

1 **Anaphylaxis – a 2019 practice parameter update and GRADE analysis**

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3 Marcus Shaker, Dana Wallace, David Golden, John Oppenheimer, Jonathan Bernstein, Ronna
4 Campbell, Chitra Dinakar, Anne Ellis, Matthew Greenhawt, David Khan, Eddy Lang, Jay
5 Lieberman, Jay Portnoy, Matt Rank, David Stukus, Julie Wang

6

7 Collaborators: Natalie Riblet, Aiyana MP Bobrownicki, Teresa Bontrager, Jennifer Foley, Becky
8 Frederick, Eyitemi Fregene, Sage Hellerstedt, Kori Hess, Kelly Huntington, Poojita Kasireddy,
9 David Keeler, Bertha Kim, Phil Lieberman, Erin Lindhorst, Fiona McEnany, Jennifer Milbank,
10 Helen Murphy, Oriana Pando, Ami K Patel, Nicole Ratliff, Robert Rhodes, Kim Robertson,
11 Hope Scott, Audrey Snell, Rhonda Sullivan, Varahi Trivedi, Azadeh Wickham

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14 **EXECUTIVE SUMMARY**

15

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

24

25 The lifetime prevalence of anaphylaxis has been estimated at 1.6% to 5.1%. (1, 4) Risk factors
26 for severe anaphylaxis include cardiovascular disease, asthma, African-American race, older age,
27 male sex, and additional coexisting comorbid conditions. (5-9) While many cases of anaphylaxis
28 are idiopathic, medications are the leading triggers in adults, with foods and stinging insects the
29 most frequently implicated in children and adolescents. (1, 10, 11) Food allergy impacts 8% to
30 11% of children and adults in the United States (12-14), while adverse drug reactions (ADRs)
31 affect up to 10% of the population (and 20% of hospitalized patients) with hypersensitivity
32 reactions accounting for 10% of all ADRs. (15) While medical complexity increases for patients
33 with prior hypersensitivity reactions to radiocontrast media (RCM), fortunately the prevalence of
34 RCM ADRs had decreased in recent decades. (16) Systemic reactions to Hymenoptera venom
35 occur in 0.5% to 3.3% of the US population, with most fatalities occurring in patients who have
36 no prior history of systemic allergic reaction to Hymenoptera.(15)

37

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

45
46 Epinephrine is the cornerstone of anaphylaxis management but continues to be underutilized.
47 (21-23) As a nonselective adrenergic agonist, intramuscular epinephrine works rapidly to
48 increase peripheral vascular resistance through vasoconstriction, increase cardiac output, reverse
49 bronchoconstriction and mucosal edema, and stabilize mast cells and basophils. (24, 25) Despite
50 underuse of rapidly acting epinephrine as first-line treatment, fatal anaphylaxis is fortunately a
51 rare outcome, with prevalence rates between 0.47 to 0.69 million persons (0.25%-0.33% of
52 anaphylaxis hospitalizations or emergency department visits). (9, 26-29) Antihistamine agents
53 are considered second line treatment for anaphylaxis, given their slow onset of action, inability to
54 stabilize or prevent mast cell degranulation, or target additional mediators of anaphylaxis. (30)
55 Unlike epinephrine, antihistamines will not effectively treat cardiovascular and respiratory
56 symptoms such as hypotension or bronchospasm when used acutely as monotherapy. Although
57 glucocorticoids are frequently used as an adjunctive therapy for anaphylaxis they should also not
58 be administered in place of epinephrine in the treatment of acute anaphylaxis. (31, 32)

59
60 Estimates of biphasic anaphylaxis vary from less than 1% to 20% of patients; however, the
61 ability of antihistamines and glucocorticoids to affect this outcome is unclear. (33-40) Despite a
62 lack of clear evidence supporting the role of antihistamines and glucocorticoids in anaphylaxis,
63 these agents continue to be routinely used in anaphylaxis management. To evaluate the role for
64 these second-line supplemental therapies, the JTFPP undertook a systematic review and GRADE
65 analysis of antihistamines and glucocorticoids in anaphylaxis. Questions evaluated were (1)
66 “What are the risk factors are associated with biphasic reactions?”, and (2) “Should
67 antihistamines or glucocorticoids be used to prevent anaphylactic reactions?”

68
69 **Question 1 Key Findings and Recommendations:** Based on *very low-quality* evidence, we
70 **suggest extended observation in the ED for patients with resolved severe anaphylaxis to**
71 **detect a biphasic reaction.** The JTFPP findings suggest biphasic anaphylaxis is associated with
72 a more severe initial presentation of anaphylaxis (OR=2.11, 95% CI 1.23-3.61) or repeated
73 epinephrine doses required with the initial presentation (OR 4.82, 95% CI 2.70-8.58). The
74 estimated number needed to monitor with extended observation to be able to detect one episode
75 of biphasic anaphylaxis before discharge would be 41 (range, 18 to 195) for patients with a more

76 severe initial presentation of anaphylaxis and 13 (range, 7 to 27) for patients with multiple
77 epinephrine doses. Prompt and adequate treatment of anaphylaxis appears central to reducing
78 biphasic anaphylaxis risk. The implications for the clinician, based upon this systematic review
79 and meta-analysis is that the patient presenting with severe anaphylaxis and/or requiring more
80 aggressive treatment (e.g., more than one dose of epinephrine), following complete resolution of
81 symptoms, may benefit from longer observation time for a potential biphasic reaction. While the
82 possibility of biphasic anaphylaxis should be emphasized in this higher risk group, it is important
83 to educate all patients on the chance of a biphasic reaction as well as avoiding known triggers,
84 identifying symptoms of anaphylaxis, the use of auto-injector epinephrine for the treatment of
85 anaphylaxis, and timely follow-up with an allergist. At present, evidence is lacking to clearly
86 demonstrate the period of universal extended observation that may be required or cost-effective
87 in all patients with severe anaphylaxis or those who require multiple doses of epinephrine.

88
89 **Question 2 Key Findings and Recommendations:** Based on *very low-quality* evidence, we
90 **suggest against glucocorticoids or antihistamines as an intervention to prevent biphasic**
91 **anaphylaxis.** As a secondary therapy, antihistamines and corticosteroids may be considerations
92 in anaphylaxis treatment.(41) In particular, antihistamines may treat urticaria and itching to
93 improve comfort during anaphylaxis, but if used prior to epinephrine administration could lead to
94 a delay in first line treatment of anaphylaxis. Furthermore, glucocorticoids can also effectively
95 prevent delayed urticaria which could confound the assessment and treatment of anaphylaxis.
96 The JTFPP analysis did not identify significant benefit in prevention of biphasic anaphylaxis
97 from either H1 antihistamines (OR 0.71, 95% CI 0.47-1.06), H2 antihistamines (OR 1.21, 95%
98 CI 0.8-1.83), or glucocorticoids (OR 0.87, 95% CI 0.74-1.02). At a biphasic anaphylaxis patient
99 expected event rate (PEER) of 5%, the number needed to treat (NNT) for H1 antihistamines and
100 glucocorticoids is 72 and 161 to prevent one episode of biphasic anaphylaxis, with significant
101 uncertainty in the estimate.

102
103 Based on *very low-quality* evidence, we **suggest administering glucocorticoids and/or**
104 **antihistamines to prevent anaphylaxis or infusion related reactions when indicated for**
105 **specific agents in chemotherapy protocols.** The JTFPP analysis did identify a significant
106 change in rates of anaphylaxis and/or infusion reactions for some chemotherapy protocols. The

107 use of premedication was associated with a decreased rate of hypersensitivity reactions for
108 chemotherapy (OR 0.46, 95% CI 0.35-0.6). In contrast to chemotherapy premedication, benefit
109 was not observed when using premedication to prevent anaphylaxis in the setting of monoclonal
110 antibody therapy without prior reaction to the administered agent (RR 1.58, 95% CI 0.87-2.87).
111 We did not evaluate premedication in the context of desensitization to chemotherapy agents and
112 to monoclonal antibodies. Furthermore, the use of premedication in patients who had previously
113 experienced anaphylaxis from these agents was not evaluated.

114
115 Based on *very low-quality* evidence, **we suggest against routinely administering**
116 **glucocorticoids and/or antihistamines to prevent anaphylaxis due to iso-osmolar, non-ionic**
117 **radiocontrast media agent.** The JTFPP analysis did not identify significant benefit from the
118 use of premedication prior to the RCM to prevent anaphylaxis (RR 1.07 95% CI 0.67-1.71). The
119 absence of benefit of premedication in patients with prior immediate hypersensitivity reactions to
120 RCM who are receiving a different low or iso-osmolar agent is consistent with prior literature;
121 however, it is important to distinguish the immediate index reaction associated with RCM from a
122 severe delayed cutaneous T-cell mediated reaction, where premedication may add value to
123 management.(42) Given the diversity of clinical circumstances evaluated and low confidence in
124 the literature base, higher quality evidence is needed to better inform practice, and future
125 recommendations could potentially change as a result of new information. As such, clinicians
126 may reasonably consider premedication in clinical circumstances associated with a high level of
127 perceived risk of anaphylaxis or comorbidities associated with greater anaphylaxis fatality risk
128 (such as underlying cardiovascular disease, use of beta-blockers, or prior severe anaphylaxis),
129 although evidence is lacking to support this practice.

130
131 Based on *very low-quality* evidence, **we suggest in favor of the administration of**
132 **glucocorticoids and/or antihistamines as an intervention to prevent anaphylaxis in patients**
133 **undergoing aeroallergen rush immunotherapy (RIT).** Evidence suggests that in the setting of
134 aeroallergen RIT premedication may provide value in reducing systemic reactions and
135 anaphylaxis (immunotherapy analysis including RIT, RR 0.62, 95% CI 0.41- 0.94). The evidence
136 base for premedication before conventional aeroallergen immunotherapy is limited; however,
137 one study suggested some benefit with fexofenadine pretreatment 2 hours before conventional

138 immunotherapy using cedar pollen or dust mite allergens.(43) The JTFPP is unable to exclude
139 the possibility that specific situations and subpopulations may exist where premedication could
140 provide benefit to immunotherapy in those with concomitant risk factors (e.g., in situations
141 associated with higher rates of systemic reactions). As such, clinicians may reasonably consider
142 immunotherapy premedication in other clinical circumstances associated with a high level of
143 perceived risk of anaphylaxis or comorbidities associated with greater anaphylaxis fatality risk
144 (such as underlying cardiovascular disease or use of beta-blockers), although evidence is lacking
145 to support this practice.

146

147 **Additional Good Practice Statements**

148

149 **Good Practice Statement # 1: Administer epinephrine as the only 1st line pharmacotherapy**
150 **for uniphasic and/or biphasic anaphylaxis.**

151

152 **Good Practice Statement #2: Do not delay the administration of epinephrine for anaphylaxis,**
153 **as doing so, may be associated with higher morbidity and mortality.**

154

155 **Good Practice Statement #3: After diagnosis and treatment of anaphylaxis, all patients should**
156 **be kept under observation until symptoms have fully resolved.**

157

158 **Good Practice Statement #4: All patients with anaphylaxis should receive education on**
159 **anaphylaxis, including avoidance of identified triggers, presenting signs and symptoms, biphasic**
160 **anaphylaxis, treatment with epinephrine, the use of epinephrine auto-injectors, and referral to an**
161 **allergist. Of note, there may be some circumstances where self-injectable epinephrine is deferred**
162 **(i.e., resolved anaphylaxis and drug trigger with high likelihood of successful avoidance) and**
163 **patient-preference sensitive decision making may play a role in some circumstances.**

164

165

166 INTRODUCTION AND DIAGNOSIS

167 Anaphylaxis is an acute, life-threatening systemic allergic reaction associated with different
168 mechanisms, triggers, clinical presentations, and severity.(1) The wide range of clinical
169 manifestations and complex underlying mechanisms of anaphylaxis contribute to the difficulty in
170 establishing a definition and diagnostic criteria for anaphylaxis. The poor sensitivity of
171 confirmatory laboratory testing further complicates accurate diagnosis of anaphylaxis.
172 Furthermore, the lack of established diagnostic criteria plays a major role in the under-diagnosis
173 and inconsistent management of anaphylaxis. (44-46) In 2005, a multinational and
174 multidisciplinary workgroup which included allergist-immunologists, emergency physicians,
175 pediatricians, critical care specialists, internists and key stakeholders was assembled by the
176 National Institutes of Allergy and Infectious Disease (NIAID) and Food Allergy and
177 Anaphylaxis Network (FAAN) to address the need for universally accepted anaphylaxis
178 diagnostic criteria. The diagnostic criteria proposed by this workgroup were published in 2006
179 (47) and describe anaphylaxis as likely when one of three criteria are fulfilled: (1) acute onset of
180 an illness (minutes to hours) with involvement of the skin, mucosal tissue, or both with either
181 respiratory compromise or reduced blood pressure / associated symptom of end-organ
182 dysfunction; or (2) two or more of the following that occur rapidly after exposure to a likely
183 allergen for the patient including (a) involvement of skin-mucosal tissue, (b) respiratory
184 compromise, (c) reduced blood pressure or associated symptoms, or (d) persistent
185 gastrointestinal symptoms; or (3) reduced blood pressure as a result of exposure to a known
186 allergen trigger. These criteria have since been recognized and endorsed by both the American
187 Academy of Allergy, Asthma, and Immunology (AAAAI), American College of Allergy,
188 Asthma, and Immunology (ACAAI)(48), and the World Allergy Organization (49).

189
190 The NIAID/FAAN criteria were developed to “provide the emergency responder or treating
191 physician with a relatively simple and rapid means to make the diagnosis of anaphylaxis.” The
192 criteria (shown in Figure 1) incorporate features related to the onset of the reaction, exposure to
193 an inciting trigger, as well as signs and symptoms. Importantly, using these criteria, anaphylaxis
194 can be identified among patients lacking hemodynamic compromise, patients lacking cutaneous
195 manifestations, and among patients with mild presentations (for example, those with a rash and
196 vomiting after exposure to a likely trigger). The NIAID/FAAN anaphylaxis diagnostic criteria

197 were prospectively validated in patients seeking care for an allergic reaction and possible
198 anaphylaxis in an emergency department setting, and shown to provide a positive likelihood ratio
199 of 3.26 and negative likelihood ratio of 0.07. (3) Thus, although these criteria are helpful
200 clinically, they should not replace clinician judgment. It is important to recognize, as those who
201 developed the criteria did, that epinephrine administration is not limited to those patients meeting
202 the NIAID/FAAN diagnostic criteria. For example, a patient undergoing immunotherapy who
203 immediately develops generalized urticaria may appropriately receive epinephrine if impending
204 anaphylaxis is suspected, despite the fact that the diagnostic criteria for anaphylaxis have not yet
205 been met. In such instances, management may rely heavily on clinical judgment, and role of pre-
206-emptive epinephrine prior to the development of anaphylaxis has been questioned.(50, 51)
207 Isolated allergen associated urticaria, which may respond to antihistamines, should be
208 distinguished from anaphylaxis for which prompt epinephrine administration is indicated. In
209 addition, a patient presenting to the emergency department who reports symptoms meeting
210 NIAID/FAAN diagnostic criteria that spontaneously resolved prior to arrival in the emergency
211 department, should be diagnosed with anaphylaxis despite the fact that epinephrine
212 administration is no longer immediately necessary in a now stable patient.

213

214 Biphasic anaphylaxis is a well-recognized potential complication of anaphylaxis and has been
215 defined as recurrent anaphylaxis *after complete improvement*; this has been reported to occur
216 between 1 to 78 hours after the onset of the initial anaphylactic reaction, and this must be
217 clinically differentiated from a reaction that does not fully respond to initial treatment and
218 persists or quickly returns. (52-54) Some (although not all) earlier studies of biphasic reactions,
219 prior to the NIAID/FAAN criteria, which included patients with severe anaphylaxis, reported
220 rates of biphasic anaphylaxis as high as 20%. (33-35) More contemporary studies of biphasic
221 anaphylaxis utilizing the NIAID/FAAN diagnostic criteria or similar criteria for diagnosis of
222 both the initial anaphylactic reaction and the biphasic reaction have demonstrated lower rates of
223 biphasic reactions closer to 4-5% (range 0.18% - 14.7%) (37, 38, 40, 55, 56) No studies have
224 systematically evaluated therapies for the late phase reaction; however, therapy for the late phase
225 is similar to the initial phase. (57)

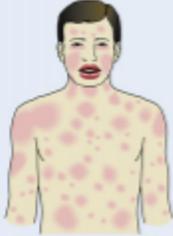
226

227 **Figure 1 (permissions needed):**

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1 Sudden onset of an illness (minutes to several hours), with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, itching or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING:

		
	Sudden respiratory symptoms and signs (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia)	Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence)

OR 2 Two or more of the following that occur suddenly after exposure to a likely allergen or other trigger* for that patient (minutes to several hours):

			
Sudden skin or mucosal symptoms and signs (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula)	Sudden respiratory symptoms and signs (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia)	Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence)	Sudden gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)

OR 3 Reduced blood pressure (BP) after exposure to a known allergen** for that patient (minutes to several hours):

 Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP***	 Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline
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* For example, immunologic but IgE-independent, or non-immunologic (direct mast cell activation)

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

*** Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years. Normal heart rate ranges from 80-140 beats/minute at age 1-2 years; from 80-120 beats/minute at age 3 years; and from 70-115 beats/minute after age 3 years. In infants and children, respiratory compromise is more likely than hypotension or shock, and shock is more likely to be manifest initially by tachycardia than by hypotension.

228

229

230 **EPIDEMIOLOGY AND RISK FACTORS**

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

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

243

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

263

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

268 in an emergency department, only 8% of patients received epinephrine. (76) While early
269 epinephrine is the bedrock of anaphylaxis management, anaphylaxis fatality is fortunately a rare
270 outcome. The overall prevalence of fatal anaphylaxis in recent years in the United States and
271 United Kingdom is between 0.47 to 0.69 million persons (8, 9, 26-28). The 3 leading causes of
272 fatal anaphylaxis are drugs (29%-58.5%) (8, 26, 77, 78), insect stings (3.3%-54%)(8, 26, 77, 78),
273 and food (2%-6.7%) (8, 26, 78). While anaphylaxis-related hospitalizations have increased,
274 general case fatality rates have been stable in the range of 0.25%-0.33% of hospitalizations or
275 ED presentations for anaphylaxis (29). However, in contrast to other causes of fatal anaphylaxis,
276 drug-induced anaphylaxis rates have increased (8). In the United Kingdom fatal drug
277 anaphylaxis has been reported to be mostly due to general anesthetics, (79) whereas antibiotics
278 predominate in Australia (26) and France (80). A review by Pichichero et al. described the
279 population incident risk of anaphylaxis to penicillin between 0.004% to 0.015% with a fatality
280 rate of 0.0002% to 0.0015% (81). The UK fatal anaphylaxis registry reported that while those
281 dying from food anaphylaxis often have a prior history of a food reaction, those with fatal
282 Hymenoptera venom and drug anaphylaxis usually do not (79, 82) Additional observational
283 case-series have shown patients dying from food anaphylaxis often have previous food-induced
284 allergic reactions. (26, 34, 83) Notably, respiratory arrest may occur more commonly with foods
285 (86% of fatalities in the UK registry) with shock more common in fatalities due to iatrogenic and
286 venom reactions. (79) It is important to note that most fatal reactions are unpredictable and
287 statistically, occur very rarely; however, appropriate management of the underlying provoking
288 allergy after recovery from a severe reaction may decrease the risk for a subsequent severe
289 reaction, including fatality. (82) Referral to an allergy specialist after recovery from anaphylaxis
290 is recommended in order to correctly identify the diagnosis, the potential cause of the reaction,
291 and to educate the patient on the risk of future reaction and measures to reduce the risk, including
292 a prescription for and education regarding the use of epinephrine.

