Phase II clincal studies (4)	127	Gastric, pancreatic, and colorectal cancer	58.5*	Docetaxel	Diphenhydramine either with or without dexamethasone	No premedication	N/A	Low
Mach, 2016	Retrospective cohort	404	Ovarian cancer	60	Carboplatin	Diphenhydramine, famotidine, and dexamethasone	dexamethasone	November 2005 – November 2006, July 2002 – September 2003	low
Seki et al. 2011	Retrospective cohort	108	Colorectal cancer	64.5	Oxaliplatin, FOLFOX 4 and/or Modified mFOLFOX 6	Steroids	No premedication	April 2005 - March 2009	Low

Shen et al. 2018	Retrospective cohort	291	Colorectal cancer	61.6*	FOLFOX, leucovorin, flourouracil, or XELOX	Chlorpheniramine and dexamethasone	No premedication	January 2008 - January 2016	Low
Thompson et al., 2014	Retrospective chart review	197	Breast cancer	51*	Trastuzumab	Standard premedication protocol for trastuzumab	No premedication	May 1, 2010 - July 31, 2010	Low
Trudeau et al., 1996	Phase II clinical trial	48	Breast cancer	55*	Docetaxel	Group 1: Diphenhydramine and dexamethasone; Group 2: Dexamethasone, diphenhydramine and ranitidine	No premedication	June 1992 - June 1993	Low
Weiss et al., 1990	Retrospective cohort study	301	Acute Myelogenous Leukemia	53*	Taxol	Dexamethasone, diphenhydramine, and ephedrine sulphate	No premedication	N/A	Low
Jung et al, 2014	Retrospective cohort study	568	Lymphoma	59.6	Rituximab	Corticosteroids	No premedication	N/A	Low
Onetto et al, 1993	Summary of phase 1 studies	253	Acute leukemia	Not specified	Taxol	Dexamethasone, diphenhydramine, cimetidine	No premedication	N/A	Moderate

Jerzak et al, 2016	Retrospective chart review	450	Ovarian cancer	57*	Carboplatin	Diphenhydramine	No premedication	2006-2012	Moderate

METHODOLOGICAL NOTES:

Data synthesis

Data synthesis was performed using random effects model because this model assumes that the different studies are estimating different, yet related, intervention effects which is consistent with the variable study designs among the studies included in this meta-analysis.

Assessment of heterogeneity. The heterogeneity of the studies used in this review was assessed using Revman and the I^2 and p-values were computed.

Limitations

The analysis was limited to English-speaking adult populations who had not previously experienced a hypersensitivity reaction to chemotherapy. Variation existed in premedication protocols used in various studies. (i.e. glucocorticoids vs. antihistamines, or a combination of both).

Q2b Included Studies and Methodologic Notes

Scholars responsible for analyzing the literature

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Table eQ2c: Characteristics of Included Studies

All studies included in the metanalysis were retrospective cohort studies. Further information for each paper is detailed below.

Included Studies

Author Year	Sample Size (n)	Procedure	Intervention	Control	Risk of Bias
Abe 2016	751	ǂCT, MRI, drip infusion cholangiography and cardiac angiography	Premedication (steroid/antihistamine) and media change	No premedication No media change	Low

Katayama 1990	14,987	Urography, CT, and DSA	Premedication (steroid/antihistamine)	No premedication	Low
Kolbe 2014	183	Not specified	Premedication (steroid/antihistamine)	No premedication	Low
Lee 2016	453	CT	Premedication (antihistamine)	No premedication	Low
Park 2017	321	CT	Premedication (steroid/antihistamine) and media change	No premedication No media change	Low
Park 2018	3,533	CT	Premedication (antihistamine) and media change	No premedication No media change	Low

[‡]CT: Computed tomography, MRI: Magnetic resonance imaging, DSA: Digital subtraction angiography

METHODOLOGICAL NOTES:

Data synthesis

Risk ratios were analyzed as dichotomous outcome - adverse reaction - for subjects with pretreatment and subjects without pretreatment. Data was abstracted using a standardized, predefined data extraction form and entered into RevMan, with the primary outcome was summarized using a random effects model, due to the heterogeneity of our sample. This analysis produced a pooled risk ratio and 95% confidence interval.