293

294 **BURDEN OF DISEASE**

295 **Food-induced Anaphylaxis**

296 *Prevalence*

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

303 *Trends*

304 According to the Centers for Disease Control and Prevention, rates of food allergies in US
305 children increased by about 50% between 1997 and 2011 (86). Whereas Clark et al (87) reported
306 stable trends in the frequency of US emergency department visits for food allergy in the period
307 of 2001-2009 , they did find a statistically significant decline among individuals ≥ 18 years of
308 age. In a retrospective cohort study of 37 pediatric hospitals from 2007-2012 (88), an increasing
309 rate of food induced anaphylaxis (FIA)-related ED visits was reported but without any increase
310 in the proportion of ED patients hospitalized or admitted to the ICU. This decrease in the
311 proportional rate of ED visits to utilization of inpatient and ICU facilities may be due to the
312 increased utilization of ED or inpatient observation units, as approximately 36% of US EDs
313 reported having observation units in 2007 (89). More recently, Motosue et al (90) reported a
314 fourfold increase in FIA related ED visits for adolescents from 2005 through 2014.

315 *Economic Burden*

316 Food allergies can burden patients and families by affecting finances, social relationships, and
317 personal perceptions of health. (91) Patients with food allergies and their families experience
318 anxiety and other stresses that affect quality of life given the risk of potentially severe reactions
319 and inability to completely control these risks. [16] The impact of food allergies is not limited to
320 just the patients and their families but can also lead to a significant economic effect on society
321 and the health care system. Food-induced anaphylaxis can result in prehospital emergency care
322 by ambulance personnel, ED visits, hospitalizations, or even death. Mild as well as more severe
323 allergic reactions require comprehensive evaluations including diagnostic studies and regular
324 follow-up outpatient visits. (92)

325 Patel et al in 2011 (92) estimated total annual direct medical costs of food allergy and
326 anaphylaxis at \$225 million (2007 US dollars). Office visits accounted for 52.5% of direct
327 medical costs, and the remaining was split between ED visits (20%), inpatient hospitalizations

328 (11.8%), outpatient department visits (3.9%), ambulance runs (3%), and epinephrine devices
329 (8.7%). Children accounted for 46.6% of the total inpatient costs, 31.5% of the ED visits, 67.3%
330 of the office visit costs, and 97.7% of the total outpatient department visit costs. US National
331 estimates for epinephrine autoinjector use after a suspected reaction triggered by a food allergy
332 obtained from the published literature suggest that between 30% and 86% of patients at risk for a
333 severe allergic reaction are prescribed an epinephrine autoinjector and have it available when
334 needed. (83, 93). Prevalence estimates and mean costs for office, inpatient, and ED visits have
335 the largest effect on total societal direct costs. Indirect costs have been estimated at \$115 million
336 (92) with morbidity-related costs accounting for 85% of indirect costs, resulting from disease
337 related sick days (lost productivity and wages). (92) Simulations from probabilistic sensitivity
338 analyses have generated mean annual direct costs of \$307 million and indirect costs of \$203
339 million in the US. (92) While evidence suggests that activation of emergency medical services
340 (EMS) and prolonged ED observation of resolved food anaphylaxis is a low-value practice,
341 prompt EMS activation is appropriate for patients who do not immediately completely respond
342 to timely epinephrine, or if recurrence of symptoms occurs. (94)

343

344 **Drug-induced Anaphylaxis**

345 Adverse drug reactions (ADR) may affect up to 1/10th of the world's population and up to 20%
346 of all hospitalized patients. More than 10% of all ADR are drug hypersensitivity reactions
347 (DHR). In a systematic review, 53 observational studies were synthesized to estimate that 8% of
348 patients self-report drug allergy, and that 11% of self-reported drug allergy is reported to be
349 anaphylaxis. (95) The most common DHR involves antibiotics such as penicillins and
350 cephalosporins, sulfonamides, aspirin, and other non-steroidal anti-inflammatory drugs. DHR
351 can be severe and life threatening and are associated with significant mortality rates. Drugs may
352 be responsible for upwards of 20% of fatalities due to anaphylaxis. The incidence of anaphylaxis
353 due to medication triggers is increasing over time. (59) DHR have a significant socioeconomic
354 impact related to both direct costs (management of reactions and hospitalizations) and indirect
355 costs (missed work/school days; alternative drugs); however, this is overall a major gap in the
356 literature for summarizing the economic burden of DHR. (15) A US nationwide cross-sectional
357 telephone self-reported survey reported a prevalence of anaphylaxis in the general population of
358 1.6% with medications being the most common trigger (35%). (1) Excluding pediatric cohorts

359 (where food is the most common trigger), medications are the most frequent cause of fatal
360 anaphylaxis in reports from the United States, as well as the United Kingdom, Australia and New
361 Zealand. (8, 15)

362
363 ADR from RCM occur less frequently than prior to 1990 when patients received high-osmolar,
364 ionic RCM. Prior ADR to RCM can contribute to burden of disease by creating medical
365 complexity associated with premedication; however, while glucocorticoid premedication has
366 become embedded in practice for patients with prior RCM hypersensitivity, evidence supporting
367 the use of prophylaxis in patient receiving low or iso-osmolar, non-ionic contrast agents is
368 lacking. ADR associated with RCM do not relate to iodine, and the term iodine allergy should
369 not be used in the context of RCM reactions. Patients receiving RCM may experience acute or
370 delayed reactions, with delayed reactions reported as frequently as acute reactions. (16) Four
371 categories of reactions to RCM have been described: benign acute-onset, anaphylaxis, benign-
372 delayed onset, and severe delayed-onset. (16) In one 2016 review of 120,822 patients receiving
373 iopromide, iodixanol, iopamidol, ioversol, iobitridol, or iohexionol, hypersensitivity reactions
374 were reported in 0.4% with only 1.4% of these reactions described as severe. (96) It has been
375 suggested that most individuals with acute RCM hypersensitivity can be effectively managed by
376 selecting an alternative RCM without premedication, but that patients should be informed that
377 delayed reactions (mostly benign rashes within one week of exposure) are as common as acute
378 reactions. (16).

379 **Insect-venom Anaphylaxis**

380 Hymenoptera venom allergy (HVA) describes both anaphylactic and non-anaphylactic
381 hypersensitivity reactions to stings. Reaction types include sting-induced large local (LL) or
382 systemic allergic reactions. A LL reaction lasts over 24 hours in which signs and symptoms are
383 confined to tissues contiguous with the sting site. In contrast to LL reactions, acute onset
384 systemic reactions involve generalized signs and symptoms and include a spectrum of
385 manifestations, ranging from mild urticarial reactions to life-threatening anaphylaxis. It is
386 estimated that 2-3% of adults and up to 1% of children have had a systemic reaction to a sting,
387 and LL reactions occur in more than 5% of adults. (97) In a review of 10 studies published
388 between 2001-2009, Bilo et al found that 23% of 2577 cases of anaphylaxis were caused by an

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

396

397 Patients often present with concern about potential anaphylaxis after having large local or
398 generalized cutaneous systemic reaction.(102) The morbidity of living with HVA may be
399 underestimated.(102) Fear of life-threatening anaphylaxis whenever one is outdoors, and the
400 burden of ensuring that injectable epinephrine is readily accessible at all times, affects the daily
401 activities and level of stress in affected individuals.(103) Even people with non-anaphylactic
402 (LL or cutaneous systemic) reactions to stings share the same concerns and can be impacted as
403 severely as the patients with anaphylactic reactions. (102) These concerns persist in these mild
404 reactors even though their risk of severe anaphylaxis is quite low and the prescription of
405 injectable epinephrine is not cost-effective in such cases.(51) Whether it is mild or severe, HVA
406 impairs long-term quality-of-life QOL and may be a cause of substantial socioeconomic
407 impairment.(104) HVA can impact career choices, especially in bee-keepers, groundskeepers,
408 gardeners, and greenhouse workers.(105) HVA has important adverse consequences in terms of
409 employment, earning capacity and leisure and sporting activities. (15) (16). For these reasons,
410 discussion of HVA usually includes not only anaphylactic, but also mild systemic and non-
411 anaphylactic reactions.(97)

412

413 **PATHOGENESIS OF ANAPHYLAXIS**

414 Data regarding pathophysiologic mechanisms and effector cells are limited on humans but mouse
415 models have offered some insight.(106) It is well established that IgE binding and cross-linking of
416 the high-affinity receptor FcEpsilonRI on the surface of mast cells and basophils is an important
417 mechanism in many cases of anaphylaxis. This causes the immediate release of preformed
418 mediators, as well as *de novo* synthesis of inflammatory mediators.(17) Interestingly, some
419 patients with life-threatening anaphylaxis have low or undetectable circulating allergen-specific

420 IgE and mouse models have demonstrated a potential role for IgG-dependent anaphylaxis.(18)
421 Furthermore, the complement system, anaphylatoxins C3a, C4a, C5a, and neutrophils (107) have
422 also been shown to be involved in anaphylaxis in human subjects. Lastly, a newly recognized
423 form of anaphylaxis occurring in patients receiving chemotherapy suggests a mixed type of
424 reaction with both features of IgE and non-IgE dependent anaphylaxis.(108) Cytokine-storm like
425 reactions have recently been described for patients with chemotherapy induced anaphylaxis.(108)

426

427 Animal and human studies have linked multiple mediators to the signs and symptoms of
428 anaphylaxis. The most important effector cells involved in anaphylaxis are mast cells, but
429 basophils, neutrophils, monocytes, macrophages, and platelets have also been implicated.(106,
430 109) Histamine is an important mediator of anaphylaxis, and studies have demonstrated that
431 intravenous histamine can induce symptoms of anaphylaxis, including flushing, airway
432 obstruction, systemic hypotension and tachycardia.(110, 111) While histamine appears to play a
433 significant role, other mediators have also been implicated. Therefore, pharmacologic targeting
434 of histamine alone, e.g., administration of antihistamines, is not appropriate and is thus
435 considered second line treatment for anaphylaxis and should not be used in place of epinephrine.
436 Given the slow onset of antihistamine agents, ineffectiveness in treating cardiovascular and
437 respiratory symptoms such as hypotension or bronchospasm, and the inability to stabilize or
438 prevent mast cell degranulation, these agents should not delay definitive treatment of
439 anaphylaxis.

440

441 Elevated tryptase levels have been less consistently found in patients presenting with
442 anaphylaxis, particularly in cases triggered by allergic response to food.(112) While the positive
443 predictive value of an elevated serum tryptase is high (93%), the negative predictive value of a
444 serum tryptase is low (17%).(2) However, several studies have reported an association between
445 elevation of tryptase and severity of anaphylaxis from food and other causes.(113-117) In a study
446 of prospectively recruited ED patients with anaphylaxis, mediators in addition to tryptase were
447 found to be correlated with hypotension, a symptom of severe anaphylaxis.(19) These included
448 histamine, IL-6, IL-10 and TNF-receptor 1.(19, 118) Several other mediators have been shown to
449 be important in murine models of anaphylaxis, but their contribution in human anaphylaxis has
450 not been clearly demonstrated – these include PAF (platelet-activating factor), CysLTs, and

451 anaphylatoxins. PAF is a lipid-derived mediator found to be elevated in serum of patients with
452 cold urticaria during cold challenge.(119) The role of PAF is supported by studies demonstrating
453 that injection of PAF into the skin of healthy volunteers can induce early wheal and flare and
454 late-phase flare responses.(120) These responses are not associated with increased dermal
455 histamine levels, (121) suggesting that the effects of PAF are independent of mast cell
456 degranulation. While some evidence suggests antihistamine attenuation of experimental
457 intradermally injected PAF mediated wheal and flare response, antihistamines had no protective
458 effect against PAF mediated bronchoconstriction during PAF bronchial provocation.(122)
459 Associations have been noted with increased PAF in cases of anaphylaxis. (113) In one study
460 increased PAF levels demonstrated the highest correlations with severe anaphylaxis (when
461 compared to histamine and tryptase levels), with PAF elevations in 20%, 67%, and 100% of
462 patients with grades 1, 2, and 3 allergic reactions, respectively (grade 1: acute allergic reactions
463 with cutaneous symptoms only; grade 2: mild to moderate anaphylaxis; grade 3: severe
464 anaphylaxis).(123) Data to support the role of CysLTs stem from studies showing that
465 intradermal injection of LTB₄, LTC₄ and LTD₄ can induce wheal and flare responses (124) and
466 aerosolized LTC₄ and LTD₄ can trigger bronchoconstriction. (125, 126) In a small study of insect
467 stinging challenges, elevated serum C3a was associated with severe anaphylaxis.(127) Additional
468 studies suggest that specific allergens such as peanut can contribute to anaphylaxis by activating
469 complement,(128) and tryptase can generate anaphylatoxins under specific conditions.(129)
470 These findings are important because they demonstrate some of the pathophysiologic
471 explanations that underpin why antihistamine use may be ineffective in management of
472 anaphylaxis.

473
474 Less is understood about the pathophysiology of protracted reactions.(130) A prospective study
475 of anaphylaxis cases seen in emergency departments in Australia reported delayed deterioration
476 (defined as any worsening of the reaction while under observation in the ED) in 17% of
477 reactions. (20) Of the delayed deteriorations, 53% were treated with epinephrine and 69% of
478 these started within 4 hours of arriving in the ED. A delay in the administration of epinephrine or
479 too small a dose of epinephrine are considered risk factors for delayed deterioration, though the
480 “optimal” timeframe for epinephrine delivery to prevent delayed deterioration has not been
481 established.(54, 131) Principal component analysis revealed an association between delayed

482 deterioration with elevated levels of histamine, tryptase, IL-6, IL-10 and TNF-receptor 1 (peak
483 concentrations on serial assessment at ED arrival, 1 hour later, and discharge). These are the
484 same mediators found to be correlated with severe anaphylaxis, (19, 20) lending support to the
485 hypothesis that severity of the initial reaction may be intrinsically linked to protracted symptoms.
486

487 Optimal duration of extended observation following resolution of biphasic anaphylaxis is
488 unknown.(54) One recent meta-analysis of twelve studies including 2,890 adult patients with
489 anaphylaxis suggested the pooled negative predictive value (NPV) of 1-hour observation was
490 95%, with an NPV for biphasic anaphylaxis after ≥ 6 hours of observation (following resolved
491 anaphylaxis) described to be 97.3%.(132) A recent cost-effectiveness analysis suggested costs of
492 observation would exceed \$10,000 per medically observed biphasic anaphylaxis unless the
493 recurrence rate exceeded 17% for patients discharged after a 1-hour asymptomatic interval
494 (Shaker et al, submitted for publication). From a healthcare sector perspective, extended
495 observation could be cost-effective at very high rates of fatality risk reduction (76%) from an
496 additional 5-hours of asymptomatic observation (Shaker et al, submitted for publication).
497

498 **TREATMENT STRATEGIES AND PARADIGMS**

500 ***Role of Epinephrine***

501 An understanding of the pathophysiology and effector cells involved in anaphylaxis reinforces
502 the recommendation to use epinephrine as first-line, while antihistamines and glucocorticoids are
503 considered solely second line therapy. As previously discussed, anaphylaxis is a clinical
504 diagnosis that can present with any combination of symptoms affecting various organ systems
505 (47). The clinical presentation and severity of symptoms differs between individuals and may
506 change over time within the same individual.
507

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

513

514 Epinephrine administered intramuscularly into the anterolateral thigh is the first-line treatment
515 for anaphylaxis.(47) Epinephrine is a nonselective agonist of all adrenergic receptors, which are
516 present within every organ system affected by anaphylaxis.(24) By increasing peripheral
517 resistance via alpha-1 receptors and increasing cardiac output via beta-1 receptors, epinephrine
518 causes vasoconstriction, which can treat hypotension, shock, urticaria, angioedema, and upper
519 airway mucosal edema. Epinephrine can reverse bronchoconstriction and treat lower respiratory
520 symptoms through its effect on beta-2 adrenergic receptors. In addition, epinephrine has been
521 shown *in vivo* to activate beta-2 adrenergic receptors on mast cells and basophils and prevent
522 additional release of histamine and other mediators.(25) Thus, epinephrine not only treats all
523 symptoms associated with anaphylaxis but it also can prevent the escalation of symptoms.

524

525 US, European, and international anaphylaxis guidelines recommend intramuscular epinephrine in
526 the anterolateral thigh rather than subcutaneous epinephrine in the deltoid region of the upper
527 arm for the treatment of anaphylaxis. (5, 133, 134) This is based upon a limited number of
528 pharmacodynamic studies in volunteers (not in anaphylaxis) which demonstrated that when
529 administered intramuscularly into the thigh, epinephrine works rapidly and reaches maximal
530 pharmacodynamic efficacy within 10 minutes of injection, though no proof exists that
531 subcutaneous delivery is not effective.(24) A small study conducted in children 4-12 years of age
532 demonstrated a higher mean peak plasma concentration (2136 ± 351 vs. 1802 ± 214 pg/ml) and
533 faster onset of action (8 ± 2 vs. 34 ± 14 minutes) for intramuscular compared with subcutaneous
534 administration of epinephrine.(135) A similar study in adult males also demonstrated higher
535 mean peak plasma concentration for intramuscular epinephrine in the thigh (9722 ± 4801 pg/ml)
536 compared with both intramuscular administration in the deltoid (1821 ± 426 pg/ml) and
537 subcutaneous administration in the deltoid region (2877 ± 567 pg/ml). From these limited data,
538 experts have advocated the intramuscular rather than the subcutaneous route of delivery, though
539 for years subcutaneous delivery was the mainstay, without any evidence that it was also not
540 effective. Importantly, studies comparing intramuscular and subcutaneous injections in the thigh
541 have not been completed. (136) Furthermore, the studies described above were conducted in
542 healthy adults and children who were not experiencing anaphylaxis, were taken from small
543 samples, and thus the generalizability of these findings to the clinical setting has not been

544 established. (133) There are also no data that have evaluated if the peak plasma concentration,
545 the time to peak plasma concentration, or the area under the curve is the most important feature
546 to effective epinephrine delivery in anaphylaxis. Efforts to develop alternative epinephrine
547 delivery routes (such as sublingual and intranasal epinephrine formulations) are underway. (137-
548 140) Intravenous administration of epinephrine is also not recommended as first-line treatment of
549 acute anaphylaxis, even in a medical setting, due to risk for cardiac adverse events such as
550 arrhythmias and myocardial infarction.(141) However, for patients with inadequate response to
551 intramuscular epinephrine and intravenous saline, intravenous epinephrine can be given by
552 continuous infusion by micro-drip, preferably using an infusion pump in a monitored hospital
553 setting. In more remote settings when immediate treatment is required on an outpatient basis, one
554 might consider using 1 mg (1 mL of 1:1,000) of epinephrine to 1,000 mL of 0.9 NL saline;
555 starting the infusion at 2 mcg/min (2 mL/min, equivalent of 120 mL/h) and increase up to 10
556 mcg/min (10 mL/min, equivalent of 600 mL/h); titrating the dose continuously according to
557 blood pressure, cardiac rate, and oxygenation. While there is a lack of evidence to inform
558 treatment approaches to biphasic anaphylaxis, the same treatment recommended for initial
559 anaphylactic events applies to the biphasic response, with prompt epinephrine the cornerstone of
560 management.(57)

561

562 An interesting conundrum surrounds those individuals who recover fully without sequelae
563 despite never receiving treatment for anaphylaxis. Variations in the cause and severity of their
564 symptoms and metabolism of mediators are likely involved but this remains poorly
565 understood.(106) Given the inability to identify which individual is at risk for life-threatening or
566 fatal anaphylaxis, particularly in the acute setting, and the well-recognized significant benefit
567 from rapid administration of epinephrine, treatment should never be withheld for ongoing
568 symptoms and this should be advocated as a best-practices strategy.(47) The mortality from
569 anaphylaxis, though real, is remarkably low at less than 0.5% per episode of anaphylaxis.(142)
570 Herein lies the anaphylaxis paradox – patients having anaphylaxis may survive despite lack of
571 treatment (or “inappropriate” treatment), but delay in treatment is widely presumed to be
572 associated with death (though limited by lack of studies that compare fatality to non-fatality
573 situations where provoking conditions and treatment factors were identical to determine a
574 relative risk).(29, 142)

575

576

577 ***Role of Antihistamines and Glucocorticoids***

578 Antihistamines are often included as adjunctive therapy for cutaneous symptoms associated with
579 anaphylaxis but should not be administered before, or in place of, epinephrine. Histamine is an
580 important mediator released during anaphylaxis, and can cause anaphylaxis when administered
581 intravenously.(110) There are four histamine receptors located through the body (H1, H2, H3,
582 and H4), but H1 receptors are the most clinically relevant during anaphylaxis. H2 receptors are
583 mostly found within the gastrointestinal tract with limited distribution in the vascular smooth
584 muscle cells and play a minor role in the pathophysiology of anaphylaxis. H1 and H2
585 antihistamine medications are widely available and often administered concurrently for the
586 treatment of anaphylaxis, without supporting data for their efficacy, in particular with H2
587 antihistamines. Compared with older first generation H1-antihistamines, second generation H1-
588 antihistamines have a longer duration of action, less anticholinergic effects, less sedation, yet
589 similar onset of action.(30) Antihistamines act as an inverse agonists at histamine receptors and
590 are effective therapy for patients with urticaria and can treat many of the cutaneous symptoms
591 associated with anaphylaxis including pruritus, flushing, and urticaria.(143) However, data
592 suggesting additive benefit of antihistamines to epinephrine administration during anaphylaxis is
593 lacking. Unlike epinephrine, antihistamines are poorly effective in treating cardiovascular and
594 respiratory symptoms such as hypotension or bronchospasm when used acutely as monotherapy.
595 Epinephrine is the first-line treatment of anaphylaxis because it has a faster onset of action and
596 more appropriate and robust pharmacologic action compared with antihistamines. When given
597 orally, the onset of action of antihistamines may occur within 30 minutes (144) but peak plasma
598 concentrations are not reached until 60-120 minutes, and an additional 60-90 minutes may be
599 necessary for diffusion of the medication into extravascular tissues to exert maximal effect.(30,
600 145, 146) Given the rapid and potentially fatal nature of anaphylaxis, the timing of onset for
601 antihistamines is considered too slow and could lead to incomplete or ineffective treatment.
602 Furthermore, antihistamines lack the vasoconstrictive, bronchodilatory, ionotropic, and mast cell
603 stabilization properties of epinephrine. While intravenous administration of H1-antihistamines
604 may be used in a medical setting or by emergency medical services, it should never be utilized in

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

607

608 Glucocorticoids are also frequently used as adjunctive (or sometimes primary) therapy in the
609 treatment of anaphylaxis but also should not be administered prior to, or in place of, epinephrine.

610 Glucocorticoids have no proven role in the treatment of an acute reaction as they work with slow
611 onset of action by binding to the glucocorticoid receptor on cell membranes, translocating the
612 glucocorticoid/glucocorticoid receptor complex to the nucleus, and inhibiting gene expression
613 and production of new inflammatory mediators. They are non-selective, ineffective in treating
614 acute symptoms, and have multiple adverse effects related to high doses and prolonged use.

615 There is a scarcity of data demonstrating the efficacy of glucocorticoids in the treatment of acute
616 anaphylaxis despite common anecdotal administration in this setting, and no studies have
617 established their benefit when combined with epinephrine and/or antihistamines.(32) Studies
618 investigating the use of glucocorticoids for treatment of anaphylaxis have shown that their use is
619 associated with reduced length of hospital stay but has not shown any benefit of preventing
620 return visits to the emergency department following discharge.(147, 148)

621

622 Given the mechanism of action, glucocorticoids may not result in clinical improvement for 4 to 6
623 hours after administration, regardless of route. Although animal studies and *in vivo* data have
624 demonstrated inhibitory effects within 5 to 30 minutes through up-regulation of anti-
625 inflammatory mediators and by decreasing mast cell mediator release on a cellular level (31,
626 149), there are no data demonstrating similar rapid onset of action or clinical improvement in
627 human subjects. As such, given the slow onset of action and inability to reverse acute symptoms,
628 it is again emphasized that glucocorticoids have a limited role in the acute management of
629 anaphylaxis.

630

631 **REVIEW OF EVIDENCE FOR SUPPLEMENTAL THERAPIES IN ANAPHYLAXIS** 632 **TREATMENT**

633 Despite a lack of clear evidence supporting the use of antihistamines and glucocorticoids in
634 anaphylaxis, these treatments continue to be a part of anaphylaxis management in routine
635 practice. While it is critical to ensure that use of these agents does not delay administration of

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

640

641 ***Methods & Overview***

642 The Anaphylaxis Workgroup that developed this guideline was composed of volunteers from the
643 AAAAI and the ACAAI with a specific interest in the topic and the guideline process. The
644 JTFPP and Anaphylaxis Workgroup were asked to submit questions regarding "anaphylaxis"
645 that they considered to be of importance for both the clinician and the patient for which currently
646 there was not a clear-cut answer. The workgroup used the Population, Intervention, Comparator,
647 Outcome (PICO) evidence-based framework for formulating each question. (150) After all
648 questions were discussed and informal preliminary searches completed, the workgroup used the
649 modified Delphi process (151, 152) to select and list top questions in priority order prior to
650 presenting them to the AAAAI/ACAAI for consideration. The top questions chosen by the
651 AAAAI/ACAAI were then submitted to the workgroup for Grading of Recommendations,
652 Assessment, Development and Evaluation (GRADE) analysis.(153)

653

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

655 The workgroup agreed to include cohort and observational studies, nonrandomized clinical trials,
656 and articles with multiple case studies provided a comparator was reported (Table 1). While
657 review articles, guidelines, and editorials were excluded from analysis, they were reviewed to
658 locate primary research studies within the bibliography. The search was limited to human
659 subjects and to articles published in the English language. For each of the questions, the
660 described databases were searched and duplicates removed, the abstracts were uploaded into
661 Covidence (Melbourne, Australia) or Rayyan (Dohan, Qatar), web-based software platforms
662 used by guideline writing groups (e.g., Cochrane Reviews) to streamline the production of
663 systematic reviews. Each abstract was reviewed by two workgroup members or collaborators and
664 categorized as relevant or irrelevant based upon the predetermined inclusion/exclusion criteria.
665 When required, a third workgroup member resolved any disagreement by consensus. For all
666 relevant abstracts, full-text articles were uploaded into Covidence or Rayyan. Two members

667 assessed each full-text article for eligibility for qualitative analysis with any disagreement
668 resolved by consensus of a third member. Supplemental searches were performed to address
669 questions more targeted areas including prophylaxis to prevent recurrence of anaphylaxis to
670 nonionic low osmolar or iso-osmolar, radiocontrast media, and prevention of index anaphylaxis
671 with chemotherapeutic agents. The resultant studies were extracted by JTFPP members and
672 methodology groups, who assessed each article to determine if they were appropriate for
673 quantitative meta-analysis. In that each question used varying databases, dates,
674 inclusion/exclusion criteria, these were discussed within the methodological review for each
675 question.

676

677 ***Quality Assessment of the Included Studies: Risk of Bias Using GRADE Analysis***

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

685

686 ***Certainty of the Body of Evidence Using GRADE Analysis***

687 For GRADE analysis of the certainty of the evidence (153), five areas were evaluated:
688 inconsistency, indirectness, imprecision, risk of bias, and publication bias.

689 **Inconsistency:** studies are reviewed in terms of populations, interventions, and outcomes for
690 similarity, or consistency, among the compared studies.

691 **Indirectness:** analysis occurs around comparisons, populations, and outcomes among
692 intervention studies. Indirectness in comparisons occurs when one drug is compared with
693 placebo and another drug is compared with placebo, but the researchers do not compare the first
694 drug and the second drug in a head-to-head comparison. Indirectness in populations means that
695 the population in which the drug was studied does not reflect the population in which the study
696 drug would be used. Indirectness of outcome refers to a primary or secondary outcome that does
697 not exactly measure the intended outcome and thus is not powered for the outcome of choice.

698 **Imprecision:** when too few study participants were enrolled or too few events occurred in the
699 study, imprecision is detected as studies do not meet optimal information size (OIS). However,
700 low OIS may be offset by critical vs important outcome or valued trade-off desirable/undesirable
701 consequences. In systematic reviews, if the confidence interval crosses a threshold of 1.0, there
702 will usually be downgrading for imprecision.

703

704 *Levels of Certainty of Evidence*

705 **High:** The team is very confident that the true effect lies close to the estimate of the effect.

706 **Moderate:** The team is moderately confident in the effect estimate. The true effect is likely to be
707 close to the estimate of the effect, but there is a possibility that it is substantially different.

708 **Low:** The team confidence in the effect estimate is limited. The true effect may be substantially
709 different from the estimate of the effect.

710 **Very low:** The team has very little confidence in the effect estimate. The true effect is likely to
711 be substantially different from the estimate of effect.

712

713 *Implications of strong and weak recommendations*

714 The implications of a strong recommendation are:

- 715 • For patients—most people in your situation would want the recommended course of action
716 and only a small proportion would not; request discussion if the intervention is not offered
- 717 • For clinicians—most patients should receive the recommended course of action
- 718 • For policy makers—the recommendation can be adopted as a policy in most situations

719

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

- 721 • For patients—most people in your situation would want the recommended course of action,
722 but many would not
- 723 • For clinicians—you should recognize that different choices will be appropriate for different
724 patients and that you must help each patient to arrive at a management decision consistent
725 with her or his values and preferences
- 726 • For policy makers—policy making will require substantial debate and involvement of many
727 stakeholders

728

729 ***Reaching Workgroup Consensus on Certainty of Evidence, Recommendations, Clinical***
730 ***Statement Profiles and Conclusions***

731 To achieve consensus and resolve any differences in judgment within the workgroup and JTFPP,
732 a modified Delphi method was used. The Delphi method is a structured, interactive, decision-
733 making process used by a panel of experts to arrive at a consensus when there are differing views
734 and perspectives. (151, 154, 155) The workgroup and/or JTFPP members discussed all the
735 answers and were encouraged to modify their answers on the next round(s) of email voting and
736 anonymous “summary of the experts” feedback until a consensus was reached.

737

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

739 The quality of evidence indicates the extent to which one can be confident that an estimate of
740 effect is correct. The GRADE system for evaluating the quality of evidence ([http://](http://gdt.guidelinedevelopment.org/app)
741 gdt.guidelinedevelopment.org/app) defines the elements that guideline writing groups need to
742 consider when evaluating the quality of references that address a specific outcome. These
743 elements include factors that assess the risk of bias and the certainty of evidence as described
744 above, as well as the article design (e.g. RCT or observation study). Methodology groups may
745 designate a method of rating the quality of individual references to assist in this analysis.
746 Following a determination of the quality of each individual reference, the GRADE handbook
747 recommends that in the final analysis for each outcome of interest, the quality of evidence for the
748 entire group of references should be determined by the guideline writing group, using their
749 collective expert opinion. The outcomes of interest are then categorized as “critical” or
750 “important but not critical” to reaching a decision for a recommendation. For the determination
751 of the “overall quality of evidence” supporting a recommendation, all “critical” outcomes are
752 reviewed together, and the lowest quality grade assigned to any critical outcome of interest will
753 determine the quality assigned for the “overall quality of evidence” to support a
754 recommendation.

755

756 ***GRADE: From Certainty in Evidence to Recommendations for diagnosis, treatment, or course***
757 ***of action***

758 The strength of a recommendation indicates the extent to which one can be confident that
759 adherence to the recommendation will do more good than harm. After the quality of evidence is

760 evaluated, the GRADE analysis continues to consider additional factors before recommending or
761 suggesting in favor or against a certain diagnostic, therapeutic approach, or course of action:
762 balance of desirable and undesirable effects, certainty of evidence, safety of the intervention,
763 cost, likelihood of achieving adherence, acceptability, feasibility, equity, and patient's
764 preference. The JTFPP primarily focused on the US population when reaching these conclusions.
765 Therefore, the GRADE analysis is not only a system focused on grading the level of evidence
766 but also a much more complete system aimed at formulating recommendations for specific
767 populations. Individual subgroups drafted the recommendations and justifications based on the
768 GRADE analysis. Subsequently, all recommendations were reviewed by the workgroup and
769 JTFPP. Both groups were provided the opportunity to comment, propose changes, and approve
770 or disapprove each statement. Consensus was sought and reached for each recommendation's
771 direction and strength. Actual or potential conflicts of interest were disclosed semiannually and
772 at the completion of the guideline with transparency maintained during all discussions.

773

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

777

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

780

781 **Patients:** Adults and children treated for anaphylaxis

782 **Intervention:** Any treatment or characteristic associated with a decreased risk of biphasic
783 anaphylaxis including medication or other trigger; epinephrine, antihistamine, glucocorticoid, or
784 other treatment; age, severity, physical examination finding, or other patient characteristic

785 **Comparator:** Dichotomous comparator of characteristic under evaluation

786 **Outcome:** Occurrence of biphasic anaphylaxis

787

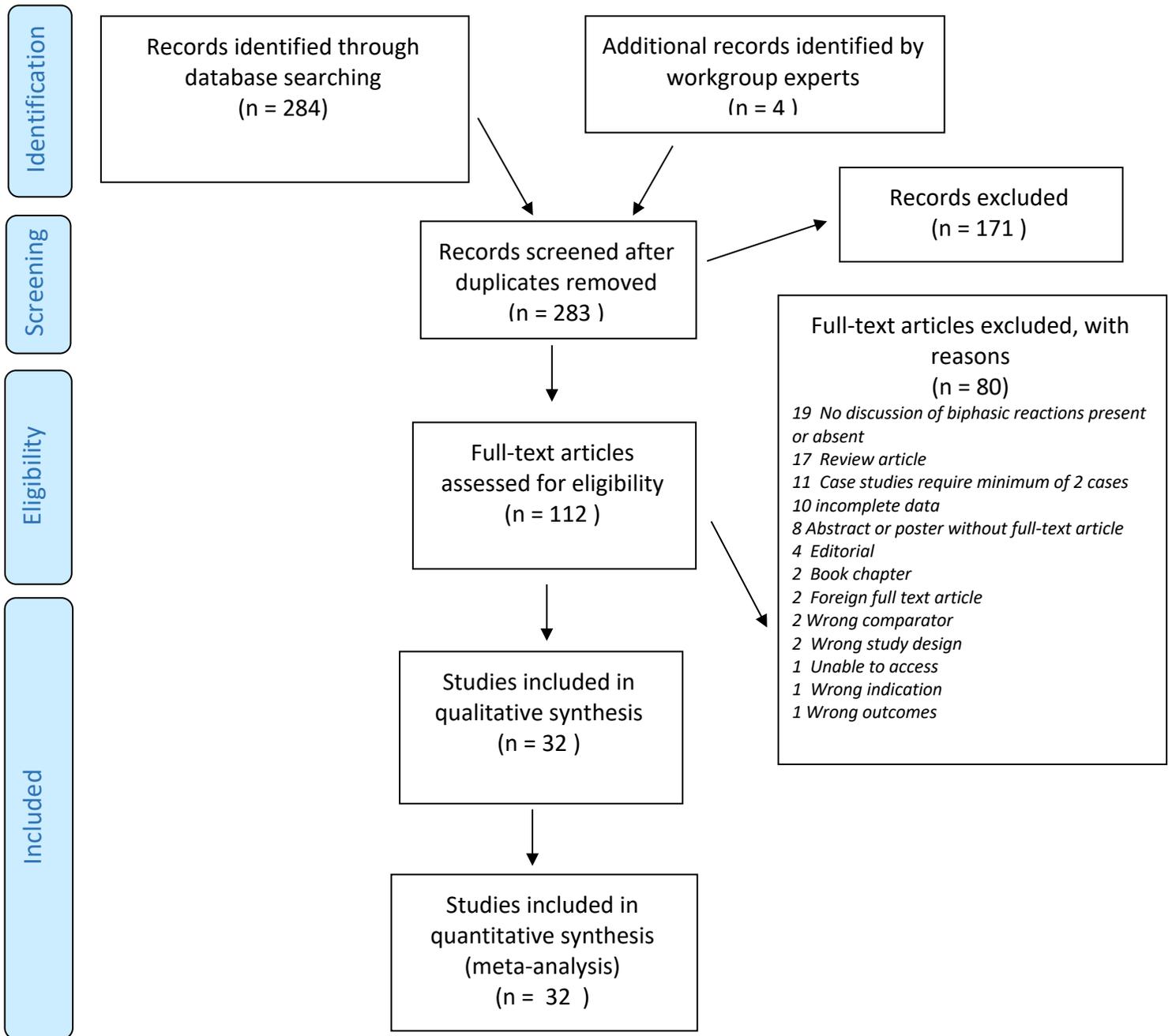
788 **Background:** A prior single-center review of biphasic anaphylaxis in 103 patients suggested
789 biphasic reactions were more common in patients who received less epinephrine ($p=0.048$) and
790 possibly less corticosteroid ($p=0.06$) treatment.(35) A systematic review by Lee et al (56) found
791 twenty-seven observational studies that reviewed predictors of biphasic anaphylactic reactions.

792 Of the studied predictors, food as an anaphylactic trigger was associated with a decreased risk of
793 a biphasic reaction, $OR = 0.62$, 95% CI [0.4, 0.94] and the ‘unknown’ anaphylactic trigger was
794 associated with increased risk of a biphasic reaction, $OR = 1.72$, 95% CI [1.0, 2.95]. An initial
795 presentation with hypotension was also associated with an increased risk of a biphasic reaction,
796 $OR = 2.18$, 95% CI [1.14, 4.15].

797

798 **Study characteristics.** The search for suitable studies was completed by the JTFPP. In the
799 search 283 articles were identified after removal of duplicates, with full text eligibility assessed
800 in 112 studies, and 32 studies included in the quantitative evidence synthesis (Q1 PRISMA
801 diagram)

802



804 **Studies Included:**

805 Alqurashi 2015 (156); Brady 1997 (157); Brazil 1998 (158);Brown 2013 (20);Calvani 2011
806 (159); Cianferoni 2011 (160); Confino-Cohen 2010 (161); Douglas 1994 (162); Ellis 2007 (35);
807 Grunau 2014 (55); Inoue 2013 (163); Jirapongsananuruk 2007 (164); Ko 2015 (165); Lee
808 (2000); Lee 2013 (166); Lee 2017 (59); Lertnawapan 2011 (167); Manivannan 2014 (168);
809 Manuyakorn 2015 (169); Mehr 2009 (170);Noone 2015 (171); Orhan 2011 (172); Poachanukoon
810 2006 (173); Rohacek 2014 (37); Sampson 1992 (34); Scranton 2009 (174); Smit 2005 (175);
811 Sricharoen 2015 (52); Stark 1986 (33); Vezir 2013 (176); Yang 2008 (177)

812

813 **Key results.** Based on very low quality evidence, the following associated factors significantly
814 increase the risk of biphasic anaphylaxis: (a) anaphylaxis caused by any drug in patients less than
815 18 years of age, *Peto OR* = 2.35, 94% *CI* [1.16, 4.76] (b) anaphylaxis caused by an unknown
816 trigger, *Peto OR* = 1.63, 95% *CI* [1.14, 2.33] (c) anaphylaxis symptoms with cutaneous
817 manifestations, *Peto OR* = 2.54, 95% *CI* [1.25, 5.15] (d) anaphylactic symptom of wide pulse
818 pressures, *Peto OR* = 2.11, 95% *CI* [1.32, 3.37] (e) severe initial anaphylaxis symptoms, *Peto OR*
819 = 2.11, 95% *CI* [1.23, 3.61] (d) anaphylaxis in patients less than 18 years of age treated with
820 steroids, *Peto OR* = 1.55, 95% *CI* [1.01, 2.38] and (e) patients requiring more than one dose of
821 epinephrine *Peto OR* = 4.82, 95% *CI* [2.70 to 8.58]. The bias of the studies ranged from
822 moderate to high due to retrospective data, exclusions due to missing data, limited patient
823 populations, and limited follow-up.