Assessment of heterogeneity

We utilized RevMan to synthesize our abstracted data and produce forest plots with assessments of heterogeneity. ur complete meta-analysis of all 6 included studies without media change yielded an I^2 of 94% and suggests a high amount of variation between studies. Additional analyses were conducted across studies with and without media change.

Limitations

The Newcastle-Ottawa scale to was used to assess the methodological quality of the included studies since all included studies were retrospective cohort studies. According to this scale, all studies were found to be "good quality" (out of options poor, fair, and good). Despite this result, there are several limitations to the included studies. The included studies were primarily retrospective studies and none of the studies were randomized or blinded. Since retrospective studies relied on existing medical records, test subjects were assigned to test vs control groups based on physician choice, introducing selection bias. There was a high level of methodological variation within and between studies.

Q2d Included Studies and Methodologic Notes:

Scholars responsible for analyzing the literature

Natlie Riblett, MD

2521 Marcus Shaker, MD, MS
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2524 **Included Studies:**

2525 ***Monoclonal Antibodies***

Author	Year	Context	Outcome	Definition of outcome	Description of intervention	Notes	Risk of Bias
Augustsson	2007	Steroid premedication to decrease infliximab infusion reactions	Immediate-type infusion reaction	Experienced immediate-type infusion reaction (anaphylactic/anaphylactoid reaction and/or urticaria and itching and had to stop infliximab	Daily oral low dose glucocorticoids (median dose 5mg/day) at baseline	glucocorticoids effective at preventing infusion reactions, p = 0.057	moderate risk
Gold (steroids) (based on infusions)	2017	Steroid and antihistamine premedication to prevent infliximab infusion reactions	acute infliximab reaction	Grade reaction severity based on predefined definitions from prior study and categorize as mild (self-limited), mod (need extensive observation/stop drug), severe (resp sxs, change in VS)	IV steroids	glucocorticoids not effective;	moderate risk
Gold (anti H1) (based on infusions)	2017		acute IFX reaction	Grade reaction severity based on predefined definitions from prior study and categorize as mild (self-limited), mod (need extensive observation/stop	IV or PO benadryl	AH's not effective	moderate risk

				drug), severe (resp sxs, change in VS)			
Jacobstein	2005	Antipyretic, antihistamine, and glucocorticoid premedication to prevent infliximab infusion reactions	Infliximab reaction	not defined but report in tables the following types of sxs chest tight, rash, n/v, HA, fever, hypotension, hypoxia, anaphylaxis, back pain, lethargy	antipyretic, antihistamine or glucocorticoid-no additional information	premed not effective to prevent 1st rxn; p<0.01 (i.e. significantly more reactions in patients who received premed than the group that didn't receive premed)	low risk

Immunotherapy

Author	Year	Context	Outcome	Definition of outcome	Description of intervention	Notes	Risk of bias
Portnoy	1994	Double blind placebo controlled trial of 22 allergic children treated with combination H1 and H2	Systemic allergic reactions including cutaneous only, generalized pruritis and/or sneezing,	Anaphylaxis: hypotension, severe wheezing, and cramping	Astemizole, ranitidine, and prednisone beginning one day before immunotherapy	Pre-treatment significantly decreased the risk of systemic reactions	low risk of bias