824

825 **Summary by Predictive Variable**

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

829

830 **Unknown Trigger.** Twenty-one retrospective observational studies ($n = 4275$) are included for
831 this outcome (Alqurashi et al., 2015; Brady Jr, Lubner, Carter, Guertler, & Lindbeck, 1997; Brazil
832 & MacNamara, 1998; Cianferoni et al., 2001; Douglas, Sukenick, Andrade, & Brown, 1994;
833 Ellis & Day, 2007; Grunau et al., 2014; Inoue & Yamamoto, 2013; Jirapongsananuruk et al.,
834 2007; J. M. Lee & Greenes, 2000; S. Lee, Peterson, Lohse, Hess, & Campbell, 2017;

835 Lertnawapan & Maek-a-nantawat, 2011; Manivannan et al., 2014; Manuyakorn et al., 2015;
836 Mehr et al., 2009; Rohacek, Edenhofer, Bircher, & Bingisser, 2014; Smit, Cameron, & Rainer,
837 2005; Sricharoen, Sittichanbuncha, Wibulpolprasert, Srabongkosh, & Sawanyawisuth, 2015;
838 Stark & Sullivan, 1986; Vezir et al., 2013; Yang et al., 2008). The pooled *Peto OR* was 1.63,
839 95% *CI* [1.14, 2.33]. Using a fixed-effect analysis, patients with anaphylaxis from an unknown
840 trigger have a higher risk of having a biphasic reaction. The evidence is graded very low quality
841 based on very serious risk of bias and serious inconsistency between the included studies. Biases
842 include (a) the use of retrospective data, (b) limited or no follow-up, (c) limited patient selection
843 (inpatient setting), and (d) exclusion of subjects due to missing data. Inconsistency was graded as
844 serious due to moderate heterogeneity as evidenced by an $I^2 = 45\%$.

845
846 **Drug Trigger in Patients ≤ 18 years of age.** Five retrospective observational studies ($n = 996$)
847 measured this outcome (Alqurashi et al., 2015; Manuyakorn et al., 2015; Mehr, Liew, Tey, &
848 Tang, 2009; Orhan et al., 2011; Vezir et al., 2013). The pooled *Peto OR* was 2.35, 95% *CI* [1.16,
849 4.76]. Using a fixed-effect analysis, patients ≤ 18 years of age who have anaphylaxis from a drug
850 trigger are at a higher risk of having a biphasic reaction than patients ≥ 18 years of age with a
851 drug trigger. The evidence is graded very low quality based on (a) very serious risk of bias as
852 the studies were retrospective in nature with limited or no follow-up; (b) serious inconsistency as
853 the studies had moderate heterogeneity, $I^2 = 46\%$; and (c) serious imprecision as the studies had
854 a low number of events.

855
856 **Cutaneous Symptoms.** Six retrospective observational studies ($n = 1949$) are included for this
857 outcome (Alqurashi et al., 2015; Grunau et al., 2014; Inoue & Yamamoto, 2013; J. Lee, Garrett,
858 Brown-Whitehorn, & Spergel, 2013; Manuyakorn et al., 2015; Mehr et al., 2009). The pooled
859 *Peto OR* was 2.54, 95% *CI* [1.25, 5.15]. Using a fixed-effect analysis, patients with cutaneous
860 symptoms are at higher risk of having a biphasic reaction than patients without cutaneous
861 symptoms. The evidence is graded very low quality based on very serious risk of bias and
862 inconsistency, and serious imprecision. The biases include (a) the use of retrospective data, (b)
863 limited or no follow-up, (c) limited patient selection (inpatient setting). The definition of
864 cutaneous symptoms varied across studies, coupled with an $I^2 = 43\%$, inconsistency is graded as

865 very serious. Finally, the included studies are downgraded for serious imprecision, as there was a
866 low number of events, and the confidence interval for the summary statistic is wide.

867

868 **Dyspnea.** Six retrospective observational studies ($n = 1841$) are included for this outcome
869 (Brazil & MacNamara, 1998; Inoue & Yamamoto, 2013; S. Lee et al., 2017; Rohacek et al.,
870 2014; Smit et al., 2005; Sricharoen et al., 2015). The pooled *Peto OR* was 0.6, 95% *CI* [0.38,
871 0.9]. Using a fixed-effect analysis, patients with dyspnea are at lower risk of having a biphasic
872 reaction than patients without dyspnea. The evidence is graded very low quality based on (a)
873 serious risk of bias as the studies are retrospective observational studies and included studies had
874 limited or no follow-up; (b) serious inconsistency as the studies had substantial heterogeneity $I^2 =$
875 73%; (c) serious imprecision as the studies had a low number of events.

876

877 **Wide Pulse Pressure.** Two retrospective observational studies ($n = 1356$) are included for this
878 outcome (Alqurashi et al., 2015; S. Lee et al., 2017). The pooled *Peto OR* was 2.11, 95% *CI*
879 [1.32, 3.37]. Using a fixed-effect analysis, patients with a wide pulse pressure are at higher risk
880 of having a biphasic reaction than patients without a wide pulse pressure. The evidence is graded
881 very low quality based on (a) serious risk of bias as the studies are retrospective observational
882 studies and (b) serious imprecision as the studies had a low number of events.

883

884 **Severe Initial Anaphylaxis.** Five retrospective observational studies ($n = 724$) are included for
885 this outcome (Brown et. Al., 2013; Confino-Cohen & Goldberg, 2010; J. M. Lee & Greenes,
886 2000; Manuyakorn et al., 2015; Vezir et al., 2013). The pooled *Peto OR* was 2.11, 95% *CI* [1.23,
887 3.61]. Using a fixed-effect analysis, patients with a severe initial anaphylaxis are at higher risk of
888 having a biphasic reaction than patients without severe anaphylaxis. The evidence is graded very
889 low quality based on (a) very serious risk of bias as the studies are retrospective observational
890 studies and included studies with limited or no follow-up; (b) serious inconsistency as the studies
891 used different definitions for severe anaphylaxis; (c) serious imprecision as the studies had a low
892 number of events.

893

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

896 2017; Mehr et al., 2009; Scranton, Gonzalez, & Waibel, 2009). The pooled *Peto OR* was 4.82,
897 95% *CI* [2.70 to 8.58]. Using a fixed-effect analysis, patients who receive more than one
898 epinephrine treatment initially are at increased risk of having a biphasic reaction. The evidence is
899 graded very low quality based on (a) very serious risk of bias as the studies are retrospective
900 observational studies and included studies with limited or no follow-up; (b) serious imprecision
901 as the studies had a low number of events.

902

903 **Steroid Treatment In Patients ≤ 18 years of age.** Seven retrospective observational studies (n
904 = 1203) are included for this outcome (Alqurashi et al., 2015; Calvani et al., 2011; Inoue &
905 Yamamoto, 2013; J. M. Lee & Greenes, 2000; Manuyakorn et al., 2015; Mehr et al., 2009; Vezir
906 et al., 2013). The pooled *Peto OR* was 1.55, 95% *CI* [1.01, 2.38]. Using a fixed-effect analysis,
907 patients ≤ 18 years of age who receive steroid treatment are at a higher risk of having a biphasic
908 reaction than patients ≥ 18 years of age who receive steroid treatment. The evidence is graded
909 very low quality based on (a) very serious risk of bias as the studies are retrospective
910 observational studies, included studies with limited or no follow-up, and included limited patient
911 selection (inpatient setting); (b) serious imprecision as the studies had a low number of events.

912

913 **Time to First Epinephrine.** Eight retrospective observational studies ($n = 1469$) are included for
914 this outcome. Reviewers were unable to perform an analysis for this outcome since the authors
915 provided interquartile range (IQR) and median values and therefore this outcome could not be
916 pooled together. Three of the eight studies showed delayed administration of epinephrine
917 resulted in higher rates of biphasic anaphylaxis while the other five studies showed no statistical
918 difference. S. Lee et al. (2017) identified 872 anaphylaxis-related visits to an emergency
919 department from 2008-2015. There was a statistically significant association with biphasic
920 reactions when the first dose of epinephrine was administered more than 60 minutes after
921 symptoms developed, $OR = 2.29$, 95% CI [1.09, 4.79]. J. M. Lee and Greenes (2000) also
922 performed a retrospective analysis of 108 children admitted to a children's hospital. The median
923 time from initial symptoms to initial dose of epinephrine for patients with a biphasic reaction
924 was 190 min and 48 min for patients without a biphasic reaction ($p = .03$). Lertnawapan and
925 Maek-a-nantawat (2011) conducted an observational study on patients ($n = 208$) presenting to an
926 emergency department with anaphylaxis. Time from symptoms onset to administration of

927 epinephrine was significantly longer in the biphasic group than the no biphasic group, at 240
 928 minutes (IQR 122.5-380) vs 70 minutes (IQR 40-135) minutes, $p = 0.002$. Alqurashi et al. (2015)
 929 found median time from the onset of the reaction to first dose of epinephrine was not statistically
 930 different between patients with biphasic reactions (64 minutes, IQR 25-175) and without
 931 biphasic reactions (59 minutes, IQR 25-105), $p = 0.35$. Ko et al. (2015) showed no association
 932 was observed between the timing of epinephrine and the occurrence of biphasic reactions ($p =$
 933 $.52$). Median time from symptoms to epinephrine was 30 minutes (IQR 20-60) in the no biphasic
 934 group and 70 minutes (IQR 20-570) in the biphasic groups. Poachanukoon and
 935 Paopairochanakorn (2006) found the median time from the onset of symptoms to the initial
 936 administration of epinephrine in the patients with biphasic reactions was longer than in the no
 937 biphasic group but it did not reach statistical significance. Median time to initial dose of
 938 epinephrine in the no biphasic group was 82 minutes and 263 minutes in the biphasic group. No
 939 range was given. Scranton et al. (2009) found no difference in mean time to epinephrine between
 940 the no biphasic group $8.5 \text{ minutes} \pm 13.8$ and the biphasic group $8.2 \text{ minutes} \pm 12.8$, $p = .94$. J.
 941 Lee et al. (2013) found no difference in time from first reaction onset to first epinephrine dose
 942 between the no biphasic group 23.0 minutes and the biphasic group 28.5 minutes, $p = .60$

943
 944 **Food Trigger:** Although previously found to be associated with a decreased risk for biphasic
 945 anaphylaxis,(56) the current analysis did not find a significant association of foods with
 946 decreased risk for biphasic anaphylaxis (Peto OR 0.89, 95% CI [0.68 , 1.17].

947
 948 **Table Q1**

949 **GRADE Summary of Findings Table**

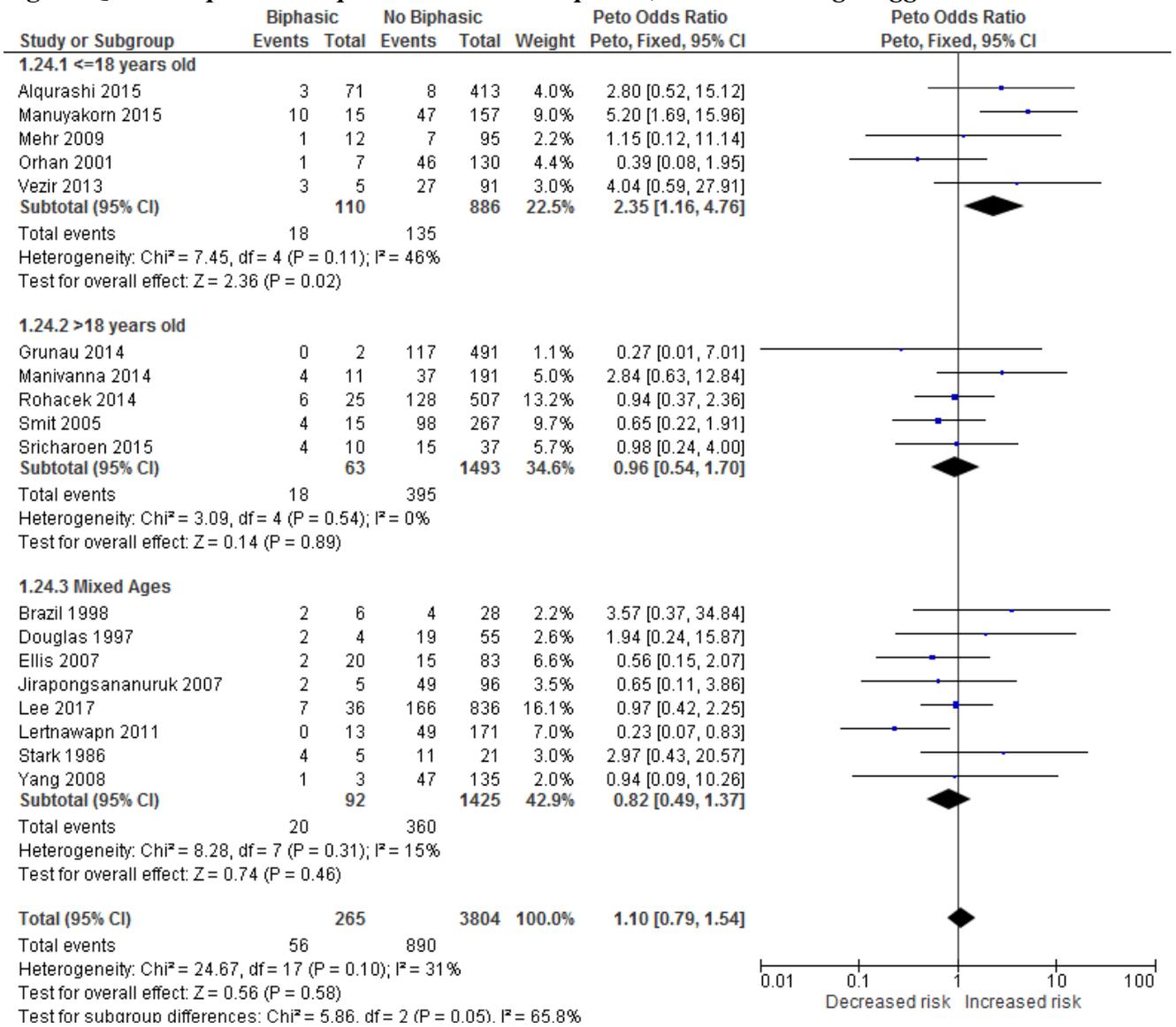
Certainty assessment							Summary of findings				
No of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With No Biphasic	With Biphasic		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	247/1 249 (19.8 %)	40/1 07 (37. 4%)	OR 2.11 (1.3 2 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	248/6 38 (38.9 %)	44/8 6 (51. 2%)	OR 2.11 (1.2 3 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	130/1 449 (9.0%)	34/1 35 (25. 2%)	OR 4.82 (2.7 0 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	632/1 089 (58.0 %)	78/11 4 (68.4 %)	OR 1.55 (1.0 1 to 2.38)	580 per 1,000	102 more per 1,000 (2 more to 187 more)

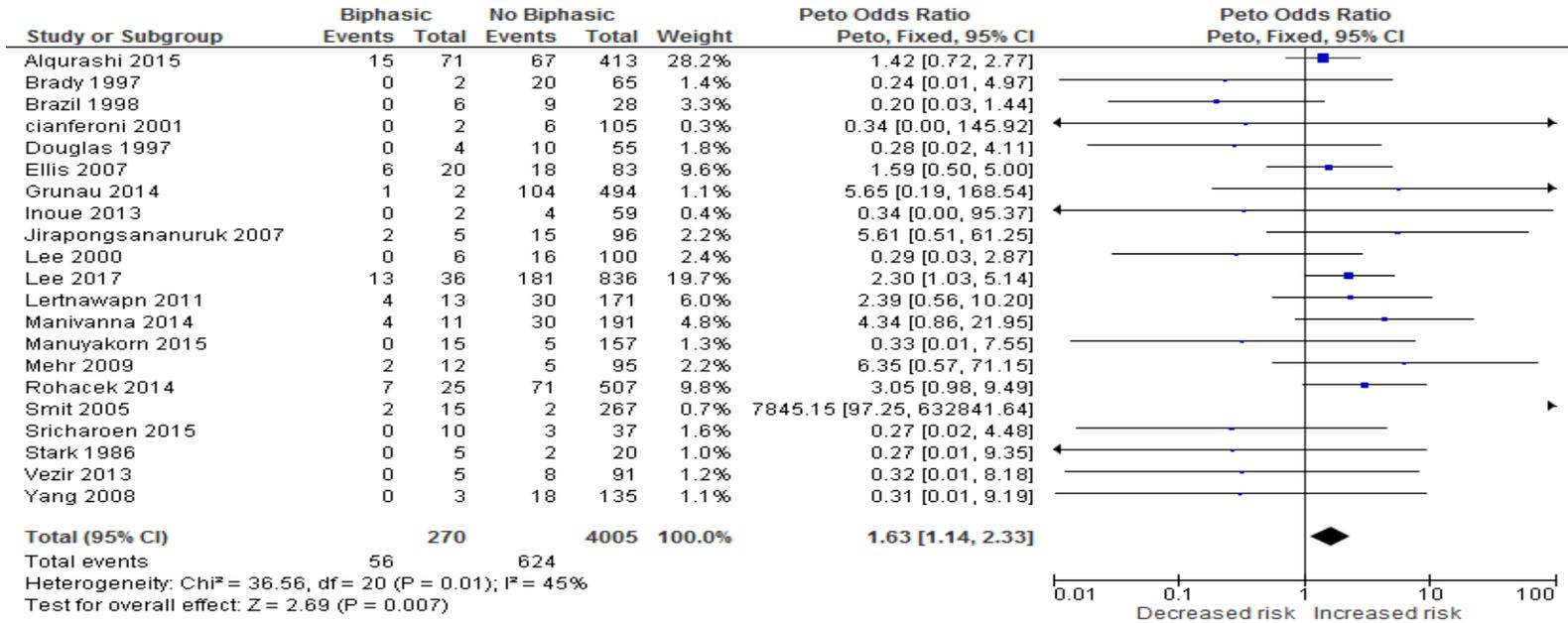
- 951 Explanations
- 952 a. Retrospective data may introduce selection bias and increase possible confounding errors
- 953 b. Low number of events (less than 250 biphasic reactions)
- 954 c. Included study or studies with limited follow-up of 24 hours or no follow-up resulting in
- 955 possible missed biphasic patients
- 956 d. Included study or studies with limited patient selection including patients from inpatient
- 957 setting or from a specialty clinic
- 958 e. Included study or studies with larger exclusion of patients due to missing data
- 959 f. Moderate heterogeneity as evidence by I^2 of 30-60%
- 960 g. Wide confidence interval
- 961 h. Substantial heterogeneity as evidence by I^2 of 50-90%
- 962 i. Different definitions of cutaneous symptoms
- 963 j. Different scales for measuring severity of anaphylactic reaction
- 964

965 **Figure Q1a: Comparison: Biphasic Versus No Biphasic, Outcome: Drug Trigger**



966
967
968

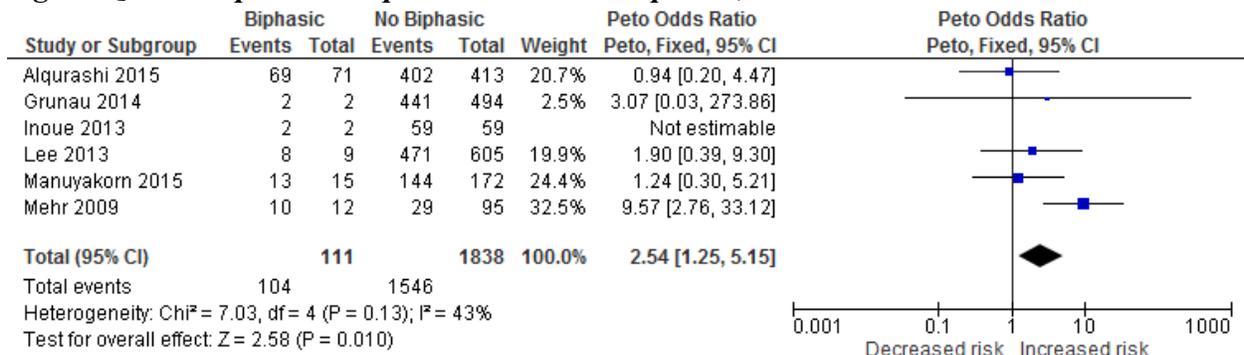
Figure Q1b : Comparison: Biphasic Versus No Biphasic, Outcome: Unknown Trigger



969

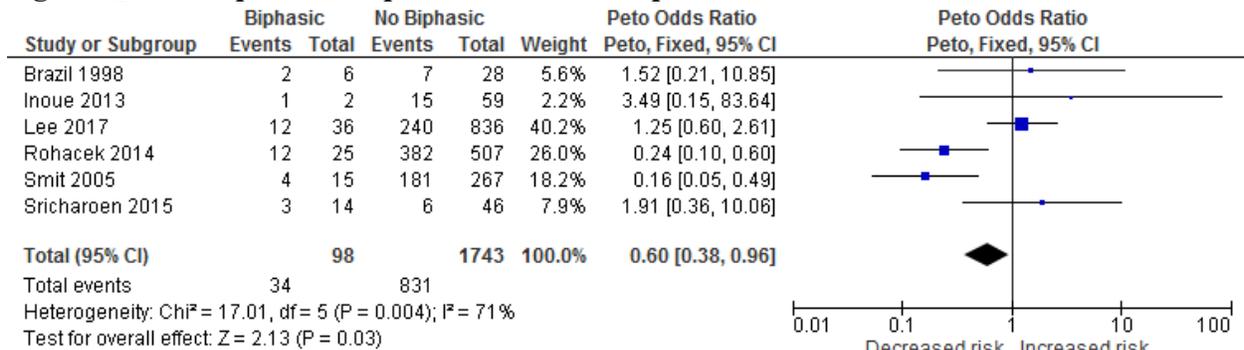
970

971 **Figure Q1c: Comparison: Biphasic Versus No Biphasic, Outcome: Cu**



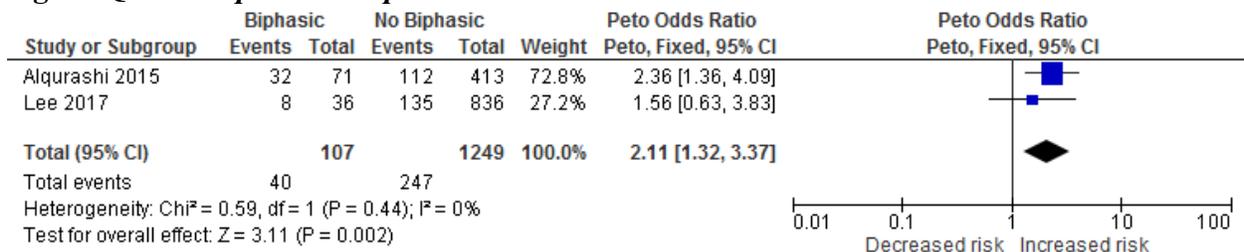
972
973 *taneous Symptoms*

974
975
976
977 **Figure Q1d: Comparison: Biphasic Versus No Biphasic,**



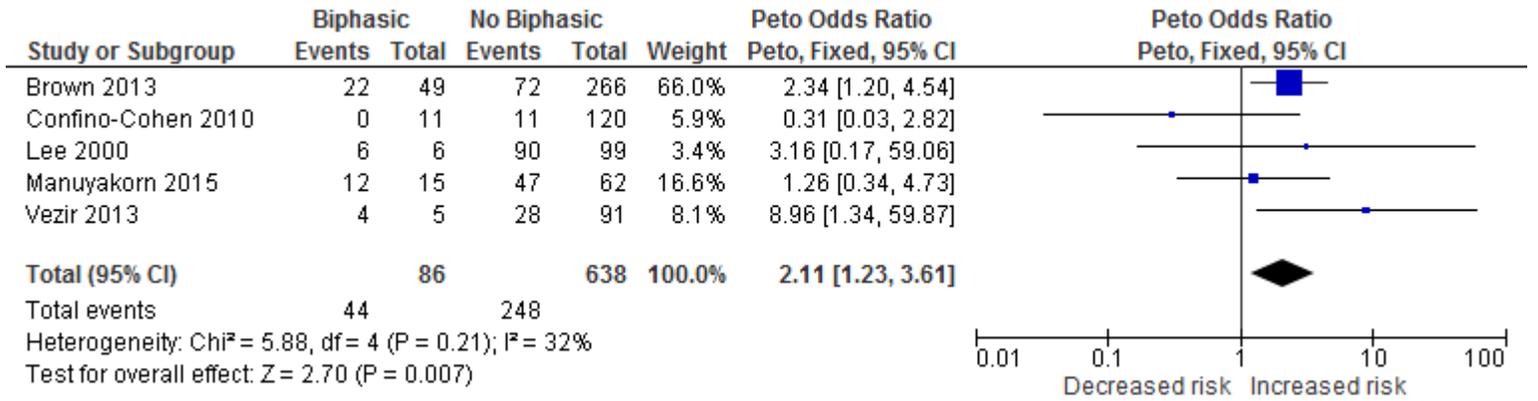
978
979 *Outcome: Dyspnea Symptoms*

980
981 **Figure Q1e: Comparison: Biphasic Versus No B**



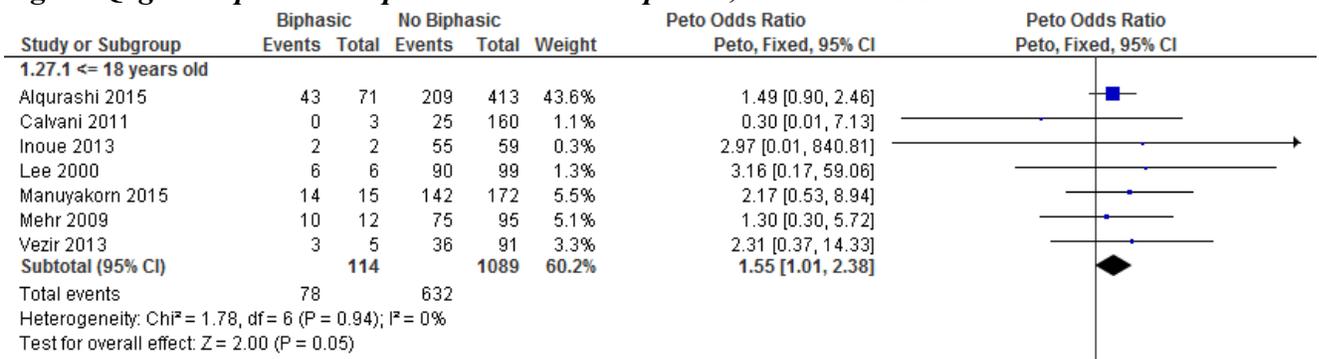
982
983 *iphasic, Outcome: Wide Pulse Pressure*

984
985
986 **Figure Q1f: Comparison: Biphasic Versus No Biphasic, Outcome: Severe Initial Symptoms**



987
 988
 989

990 **Figure Q1g: Comparison: Biphasic versus No Biphasic, Outcome: Steroids**

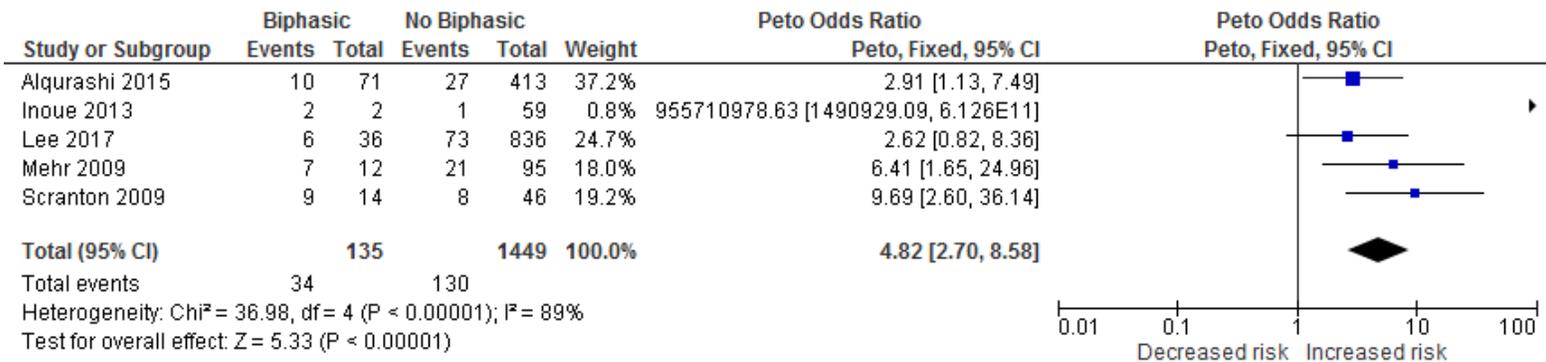


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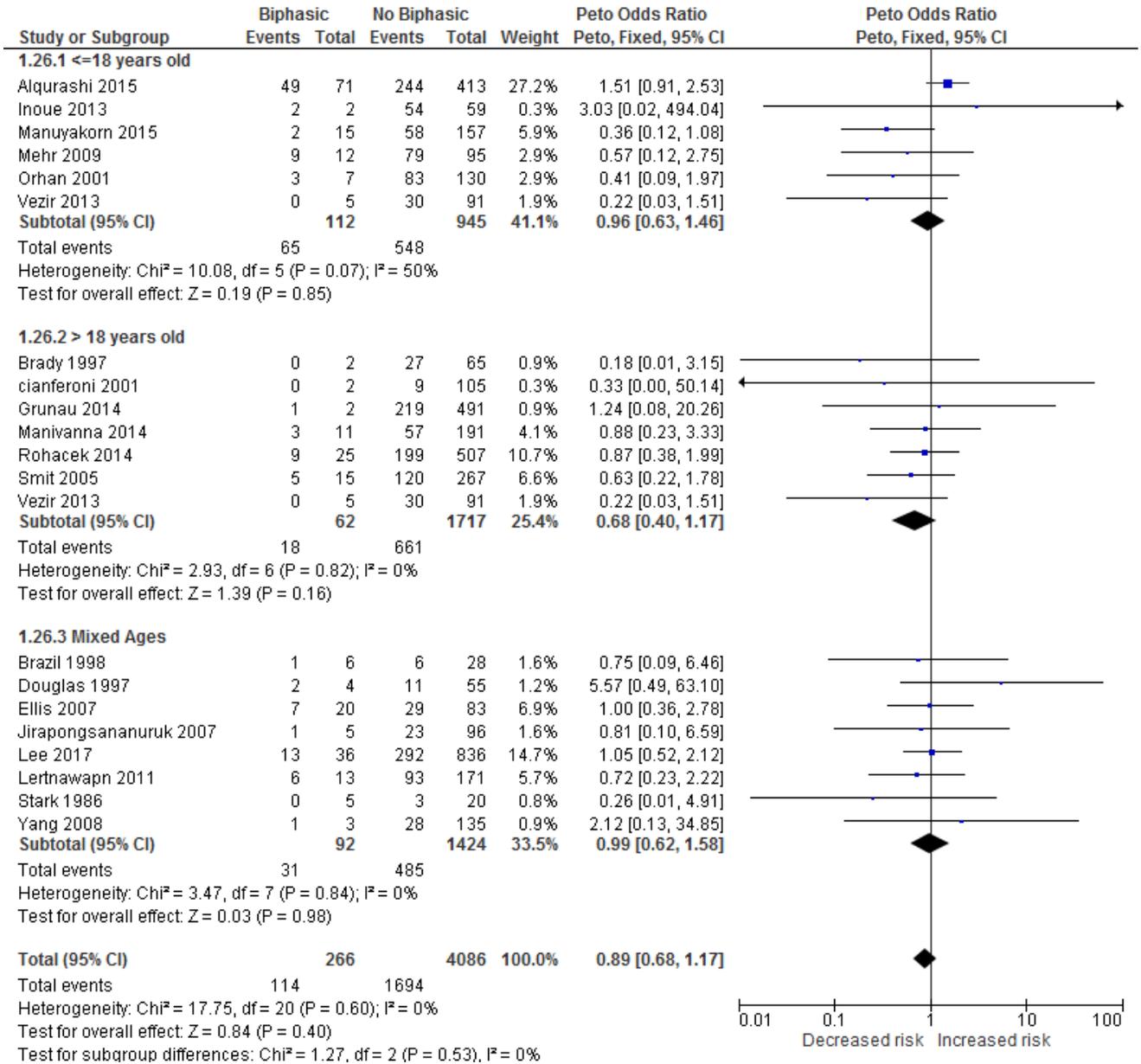
993 **Figure Q1h: Comparison: Biphasic versus No Biphasic, Outcome: Greater than One**
 994 **Epinephrine**

995



996

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



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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

1003

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.

1005

1006 ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes • Yes ○ Varies ○ Don't know 	<p>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)</p> <p>The prevalence of fatal</p>	<p>There is some uncertainty as to the exact rate of biphasic anaphylaxis and evidence regarding optimal treatment for biphasic anaphylaxis is scant.</p>

	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
<ul style="list-style-type: none"> ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know 	<p>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].</p> <p>Additional associations include: (d) anaphylaxis caused by any drug in patients</p>	<p>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).</p>

	<p>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].</p>	
--	--	--

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know 	<p>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</p>	<p>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.</p>

	<p>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.</p>	
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Certainty of evidence (Intentional vagueness)		
What is the overall certainty of the evidence of effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> • Very low ○ Low ○ Moderate ○ High ○ No included studies 	<p>Across variables evaluated, heterogeneity ranged from low ($I^2=0\%$) to high ($I^2=89\%$).</p> <p>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 ≥ 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)</p>	<p>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)</p>

Values (Value judgments)		
Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability 	<p>All patients would prefer to avert biphasic anaphylaxis.</p> <p>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.</p>	<p>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.</p>

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
<ul style="list-style-type: none"> ○ 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 	<p>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.</p>	<p>Biphasic anaphylaxis may occur in any patient with anaphylaxis and all patients should seek care if anaphylaxis recurs after initial resolution.</p>

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings 	<p>Direct and indirect costs may vary depending on how risk factors are incorporated into patient management.</p> <p>Prolonged emergency department observation or</p>	<p>Anaphylaxis patient education, referral to an allergist, and prescription of an epinephrine auto-injector at discharge are important for all patients with anaphylaxis.(41)</p>

<ul style="list-style-type: none"> • Varies ○ Don't know 	<p>inpatient admission could dramatically increase costs of anaphylaxis management.</p> <p>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.</p>	
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Certainty of evidence of required resources
 What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low • Low ○ Moderate ○ High ○ No included studies 	<p>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)</p>	<p>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.</p>

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ 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. 	<p>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.</p>	<p>Cost-effectiveness may be sensitive to rates of biphasic reactions, cost of observation, hospitalization rates, and anaphylaxis fatalities.</p>

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Reduced ○ Probably reduced 	<p>The impact on equity may vary depending on how risk</p>	<p>All patients experiencing anaphylaxis should be closely</p>

<ul style="list-style-type: none"> ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know 	<p>factors are incorporated into patient management.</p> <p>Prolonged periods of medical observation in patients with resolved anaphylaxis could negatively impact equity and may discourage patients from seeking medical care.</p>	<p>observed until they are stable and suitable for discharge.</p> <p>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.</p> <p>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.</p>
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Acceptability & Quality improvement opportunity
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know 	<p>Evidence suggests that a 1-hour symptom-free observation period of non-severe anaphylaxis has a 95% NPV for biphasic anaphylaxis.(132)</p>	<p>The concept that more severe anaphylaxis is associated with a greater risk for biphasic anaphylaxis is intuitive and would be acceptable to most stakeholders.</p>

Feasibility		
Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know 	<p>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)</p>	<p>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).</p>
Intentional Vagueness		
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know 	<p>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)</p>	<p>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.</p>

Role of Patient Preference		
<ul style="list-style-type: none"> ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know 	<p>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.</p>	<p>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.</p>
Exclusions		
<ul style="list-style-type: none"> ○ No ● Probably no ○ Probably yes ○ Yes ○ Varies 	<p>It is important to distinguish biphasic anaphylaxis from uniphasic anaphylaxis without complete resolution (protracted anaphylaxis).</p>	<p>Additional factors associated with biphasic anaphylaxis would be difficult to incorporate into clinical triage strategies, such as anaphylaxis</p>

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		
<ul style="list-style-type: none"> <input type="radio"/> No <input checked="" type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> 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	<u>Yes</u>		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	<u>Moderate</u>	Large		Varies	Don't know

	JUDGEMENT						
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		<u>Varies</u>	Don't know
CERTAINTY OF EVIDENCE	<u>Very low</u>	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	<u>Possibly important uncertainty or variability</u>	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS BENEFITS, HARMS AND BURDENS	Favors the comparison	<u>Probably favors the comparison</u>	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	<u>Varies</u>	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	<u>Low</u>	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	<u>Probably favors the intervention</u>	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	<u>Varies</u>	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	<u>Yes</u>		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		<u>Varies</u>	<u>Don't know</u>

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1011 **QUESTION 2: Should antihistamines or glucocorticoids be used to prevent anaphylactic**
1012 **reactions?**

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1014 **Patients:** Adults and children experiencing anaphylaxis who are treated with glucocorticoids,
1015 antihistamines, or both to: (a) prevent biphasic anaphylaxis, (b) prevent index anaphylaxis with
1016 chemotherapeutic, (c) prevent recurrence of anaphylaxis to nonionic low osmolar or iso-osmolar,
1017 radiocontrast media, and (d) prevent index anaphylaxis with non-chemotherapeutic agent. The
1018 analysis did not include patients with prior reactions attributed to chemotherapy or preventative
1019 treatment for children receiving chemotherapy.