		antihistamines together with corticosteroid or placebo during inhalant rush inhalant immunotherapy	pulmonary, anaphylaxis, or cardiopulmonary arrest		continued for a total of 3 days		
Hejjaoui	1990	Prospective cohort evaluating premedication before rush immunotherapy	Systemic reactions classified as asthma, urticaria, or anaphylaxis.	Anaphylaxis was characterized symptoms including tachycardia, hypotension, generalized urticaria and/or angioedema, laryngoedema, and possibly wheezing.	Effectiveness of methylprednisolone + ketotifen + theophylline for dust mite rush immunotherapy	Pretreatment reduced the risk of systemic reacitons	moderate risk of bias
Brockow	1997	Effectiveness of H1/H2 blockade against systemic reaction to venom immunotherapy	Systemic allergic reaction to venom immunotherapy	CV, resp, GI, skin/mucosal, subjective and additional; systemic sfx that required cessation of therapy	1,120mg terfenadine+300mg ranitidine'	Pre-treatment w/ AH decreased systemic runs.	low risk of bias

Mueller	2008	Effectiveness of H1 antihistamine against systemic reaction to ultrarush honeybee immunotherapy	Occurrence of systemic allergic reaction to honeybee immunotherapy	Systemic allergic reactions (Mueller grade) and evaluated both objective and subjective side-effects	5mg daily of levocetrizine days-2 to day 21	AH premed reduced systemic sfx of VIT.	low risk of bias
Reimers	2000	Effectiveness of H1 antihistamine against systemic reactions to ultrarush honeybee immunotherapy	Systemic allergic reaction during ultrarush honeybee immunotherapy treated with Antihistamine H1 prophylaxis	Classified as typical (cutaneous-itching, urticaria, angioedema); cutaneous non-specific (heat sensation, flush, erythema); more severe (GI, resp, CV)	Fexofenadine 180mg pretreatment; before protocol start; before first injection on day 1, 8, 22, and 50	AH premed did not reduce systemic sfx	low risk of bias
Tankersley	2002	Effectiveness of pretreatment with H1/H2 antihistamine and steroid to prevent systemic reaction in ultrarush fire	Systemic reactions from fire ant immunotherapy	Reported on systematic reactions during the rush protocol with or without pretreatment with Antihistamine	Terfenadine 60mg; raniditine 150mg and prednisone 30mg x 5days	No sig difference with premed	low risk of bias

		ant immunotherapy		H1+H2 and steroid			
Jagdis	2014	Pretreatment with Ketotifen to prevent systemic reactions to peanut oral immunotherapy	Rate and severity of adverse reactions on initial escalation day of peanut oral immunotherapy in antihistamine H1 premedication	Anaphylaxis	Ketotifen	Lower rate of reactions in premedication arm but small n	low risk of bias
Yoshihiro	2006	Pretreatment with H1 antihistamine to prevent systemic reactions to Japanese cedar or dust mite immunotherapy	Systemic reaction to aeroallergen immunotherapy	Symptoms due to antigen injection such as asthma, systemic anaphylaxis requiring tx	Fexofenadine	Premedication reduced reaction rate	unclear risk of bias
Berchtold	1992	Pretreatment with H1 antihistamine to prevent systemic reactions to ultrarush honey	Rush venom immunotherapy treated with H1 antihistamine	systemic side effects	Terfenadine	No sig difference with premed	low risk of bias

		bee immunotherapy					
Nielson	1996	Pretreatment with H1 antihistamine to prevent systemic reactions to birch or grass immunotherapy	Antihistamine H1 prophylaxis for aeroallergen immunotherapy	systemic allergic reactions	Loratadine	AH prophylaxis effective	low risk of bias

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2530 ***Other Studies***

Author	Year	Context	Outcome	Definition of outcome	Description of intervention	Notes	Risk of bias
Braaten	2015	Premedication with IV steroids to prevent anaphylactic reactions to IV iron	Hypersensitivity reactions	Any documented hypersensitivity reaction graded by National Cancer Institute Common Terminology criteria for adverse events	ferumoxytol + dexamethasone	steroid premed effective	moderate risk