1020 Intervention: Use of antihistamine and/or glucocorticoid

1021 Comparator: Management without antihistamine and/or glucocorticoid

1022 Outcome: Occurrence of (a) biphasic anaphylaxis and (b-d) anaphylaxis.

1023

1024 **Background:** A systematic review by Alqurashi et al found thirty-one observational studies that
1025 reviewed the role of glucocorticoids for the treatment of anaphylaxis, suggesting that biphasic
1026 reactions were more likely to occur in moderate to severe anaphylaxis or when anaphylaxis was
1027 not treated with timely epinephrine. The authors concluded there was a lack of compelling
1028 evidence to support the routine use of glucocorticoids to prevent biphasic anaphylaxis.(40)
1029 Similar to the assumption that glucocorticoids provide proven benefit in acute anaphylaxis
1030 management, common practice has adopted the use of antihistamines, glucocorticoids, or both
1031 prior to chemotherapy, radiocontrast dye administration, and many other procedures or
1032 medications thought to involve risk of allergic reactions or anaphylaxis. However, the actual
1033 rigor to which these therapies has been evaluated is questionable. Taxol, an antitumor agent, is
1034 one example with hypersensitivity reaction to this agent reported since early clinical use. In one
1035 early report (181), of 301 patients treated, 32 patients had definite (27 patients) or possible (5
1036 patients) hypersensitivity reactions (HSRs) and all but one patient had the reaction from the first
1037 or second exposure. Of interest, 13 patients (41%) had received premedication to prevent toxicity
1038 but nonetheless experienced HSRs. While prolongation of infusion time appears to have
1039 decreased the rate of HSRs, the addition of premedication has also become common practice in
1040 some circumstances. (181). However, it has been suggested that the most important change in
1041 decreasing rates of HSR associated with RCM has been use of low or iso-osmolar non-ionic

1042 agents. Evidence supporting the use of premedication in the setting of non-ionic RCM agents is
1043 poorly described and there is concern that the routine use of glucocorticoid premedication in the
1044 setting of prior HSR to RCM may cause more morbidity than benefit. (16)

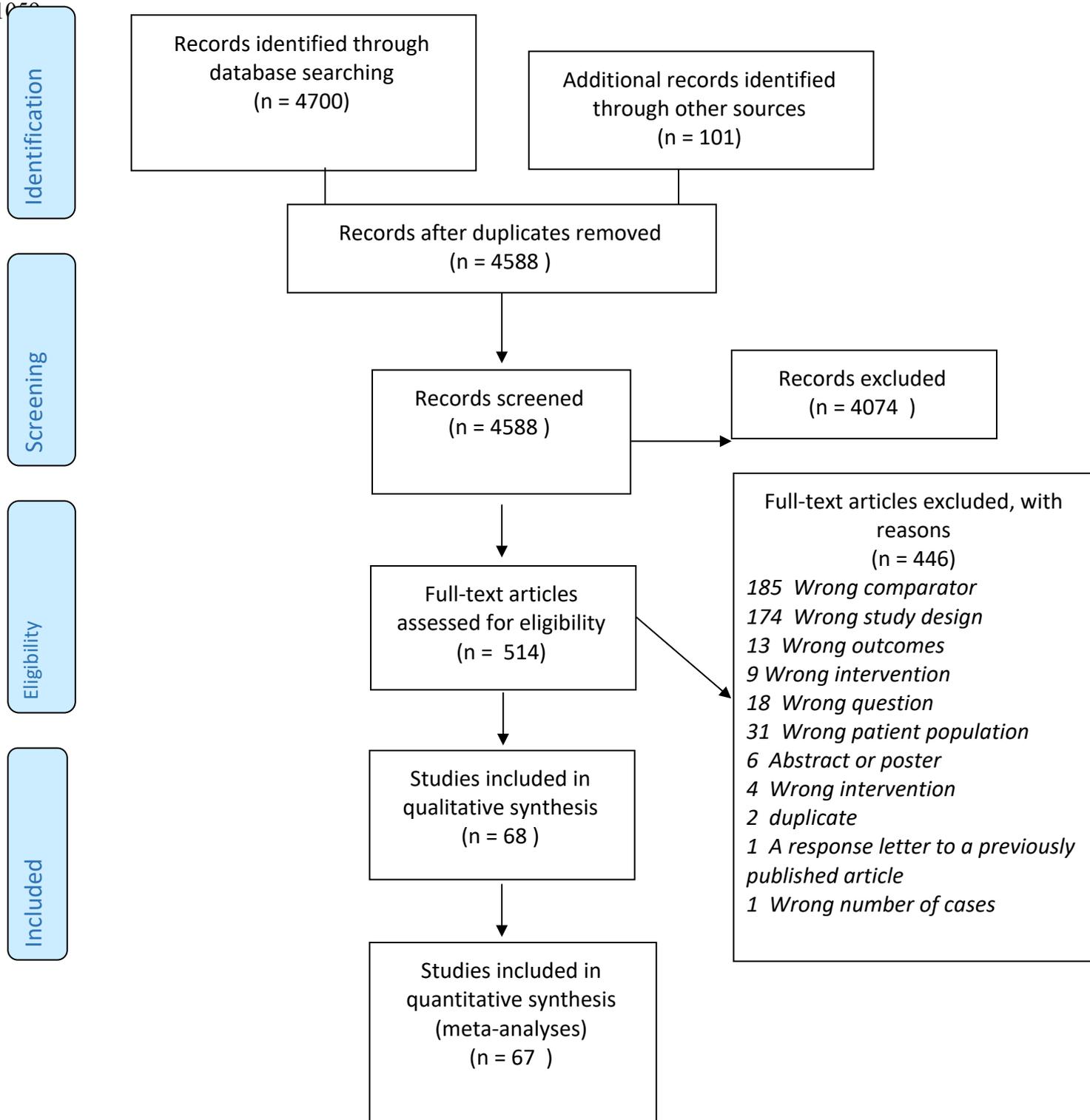
1045
1046 **Study characteristics.** The search for suitable studies was completed by the JTFPP (Figure
1047 eQ2). Sixty-five articles were identified for inclusion. Odds ratios (OR) were used in analysis of
1048 Q2a and Q2b due to the case-control analytic strategy as biphasic and uniphasic anaphylaxis
1049 were analysed by retrospective evaluation of therapies received before the outcome of interest.
1050 Conversely, Q2c and Q2d were evaluated using the risk ratio (RR), which is useful in the setting
1051 of a prospective analysis plan to evaluate differences in outcome between exposure and control.
1052 Of note, if the prevalence/incidence of the event is low then the RR and OR typically give very
1053 similar results. The Peto OR can be useful if there are no events or low number of events in
1054 arms evaluated, but was avoided in the Q2 analysis due to unbalanced arms which could lead to
1055 skewed findings using the Peto OR. (182)

1056

1057 Q2 PRISMA Flow Diagram

1058

1059



1060 **Included Studies:**

1061 **Q2a:** Adults and children treated for anaphylaxis who are treated with glucocorticoids,
1062 antihistamines, or both to: (a) prevent biphasic anaphylaxis:

1063 Alqurashi 2015 (156); Brady 1997 (183); Brown 2013 (20); Calvani 2011 (159); Douglas 1994
1064 (162); Ellis 2007 (35); Grunau 2015 (184); Guiot 2017 (185); Inoue 2013 (163);
1065 Jirapongsanunuruk 2007 (164); Kawano 2017 (186); Ko 2015 (187); Lee 2017 (188); Lee 2000
1066 (131); Lee 2013 (166); Lertnawapan 2011(167); Lin 2000 (189); Manuyakorn 2015 (169); Mehr
1067 2009 (190)Michelson 2015 (148); Oya 2014 (191); Poachanukoon 2006 (173);Rohacek 2014
1068 (37); Scranton 2009 (192); Smit 2005 (175); Sricharoen 2015 (52); Stark 1986 (33); Vezir 2013
1069 (176)

1070

1071 **Q2b:** Adults treated for anaphylaxis who are treated with glucocorticoids, antihistamines, or both
1072 to prevent index anaphylaxis with chemotherapeutic:

1073 Chang 2016 (193); Francis 1994 (194); Jerzak 2018 (195); Mach 2016 (196); Onetto 1993
1074 (197); Rougier 1995 (198); Seki 2011 (199); Shen 2018 (200); Thompson 2014 (201); Trudeau
1075 1996 (202); Weiss 1990 (181)

1076

1077 **Q2c:** Adults and children treated for anaphylaxis who are treated with glucocorticoids,
1078 antihistamines, or both to prevent recurrence of anaphylaxis to radiocontrast media:

1079 Abe 2016 (203); Katayama 1990 (204); Kolbe 2014 (205); Lee 2016 (206); Park 2017 (207);
1080 Park 2018 (208)

1081

1082 **Q2d:** Adults and children treated for anaphylaxis who are treated with glucocorticoids,
1083 antihistamines, or both to prevent index anaphylaxis with non-chemotherapeutic agent:

1084 Augustsson 2007 (209); Berchtold 1992 (210); Braaton 2015 (211); Brockow 1997 (212); Caron
1085 2009 (213); Fan 1999 (214); Gold 2017 (215); Hejjaoui 1990 (216); Jacobstein 2005 (217);
1086 Jagdis 2014 (218); Lorenz 1980 (219); Mueller 2008 (220); Neilson 1996 (221); Portnoy 1994
1087 (222); Reimers 2000 (223); Sanders 2005 (224); Schoening 1982 (225); Tankersley 2002 (226);
1088 Yoshihiro 2006 (227)

1089

1090 **Key results (Q2a1)**

1091 As shown in Figure Q2a, very low-quality evidence suggests that glucocorticoids do not provide
1092 benefit in terms of reducing the risk for biphasic anaphylactic reactions (OR 0.87, 95% CI 0.74-
1093 1.02). Prolonged hospitalization and revisits were analysed as surrogate markers in Michelson
1094 2015 (148), in which glucocorticoids was associated with decreased length of hospital stay but
1095 not with 3-d day ED revisit among hospitalized children. However, the addition of this study
1096 was limited by the poor distinction between protracted or biphasic anaphylaxis, with the
1097 distinction between outcomes possibly representing this classification bias. Meta-regression
1098 analyses were performed to address potential confounding by differential rates of epinephrine
1099 use, with the summary estimate adjusted by accounting for whether there were differences across
1100 studies with regards to the odds of the biphasic versus the monophasic group also receiving
1101 epinephrine at baseline. In meta-regression analyses epinephrine use accounted for about half of
1102 the between study variance, with moderate variance remaining after this correction ($\text{Tau}^2 = 0.4$).

1103

1104 **Key results (Q2a2)**

1105 Similar to findings regarding glucocorticoid use in anaphylaxis, antihistamines also did not
1106 provide benefit in reduction of biphasic reactions (Figure Q2a2; OR 0.71, 95% CI 0.47-1.06 for
1107 H1-antihistamines and OR 1.21, 95% CI 0.8-1.83 for H2-antihistamines). Additional analyses
1108 were performed excluding Mehr 2009 (190) and Lee 2013 (228) to account for uncertainty in
1109 antihistamine preparations used without change in findings (OR 0.69, 95% CI 0.44-1.09 for H1-
1110 antihistamine). To address potential confounding by differential rates of epinephrine use, the
1111 summary estimate was adjusted by accounting for whether there were differences across studies
1112 with regards to the odds of the biphasic versus the monophasic group also receiving epinephrine
1113 at baseline. In the meta-regression analysis epinephrine use did not account for significant
1114 variation across studies. Kawano 2017 reported findings of a retrospective cohort to evaluate the
1115 effect of antihistamine treatment to prevent progression of anaphylaxis, so was excluded from
1116 the final analysis.(186) However, the inclusion of Kawano did result in a significant OR in favor
1117 of antihistamine use (OR 0.65, 95% CI 0.47-0.91). The significance of Kawano 2017 is difficult
1118 to interpret because patients were selected using an ED diagnostic code of “allergic reaction”
1119 (ICD-9 code 995.3) and patients receiving H1 antihistamines were more likely to receive
1120 epinephrine and steroids in their report. Similarly, Lin 2000 was excluded as the comparator in

1121 this analysis was an antihistamine. (189). Sricharoen was excluded as all subject received
 1122 antihistamines.

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1126 **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)		IMPORTANT

1127 CI: Confidence interval; OR: Odds ratio

1128 **Explanations**

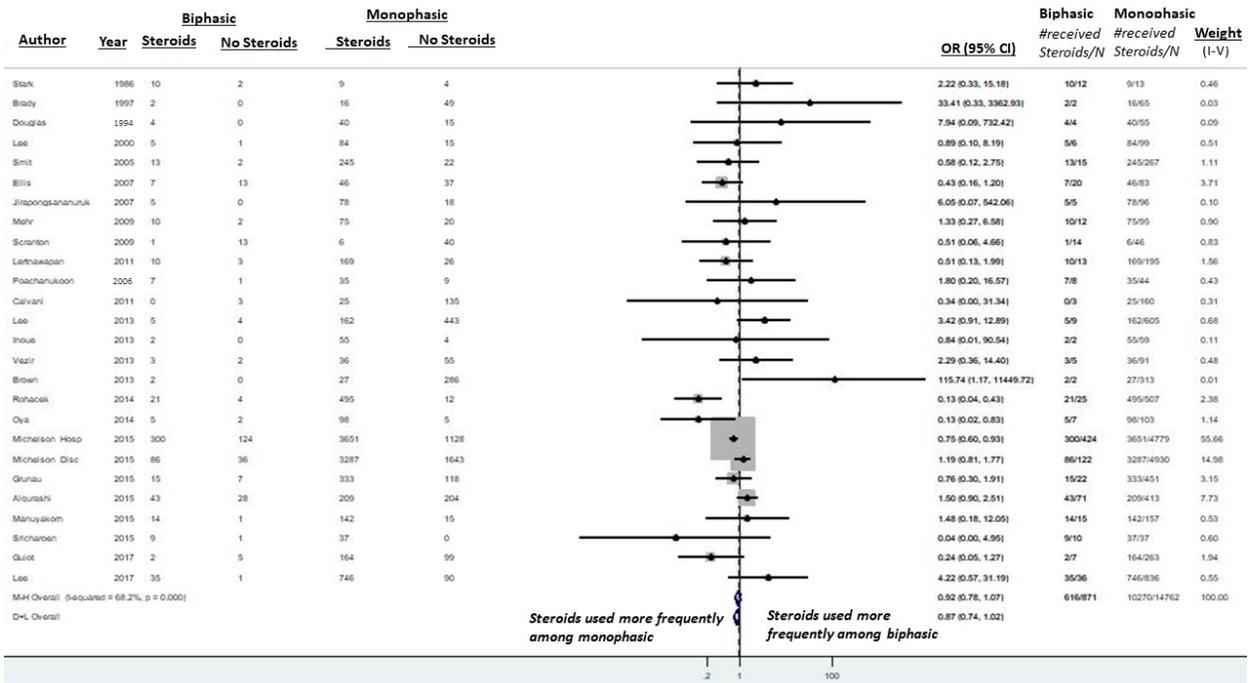
- 1129 a. Risk of bias across studies related to lack of blinding, lack of randomization, potential confounding by severity of presentation, practice variation, and differential use of epinephrine
 1130 b. Significant heterogeneity across studies
 1131 c. Indirect outcomes reported as surrogate to biphasic reactions included emergency department revisits, hospitalizations, and length of stay - with some disparity occurring among
 1132 surrogates measured.
 1133 d. Several studies with wide ranging 95% Confidence Intervals

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1137 **Figure Q2a1. Use of steroids among patients with biphasic versus monophasic outcomes**



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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

1145 CI: Confidence interval; OR: Odds ratio

1146 Explanations

- 1147 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
- 1148 b. Significant heterogeneity across studies
- 1149 c. Endpoint included outcomes reported as surrogate to biphasic reactions included emergency department revisits
- 1150 d. Several studies with wide ranging 95% Confidence Intervals

1151
1152 **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

1153 CI: Confidence interval; OR: Odds ratio

1154 Explanations

- 1155 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
 1156 b. Endpoint included outcomes reported as surrogate to biphasic reactions included emergency department revisits
 1157 c. Several studies with wide ranging 95% Confidence Intervals

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1160 **Figure Q2a2. Use of H1 and H2 blockers among patients with biphasic versus monophasic outcomes**

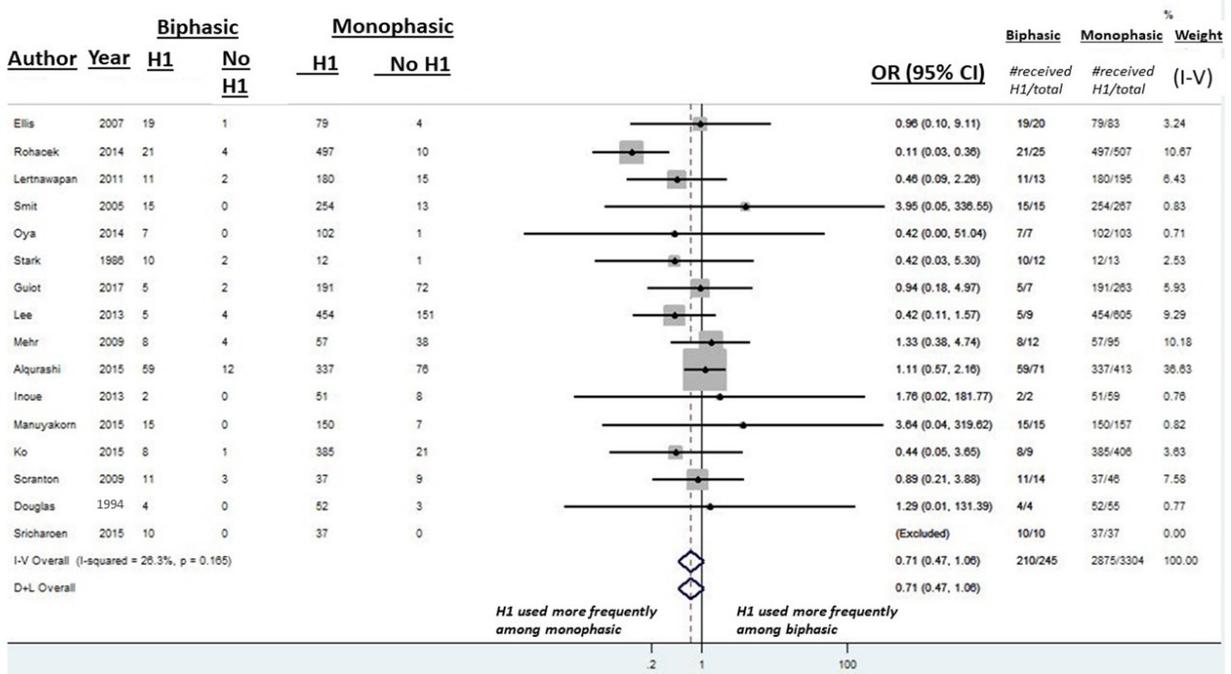
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1163 H1 antihistamines

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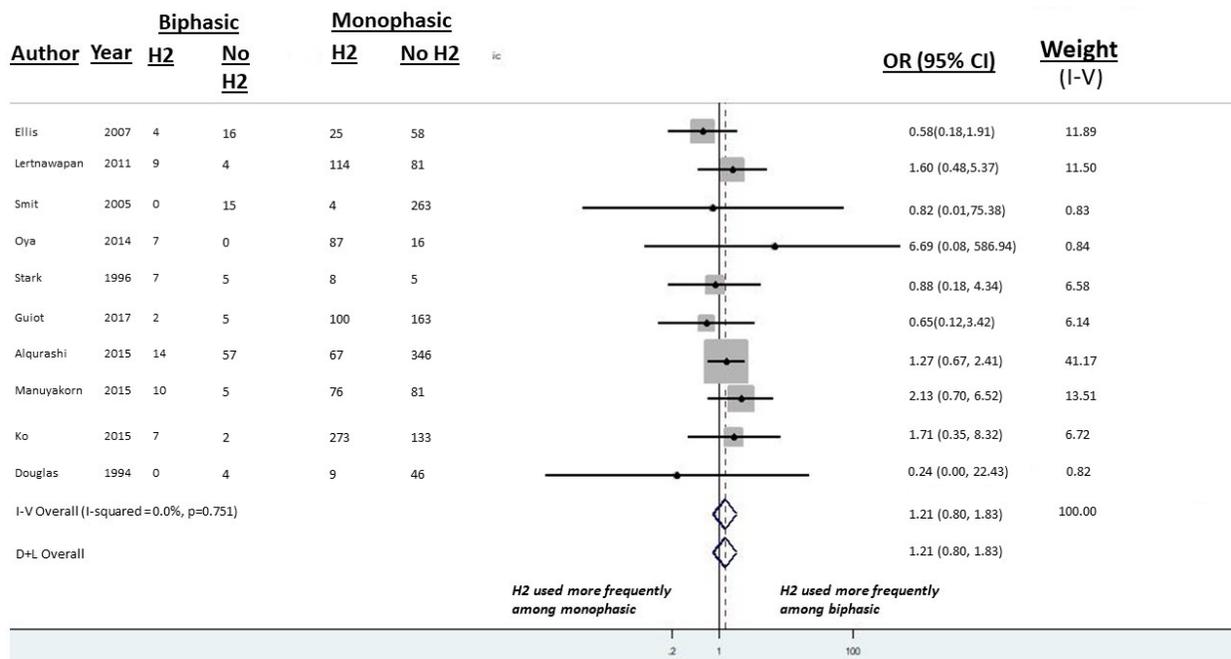
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1168 **H2 antihistamines**



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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; I²=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

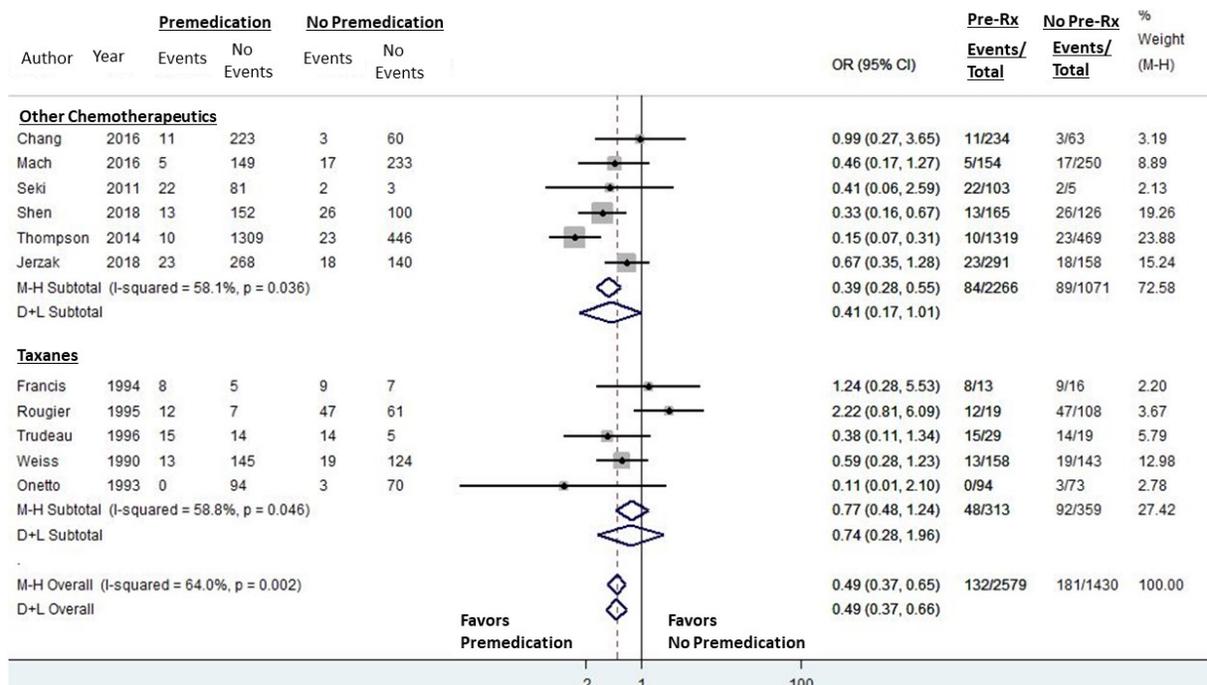
9	observational studies	serious ^a	serious ^b	serious ^c	serious ^d	none	132/2579 (5.1%)	180/1429 (12.6%)	OR 0.49 (0.37 to 0.66)	60 fewer per 1,000 (from 75 fewer to 39 fewer)	⊕○○○ ○ VERY LOW	IMPORTANT
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1188 CI: Confidence interval; OR: Odds ratio

1189 **Explanations**

- 1190 a. some inconsistency in protocol design could affect outcome assessments
 1191 b. Moderate heterogeneity identified in meta-analysis
 1192 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
 1193 populations is unclear.
 1194 d. Several studies with wide ranging 95% Confidence Intervals

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1197 **Figure Q2b: Forest Plot of Chemotherapy Studies**



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1204 **Events** = Hypersensitivity or Infusion Related Reactions; **Premedication** = Glucocorticoids
1205 and/or Antihistamines; **Odds Ratio** = Displaying the odds of hypersensitivity reactions with
1206 premedication compared to without premedication

1207
1208 **Key results (Q2c)**

1209 Very low-quality evidence suggests that glucocorticoid and/or antihistamine premedication does
1210 not provide benefit in terms of reducing the risk for hypersensitivity reactions either patients with
1211 prior RCM reactions (RR 1.07 95% CI 0.67-1.71). The test for heterogeneity yields a statistically
1212 significant difference between studies ($P < 0.001$; $I^2 = 93\%$). It is important to note that specific
1213 evaluation of patients with prior severe delayed onset allergic reactions for RCM is not well
1214 studied and was not addressed in the current analysis. Severe delayed RCM reactions have
1215 included Stevens-Johnson syndrome, Toxic epidermal necrolysis, drug-related eosinophilia with
1216 systemic symptoms (DRESS), and vasculitis, with fatalities reported. (230-238) For instance,
1217 although iodixanol is a low-osmolar nonionic dimer delayed T-cell mediated have been
1218 described.(232) While skin testing with delayed readings at 48 and 72 hours may play a role in
1219 identifying non-cross reactive agents (232), there remains uncertainty as to whether such an
1220 approach is necessary when compared to simply choosing a non-cross reactive RCM for
1221 presumed T cell mediated severe delayed onset reactions. (42) Similarly, the necessity of other
1222 measures to prevent recurrent severe delayed reactions have included IVIG, desensitization, and
1223 cyclosporine is unknown.(239-241) A simple approach was recently proposed by Macy who
1224 reviewed RCM hypersensitivity reactions and contrasted Group A RCM agents (which include
1225 the low-osmolar monomers iopamidol, iomeprol, iversol, iohexol and low-osmolar dimer
1226 iodixanol) from Group B (including the low-osmolar monomer iobitridol and low-osmolar dimer
1227 ioxaglate), Group C (high-osmolar ionic monomer amidotrizoate/diatrizoate), and ungrouped
1228 agents (low-osmolar monomers iopamide, iopamidol, iothalamate), suggesting that
1229 glucocorticoid premedication begun one day before the procedure (and continued for five days)
1230 may have a role in severe delayed-onset reactions to Group A RCM agents together with
1231 selection of a non-cross reactive group (such as iopromide or iopamidol).(42) The optimal
1232 approach to patients with delayed severe RCM reactions requires further study.

1233
1234 **Table Q2c: Should Antihistamine and/or Glucocorticoid Premedication Be Used To**
1235 **Prevent Recurrent Hypersensitivity Reactions Radiocontrast Media?**

1236
1237

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)		
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

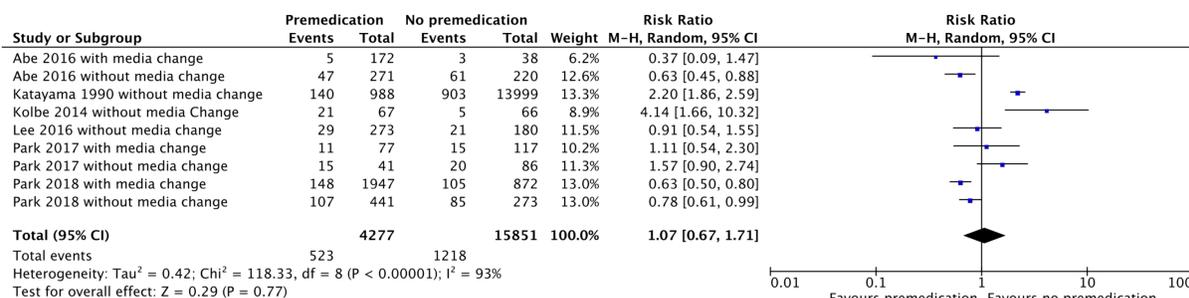
1238 CI: Confidence interval; RR: Risk ratio

1239 Explanations

- 1240 a. Due to observations study design sources of bias could affect effect estimate
- 1241 b. Significant heterogeneity among studies
- 1242 c. Several studies with wide ranging 95% Confidence Intervals
- 1243

1244 Figure Q2c. Forest Plot: All Included Studies

1246
1247



1248 Key results (Q2d)

1250 Very low certainty evidence suggests that glucocorticoid and/or antihistamine premedication also
 1251 does not provide benefit in terms of reducing the risk for hypersensitivity reactions in subjects
 1252 receiving monoclonal antibodies, allergen immunotherapy, or other (non-chemotherapy, non-
 1253 RCM) medications (RR 0.74, 95% CI 0.49-1.11). However, the subgroup analysis of allergen
 1254 immunotherapy did demonstrate a significant benefit of premedication, driven largely by studies
 1255 of premeditation in accelerated allergen immunotherapy schedules, which present greater risks of
 1256 anaphylaxis (RR 0.62, 95% CI 0.41-0.94). This benefit may relate to a high baseline rate of
 1257 systemic reactions. For example, Portnoy 1994 (222) reported a double-blind placebo controlled
 1258 trial of rush immunotherapy in 22 allergic children aged 6 to 18 years of age. Systemic reactions
 1259

1260 (inclusive of isolated urticaria) were reported in 27% of subjects treated with H1 antagonist, H2
 1261 antagonists, and glucocorticoids compared with 73% of placebo subjects. One of 11 children
 1262 experienced anaphylaxis in the treatment group compared to 3/11 in the placebo group.
 1263 However, if additional consideration was given to patients receiving rush immunotherapy who
 1264 experienced either anaphylaxis or investigator classified pulmonary symptoms (wheezing,
 1265 shortness of breath, or chest tightness), the difference between active treatment and placebo was
 1266 18% vs 45%, respectively. (222) Additional sensitivity analysis performed using this modified
 1267 definition of anaphylaxis from Portnoy 1994 and did not significantly change results. Exclusion
 1268 of the RIT patients from Portnoy 1994 and Hejjaoui 1990 resulted in an OR of 0.65 (95% CI,
 1269 0.41-1.04) for patients in the immunotherapy subgroup.

1270
 1271 **Table Q2d: Should Antihistamine and/or Glucocorticoid Premedication Be Used To**
 1272 **Prevent Hypersensitivity Reactions to Monoclonal Antibodies, Allergen Immunotherapy,**
 1273 **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)		IMPORTANT

1274 CI: Confidence interval; RR: Risk ratio

1275

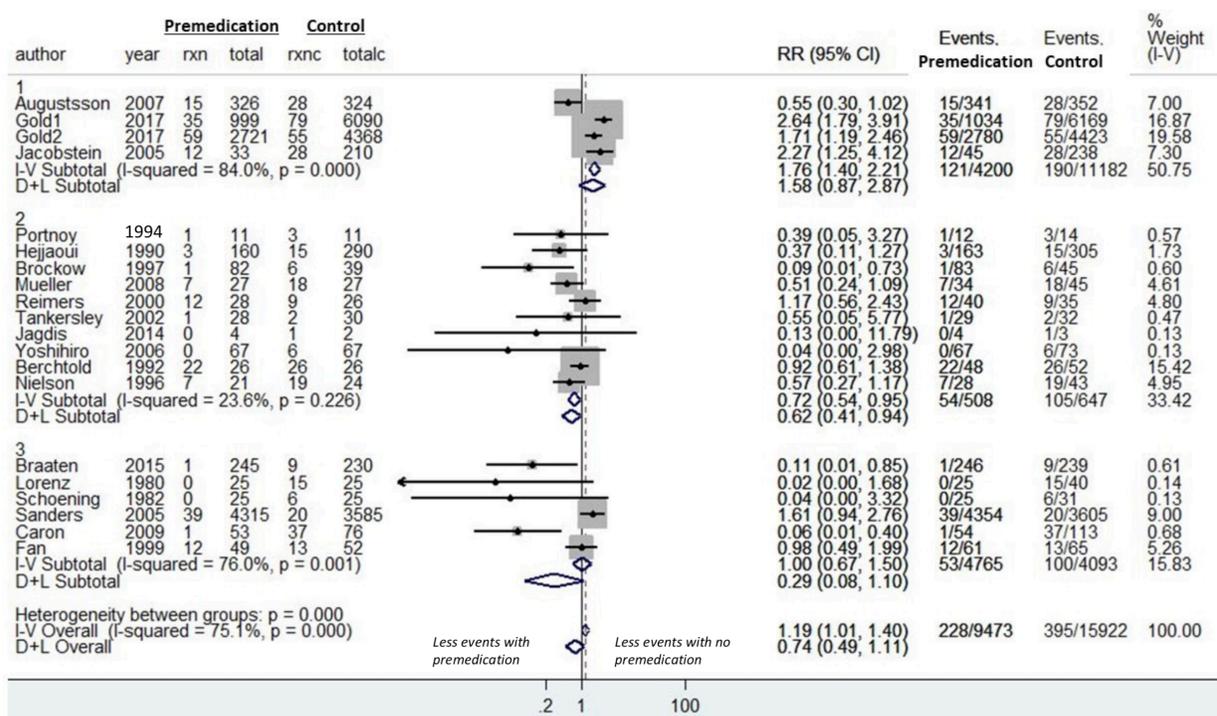
1276 **Explanations**

- 1277 a. Risk of bias across studies related to lack of blinding, lack of randomization, potential confounding by severity of presentation, practice variation
 1278 b. Significant heterogeneity across studies
 1279 c. Significant degree of heterogeneity in outcomes reported
 1280 d. Several studies with wide ranging 95% Confidence Intervals

1281

1282 **Figure Q2d Use of premedication among patients with at risk for allergic reactions**

1283



1284

1285

1286

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.
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Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes • Yes ○ Varies ○ Don't know 	<p>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,</p>	<p>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.</p>

	allergen immunotherapy, and others)	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know 	<p>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).</p> <p>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,</p>	<p>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</p>

	<p>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 alternative 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.</p>	<p>only manifestation of an allergic response.</p>
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Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know 	<p>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</p>	<p>Additional medical complexity of these treatments may create obstacles to efficient healthcare delivery.</p>

	<p>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.</p>	
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Certainty of evidence (Intentional vagueness)
 What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> • Very low ○ Low ○ Moderate ○ High ○ No included studies 	<p>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</p>	<p>The evidence base is of low certainty and a randomized controlled trial in regard to premedication may be warranted.</p>

Values (Value judgments)		
Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> • Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability 	<p>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.</p>	<p>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.</p>

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
<ul style="list-style-type: none"> ○ 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 	<p>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.</p> <p>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.</p>	<p>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.</p>

Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know 	<p>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.</p>	<p>If extended observation times are associated with additional treatment, or if parenteral treatments are administered costs would be greater.</p>

Certainty of evidence of required resources
 What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ● No included studies 	<p>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)</p>	<p>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</p>

Cost effectiveness
 Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison 	<p>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</p>	<p>Cost-effectiveness would likely be sensitive to rates of anaphylaxis, hospitalization, and fatality risk reduction.</p>

<ul style="list-style-type: none"> ○ Probably favors the intervention ○ Favors the intervention ○ Varies Don't know ● No included studies 	<p>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.</p>	
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Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased 	<p>Increased medical complexity may increase disparities in health equity. In rural settings, access to 24-hour pharmacies may limit</p>	<p>Oral antihistamines and oral corticosteroids are relatively inexpensive, so it is possible in some</p>

<ul style="list-style-type: none"> ○ Increased ○ Varies ○ Don't know 	<p>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 care is uncertain. Patients with poor health literacy may be at risk for incorrect dosing of home regimens as preventative anaphylaxis strategies become more complicated.</p>	<p>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</p>
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Acceptability & Quality Improvement Opportunity
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes 	<p>Antihistamines and corticosteroids are common medications used to treat and prevent allergic reactions. While these treatments should not</p>	<p>The practice of treating patients experiencing anaphylaxis with antihistamines and</p>

<ul style="list-style-type: none"> • Varies ○ Don't know 	<p>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</p>	<p>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.</p>
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	<p>not a primary treatment for anaphylaxis will require continued educational efforts.</p> <p>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.</p> <p>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</p>	
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	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
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know 	<p>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.</p> <p>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 patients with prior RCM anaphylaxis receiving an</p>	<p>Additional high-quality evidence is needed to better inform practice as to the role of antihistamines and corticosteroids for the purpose of preventing anaphylaxis.</p>

	<p>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)</p>	
Intentional Vagueness		
Yes	<p>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.</p>	<p>Additional high-quality evidence is needed to better inform practice.</p>
Role of Patient Preference		
Probably yes	<p>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</p>	<p>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</p>

	<p>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.</p>	<p>practice variation to prevent biphasic anaphylaxis, monoclonal antibody anaphylaxis, and RCM anaphylaxis prevention.</p>
Exclusions		
Yes	<p>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</p>	

	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.	

1290 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	<u>Moderate costs</u>	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			<u>No included studies</u>
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	<u>No included studies</u>
EQUITY	Reduced	Probably reduced	<u>Probably no impact</u>	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		<u>Varies</u>	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		<u>Varies</u>	Don't know

1291
1292

1293 **RECOMMENDATIONS:**

1294 **QUESTION #1**

1295

1296 **We suggest extended observation in the ED for patients with resolved severe anaphylaxis to**
1297 **detect a biphasic reaction**

1298

1299 **Recommendation: Conditional**

1300 **Certainty of evidence: Very low**

1301

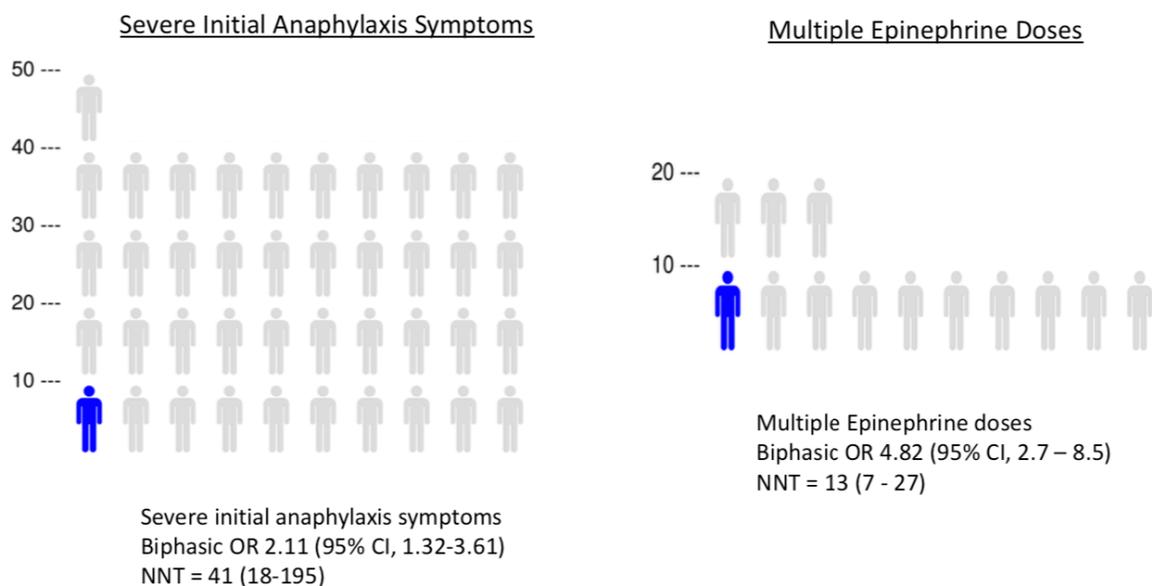
1302 **Technical statement:** The JTFPP findings suggest biphasic anaphylaxis is associated with a
1303 more severe initial presentation of anaphylaxis (OR=2.11, 95% CI 1.23-3.61) or repeated
1304 epinephrine doses required with the initial presentation (OR 4.82, 95% CI 2.70-8.58). At
1305 present, evidence is lacking to clearly demonstrate the period of universal extended observation

1306 that may be required or cost-effective in all patients with severe anaphylaxis or those who
1307 require multiple doses of epinephrine. A recent meta-analysis of observation times suggested 1-
1308 hour observation was associated with a 95% negative predictive value (NPV) of biphasic
1309 anaphylaxis, while a 6-hour or longer observation period was associated with a 97.3% NPV of
1310 biphasic anaphylaxis occurring after discharge.(132) Based on this analysis, the incremental
1311 patient expected biphasic event rate (PEER) between asymptomatic 1-hour and ≥ 6 -hour
1312 observation is 2.3%. Therefore, the number needed to treat (NNT) with extended observation to
1313 be able to detect one episode of biphasic anaphylaxis before discharge (Figure Q1rec) would be
1314 41 (range, 18 to 195) for patients with a more severe initial presentation of anaphylaxis and 13
1315 (range, 7 to 27) for patients with multiple epinephrine doses.(178) For patients at high risk for
1316 biphasic anaphylaxis or those with a higher risk of anaphylaxis fatality (e.g., serious medical co-
1317 morbidities), more prolonged monitoring can be cost-effective. In a recent analysis 6-hour
1318 observation was cost-effective only if it was able to provide a high-degree of protection against
1319 anaphylaxis fatality (24% fatality relative risk for extended vs 1-hour observation), and
1320 otherwise this more prolonged observation time was not cost-effective or providing superior
1321 value. (*Shaker et al. Estimation of Health and Economic Benefits of Extended Observation of*
1322 *Resolved Anaphylaxis: A Cost Effectiveness Analysis. Submitted*). Patients with comorbidities
1323 such as severe respiratory or cardiac disease and corresponding higher risks for poor anaphylaxis
1324 outcomes may therefore benefit from more extended observation. Conversely, in patients
1325 presenting with non-severe anaphylaxis and promptly responding to a single dose of epinephrine
1326 without recurrence, evidence suggests that a 1-hour observation may be reasonable in the context
1327 of appropriate patient education. Such lower risk patients would be characterized as having a
1328 very small risk of biphasic anaphylaxis (<5%) following discharge associated with a less than
1329 50% fatality risk reduction from extended observation. Therefore, the JTFPP suggests than in in
1330 patients with a severe initial presentation of anaphylaxis (for example, those with hypotension,
1331 wide pulse pressures, multiple doses of epinephrine, or other markers of severity) extended
1332 observation be considered following resolution of the index episodes without recurrence. At
1333 present, evidence is lacking to clearly demonstrate the period of universal extended observation
1334 that may be required or cost-effective in all patients with severe anaphylaxis or those who
1335 require multiple doses of epinephrine.(54) In some circumstances a role may exist for shared
1336 decision making tools around the duration of prolonged ED observation.