Lorenz	1980	Premedication with H1 and H2 antihistamines to prevent reactions to a plasma substitute in volunteers	Anaphylaxis or urticaria	Hives or anaphylaxis (defined as rhinorrhea, throat tightness, nausea, vomiting, diarrhea, hypotension, tachycardia, or cardiac arrest)	H1+H2 (dimethprindene and cimetidine)	lower rate of clinical allergic sx in pre-medication group	unclear risk of bias
Schoening	1982	Pretreatment with H1 and H2 antihistamines to prevent reactions to a plasma substitute	Anaphylaxis	Anaphylaxis characterized by generalized skin reactions and tachycardia, arrhythmias, hypotension, or respiratory distress	H1+H2 (dimethprindene and cimetidine)	lower rate of clinical allergic sx in pre-medication group	unclear risk of bias
Sanders	2005	Premedication with H1 antihistamine to prevent allergic reactions to leucoreduced blood products in children	Allergic reaction	Urticaria or other rash, pruritus, wheezing, or angioedema	Diphenhydramine	AH premed not effective	moderate risk
Caron	2009	Premedication with H1 antihistamine and steroid with slow infusion of antivemon for	Allergic reactions including urticaria, angioedema, respiratory, cardiovascular,	Described by none, mild, moderate and severe as defined by Brown's grading of severity of anaphylaxis	IV hydrocortisone (100mg-adults, 2mg/kg-kids); IV diphenhydramine (50mg-adults; 2mg/kg-kids)	premedication with steroids and AH effective	moderate risk

		snake bite reactions to prevent allergic reactions	gastrointestinal, or neurologic symptoms				
Fan	1999	Premedication with H1 antihistamine to prevent allergic reactions to antivenom in the treatment of snake bites	Any allergic reactions	Symptoms including urticarial, flush, cough, hoarseness, vomiting, abd cramps, diarrhea, bronchospasm, severe glottis edema, hypotension, or shock	Antihistamine: 25mg promethazine	premedication not effective.	low risk

METHODOLOGICAL NOTES:

Measurement of Treatment Effect and Data Synthesis

- Findings were pooled using a relative risk because the included studies were described as prospective studies (some of which were randomized controlled trials) and reported their findings based on outcomes that occurred in patients who were exposed versus not exposed to the intervention of interest.
- For the primary analysis, data were pooled together for the subgroup immunotherapy using the Inverse Variance fixed effect method in the event that the test of heterogeneity suggested that there was not significant heterogeneity (i.e. I^2 <50% and P < 0.1). Because substantial and meaningful heterogeneity was encountered in the analysis of two subgroups (the monoclonal antibody therapy and "other therapy"), the DerSimonian Laird method was ysed, This is because the Cochrane recommends using this method as it employs a random effects model and is more conservative in the case of significant and meaningful heterogeneity. Significant and meaningful heterogeneity in analysis was

not unexpected, because the populations grouped together had important differences with respect to both condition and exposures of interest.

Zero Cell Correction

- Some studies that reported zero cells. Unfortunately, the Inverse variance fixed effect and the DerSimonian and Laird random effects methods are unable to handle these situations and will not be able to perform the calculation. As discussed in the Cochrane Handbook (16.9.2), it is common for meta-analytic software such as Revman to correct for zero counts by adding a fixed value (typically 0.5) to all zero cells. While there are benefits to applying a "fixed correction method" to a meta-analysis, there are also risks including the possibility that it may bias estimates towards no difference or overestimate variance of study estimates. There is also concern for bias in one direction if the sizes of the study arms are unequal. To minimize introducing additional bias into our current study, a more conservative correction factor of 0.2 was applied.

Assessment of heterogeneity

- Heterogeneity across included studies was assessed by performing a chi-squared test and calculating a corresponding Cochran Q statistic and p-value. A p-value <0.10 was considered to be statistically significant. In addition, inconsistency across included studies was calculated and considered an I^2 >50% to be reflective of substantial and meaningful heterogeneity (Cochrane Handbook 9.5.2).

References:

1. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Collaboration 5.1.0 [updated March 2011]. Higgins JPT, Green S (editors). https://handbook-5-1.cochrane.org/front_page.htm

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