1337

1338 Figure Q1R

Extended Observation to Detect Biphasic Anaphylaxis: Number Needed to Treat



1339

1340 The JTFPP analysis found additional factors associated with risk of biphasic anaphylaxis that
1341 would be difficult to incorporate into clinical triage strategies, such as anaphylaxis caused by a
1342 drug trigger in children, anaphylaxis with cutaneous symptoms, and use of glucocorticoids in
1343 children. Some of these associations may be confounded by anaphylaxis severity and practice
1344 variation, with very low quality of evidence challenging the applicability of these factors to
1345 patient care until they can be further substantiated. For instance, it is highly unlikely that
1346 administration of more than one dose of epinephrine or corticosteroids contributed to biphasic
1347 reactions, but very likely that these were indicative of a more significant anaphylactic reaction. It
1348 is possible that medication induced anaphylaxis in children, may be a risk factor for biphasic
1349 anaphylaxis, but it is not possible to determine if this is due to having more severe anaphylaxis or
1350 if medication, as a trigger, is an independent risk factor for biphasic anaphylaxis in children. In
1351 regard to the association of idiopathic anaphylaxis, follow-up for post ED identification of a
1352 specific trigger was not explored, therefore, the significance of this factor is uncertain. There was
1353 no signal that any medication used for treatment of initial anaphylaxis reduced the risk of
1354 biphasic anaphylaxis. However, while the timing of epinephrine administration following the

1355 onset of symptoms of anaphylaxis in relationship to the subsequent development of biphasic
1356 anaphylaxis was not part the meta-analysis, there does appear to be a trend to lower rates of
1357 biphasic reactions with earlier epinephrine administration following development of anaphylaxis.
1358 While early epinephrine in the setting of anaphylaxis is important, evidence suggests pre-
1359 emptive epinephrine before symptom onset is generally not a cost-effective strategy.(247)

1360

1361 Prompt and adequate treatment of anaphylaxis appears central to reducing biphasic anaphylaxis
1362 risk. The implications for the clinician, based upon this systematic review and meta-analysis is
1363 that the patient presenting with severe anaphylaxis and/or requiring more aggressive treatment
1364 (e.g., more than one dose of epinephrine), following complete resolution of symptoms, may
1365 benefit from longer observation time for a potential biphasic reaction. While the possibility of
1366 biphasic anaphylaxis should be emphasized in this higher risk group, it is important to educate all
1367 patients on the chance of a biphasic reaction as well as avoiding known triggers, identifying
1368 symptoms of anaphylaxis, the use of auto-injector epinephrine for the treatment of anaphylaxis,
1369 and timely follow-up with an allergist.

1370

1371 QUESTION #2

1372

1373 **We suggest against glucocorticoids or antihistamines as an intervention to prevent biphasic**
1374 **anaphylaxis**

1375

1376 **Certainty of evidence: Very low**

1377 **Strength of recommendation: Conditional**

1378

1379 **Technical comment:** As a secondary therapy, antihistamines and corticosteroids may be
1380 considerations in anaphylaxis treatment.(41) In particular, antihistamines may treat urticaria and
1381 itching to improve comfort during anaphylaxis, but if used prior to epinephrine administration
1382 could lead to a delay in first line treatment of anaphylaxis. Furthermore, glucocorticoids can
1383 also effectively prevent delayed urticaria which could confound the assessment and treatment of
1384 anaphylaxis. The JTFPP analysis did not identify significant benefit in prevention of biphasic
1385 anaphylaxis from either H1 antihistamines (OR 0.71, 95% CI 0.47-1.06), H2 antihistamines (OR

1386 1.21, 95% CI 0.8-1.83), or glucocorticoids (OR 0.87, 95% CI 0.74-1.02). Evaluation of the
1387 number of patients needed to treat (NNT) to potentially reduce biphasic anaphylaxis rates is
1388 useful:(178)

1389
1390 *H1 antihistamines:* At a biphasic anaphylaxis patient expected event rate (PEER) of 5%, the
1391 number needed to treat (NNT) for H1 antihistamines is 72 to prevent one episode of biphasic
1392 anaphylaxis. At a biphasic anaphylaxis PEER of 20%, the NNT (to prevent one case of biphasic
1393 anaphylaxis) for H1 antihistamines is 20. However, neither of these values was certain and
1394 confidence in the benefit of treatment is low, with an association of increased biphasic
1395 anaphylaxis rates within the confidence estimate.

1396
1397 *H2 antihistamines:* At a biphasic anaphylaxis PEER of 5% and 20%, H2 antihistamine use was
1398 not associated with a decreased risk of biphasic anaphylaxis. However, the degree of certainty
1399 that H2 antihistamine therapy did not provide any possibility of benefit was uncertain.

1400
1401 *Glucocorticoids:* At a biphasic anaphylaxis PEER of 5%, the number needed to treat (NNT) for
1402 glucocorticoids is 161 to prevent one case of biphasic anaphylaxis (and 47 at a biphasic
1403 anaphylaxis PEER of 20%). Again, neither of these values was certain and confidence in the
1404 benefit of treatment is low, with an association of increased biphasic anaphylaxis rates within the
1405 confidence estimate.

1406
1407 Certainty of evidence is very low, and additional well-designed controlled trials are be needed to
1408 further inform this practice. However, the JTFPP strongly recommends that secondary therapies
1409 never interfere with early epinephrine treatment, as this is the primary medication for the
1410 treatment of anaphylaxis.(41) The use of antihistamines may be associated with side-effects that
1411 could confound assessment of anaphylaxis, such as altered level of consciousness with 1st
1412 generation antihistamines. Harms from high dose glucocorticoids may also outweigh benefits;
1413 however, due to the very-low certainty of evidence (risk of bias, inconsistency, and imprecision),
1414 there remains uncertainty in the assessment of benefit vs. no benefit from supplemental
1415 therapies.

1416

1417 **We suggest administering glucocorticoids and/or antihistamines to prevent anaphylaxis or**
1418 **infusion related reaction when indicated for specific agents in chemotherapy protocols.**

1419

1420 **Certainty of evidence: Very low**

1421 **Strength of recommendation: Conditional**

1422

1423 **Technical Comment:** The JTFPP analysis did not identify a significant change in rates of
1424 anaphylaxis from premedication with glucocorticoids and/or antihistamines before chemotherapy
1425 or monoclonal antibody treatment. The use of premedication was associated with a non-
1426 significant increased rate of hypersensitivity reactions for chemotherapy (OR 1.34, 95% CI 0.69-
1427 2.61) and monoclonal antibody therapy (RR 1.58, 95% CI 0.87-2.87). We did not evaluate
1428 premedication in the context of desensitization to chemotherapy agents and to monoclonal
1429 antibodies. Furthermore, the use of premedication in patients who had previously experience
1430 anaphylaxis from these agents was not evaluated. Evaluation of the number of patients needed to
1431 treat (NNT) to produce benefit (positive number) or harm (negative number), as discussed
1432 below, is useful:

1433

1434 *Chemotherapy Predication:* At an anaphylaxis PEER of 12.9%, premedication was associated
1435 with a decreased risk of anaphylaxis. The NNT was 15 (range, 13 – 19).

1436

1437 *Monoclonal Antibody Premedication:* At an anaphylaxis PEER of 2%, premedication was not
1438 associated with a decreased risk of anaphylaxis. However, the degree of certainty that therapy
1439 did not provide any possibility of benefit was uncertain.

1440

1441 It is not possible to exclude some potential benefit from the use of glucocorticoids and/or
1442 antihistamines to prevent anaphylaxis, and additional well-designed controlled trials are needed
1443 to further inform this practice. A clinician may reasonably defer premedication use for the
1444 intention of preventing anaphylaxis. If standard practice dictates the use of premedication prior
1445 to the administration of a monoclonal antibody, it would be reasonable to discontinue the
1446 premedication following tolerance of the 1st or 2nd course of treatment.

1447

1448 **We suggest against routinely administering glucocorticoids and/or antihistamines to**
1449 **prevent anaphylaxis due to iso-osmolar, non-ionic radiocontrast media agent**

1450

1451 **Certainty of evidence: Very low**

1452 **Strength of recommendation: Conditional**

1453

1454 **Technical Comment:** The JTFPP analysis did not identify significant benefit from the use of
1455 premedication prior to the RCM to prevent anaphylaxis (RR 1.07 95% CI 0.67-1.71). The
1456 absence of benefit of premedication in patients with prior immediate hypersensitivity reactions to
1457 RCM who are receiving a different low or iso-osmolar agent is consistent with prior literature;
1458 however, it is important to distinguish the immediate index reaction associated with RCM from a
1459 severe delayed cutaneous T-cell mediated reaction, where premedication may add value to
1460 management.(42) Risk of bias, inconsistency, imprecision, and indirectness attenuate the
1461 confidence in this guidance.

1462

1463 *RCM Predication:* At a PEER of 8.7%, premedication was not associated with a decreased risk
1464 of anaphylaxis. However, the degree of certainty that therapy did not provide any possibility of
1465 benefit was uncertain.

1466

1467 Given the diversity of clinical circumstances evaluated and low confidence in the literature base,
1468 higher quality evidence is needed to better inform practice, and future recommendations could
1469 potentially change as a result of new information. As such, clinicians may reasonably consider
1470 premedication in clinical circumstances associated with a high level of perceived risk of
1471 anaphylaxis or comorbidities associated with greater anaphylaxis fatality risk (such as underlying
1472 cardiovascular disease or use of beta-blockers, prior severe anaphylaxis), although evidence is
1473 lacking to support this practice. Additional well-designed controlled trials are be needed to
1474 further clarify the need for premedication prior to alternative low or iso-osmolar RCM use in
1475 patients with prior anaphylaxis to prevent recurrence.

1476

1477 **We suggest in favor of the administration of glucocorticoids and/or antihistamines as an**
1478 **intervention to prevent anaphylaxis in patients undergoing aeroallergen rush**
1479 **immunotherapy (RIT)**

1480

1481 **Certainty of evidence: Very low**

1482 **Strength of recommendation: Conditional**

1483

1484 **Technical Comment:** Evidence suggests that in the setting of aeroallergen RIT premedication
1485 may provide value in reducing systemic reactions and anaphylaxis (immunotherapy analysis
1486 including RIT, RR 0.62, 95% CI 0.41- 0.94). In the study by Portnoy et al, patients received H1
1487 and H2 antagonists and oral corticosteroids for 3 days, beginning one day before the 2-day rush
1488 immunotherapy protocol.(222) The evidence base for premedication before conventional
1489 aeroallergen immunotherapy is limited; however, one study by Ohashi Yoshirio et. al. suggested
1490 some benefit with fexofenadine pretreatment 2 hours before conventional immunotherapy using
1491 cedar pollen or dust mite allergens.(43) The evaluation of the number of patients needed to treat
1492 (NNT) to prevent one episode of anaphylaxis is useful:

1493

1494 *RIT Premedication:* The NNT to prevent one case of anaphylaxis with RIT premedication at a
1495 4.5% rate of anaphylaxis is 58, based on the immunotherapy analysis including RIT studies. At a
1496 9% rate of anaphylaxis, the NNT of premedication for RIT is 29. Assuming a patient expected
1497 anaphylaxis event rate of 14%, the premedication NNT is 19. However, none of these values was
1498 certain and confidence in the benefit of treatment is low, with an association of increased
1499 anaphylaxis rates within the confidence estimate.

1500

1501 The JTFPP is unable to exclude the possibility that specific situations and subpopulations may
1502 exist where premedication could provide benefit to immunotherapy in those with concomitant
1503 risk factors (e.g., in situations associated with higher rates of systemic reactions). Given the
1504 diversity of clinical circumstances evaluated and low confidence in the literature base, higher
1505 quality evidence is needed to better inform practice, and future recommendations could
1506 potentially change as a result of new information. As such, clinicians may reasonably consider
1507 immunotherapy premedication in other clinical circumstances associated with a high level of

1508 perceived risk of anaphylaxis or comorbidities associated with greater anaphylaxis fatality risk
1509 (such as underlying cardiovascular disease or use of beta-blockers), although evidence is lacking
1510 to support this practice.

1511

1512

Additional Good Practice Statements

1513

1514 **Good Practice Statement # 1: Administer epinephrine as the only 1st line pharmacotherapy**
1515 **for uniphasic and/or biphasic anaphylaxis.**

1516

1517 **Good Practice Statement #2: Do not delay the administration of epinephrine for anaphylaxis,**
1518 **as doing so, may be associated with higher morbidity and mortality.**

1519

1520 **Good Practice Statement #3: After diagnosis and treatment of anaphylaxis, all patients should**
1521 **be kept under observation until symptoms have fully resolved.**

1522

1523 **Good Practice Statement #4: All patients with anaphylaxis should receive education on**
1524 **anaphylaxis, including avoidance of identified triggers, presenting signs and symptoms, biphasic**
1525 **anaphylaxis, treatment with epinephrine, the use of epinephrine auto-injectors, and referral to an**
1526 **allergist. Of note, there may be some circumstances where self-injectable epinephrine is deferred**
1527 **(i.e., resolved anaphylaxis and drug trigger with high likelihood of successful avoidance) and**
1528 **patient-preference sensitive decision making may play a role in some circumstances.**

1529

Limitations

1531 Unfortunately, the quality of evidence around supplemental therapies in anaphylaxis
1532 management is very low. While early epinephrine is recommended by the JTF when
1533 anaphylaxis is recognized in any setting, whether or not clinicians should also administer
1534 antihistamines and/or glucocorticoids is a question that has not been subjected to rigorous
1535 methodologic evaluation.

1536

1537 All patients with anaphylaxis should be educated regarding the risk for biphasic reactions, and
1538 self-injectable epinephrine should be available at discharge for prompt treatment if this occurs.

1539 Patients who experience greater severity of anaphylaxis are at greater risk for biphasic reaction,
1540 but the absolute risk of biphasic reactions in this population is less clear. It is important to
1541 distinguish biphasic anaphylaxis (with an interval period of clear resolution) from protracted
1542 anaphylaxis

1543
1544 Our analysis is similar to results obtained by Ellis et al in which corticosteroids demonstrated a
1545 non-significant inverse trend with biphasic anaphylaxis (35); however caution is warranted in
1546 interpretation of these findings – particularly given the opposite association of corticosteroids
1547 with biphasic anaphylaxis in children (which may be confounded by severity of index
1548 anaphylaxis and practice variation). Ultimately a randomized controlled trial of supplemental
1549 glucocorticoids and antihistamines in patients adequately treated with epinephrine with resolved
1550 anaphylaxis is needed to determine if these agents prevent biphasic anaphylaxis. The role of
1551 glucocorticoid and/or antihistamine premedication in more high-risk settings (such as rush
1552 immunotherapy) may be significant, and until additional evidence better informs practice,
1553 premedication may be appropriate in circumstance where a high risk of anaphylaxis exists. The
1554 absence of benefit of premedication in patients with prior immediate hypersensitivity reactions to
1555 RCM who are receiving a different low or iso-osmolar agent is consistent with prior literature.
1556 (42); however, it is important to distinguish the immediate index reaction associated with RCM
1557 from a severe delayed cutaneous T-cell mediated reaction, where premedication may add value
1558 to management. Large heterogeneity in analyses and limitations in study design attenuate the
1559 confidence in this evidence synthesis. We did not evaluate premedication in the context of
1560 desensitization to chemotherapy and monoclonal antibodies. (248) The JTF continues to
1561 recommend prompt treatment of anaphylaxis with epinephrine, and highlight that the addition of
1562 glucocorticoids and antihistamines should never delay or substitute for this primary management.

1563

1564 **Conclusion**

1565 Anaphylaxis is a multi-system allergic emergency. Early recognition and prompt administration
1566 of intramuscular epinephrine remain the cornerstone of management. Although treatment of
1567 anaphylaxis in the United States also traditionally has included use of antihistamines and
1568 glucocorticoids, data demonstrating the benefit of these additional approaches is very low quality
1569 and when evaluated on the whole does not offer clear support for this practice. Supplemental

1570 therapies such as glucocorticoids and antihistamines should never delay the rapid administration
1571 of epinephrine as soon as anaphylaxis is recognized. Consistent with the lack of clear benefit of
1572 antihistamines and/or glucocorticoids in prevention of biphasic anaphylaxis, current evidence is
1573 poor that these therapies prevent anaphylaxis in patients with a history of RCM anaphylaxis or in
1574 adult patients receiving monoclonal antibody without prior anaphylaxis.

1575

1576 **Future Directions**

1577 At present it is unclear whether antihistamines and/or glucocorticoids provide benefit as
1578 supplemental therapies in anaphylaxis management in patients promptly and appropriately
1579 treated with epinephrine. In addition, it seems unlikely that antihistamine and/or glucocorticoid
1580 premedication is likely to offer clear benefit in the prevention of RCM anaphylaxis in patients
1581 with a history of immediate RCM hypersensitivity receiving an alternative RCM agent or in
1582 patients receiving monoclonal antibody who have not previously experienced drug
1583 hypersensitivity. However, because the evidence synthesis contained in this report is derived
1584 from low-quality, non-randomized trials, further research evaluating common practices in
1585 anaphylaxis treatment and prevention is urgently needed. Evaluation of premedication in
1586 children receiving chemotherapy and the use of premedication in subjects treated with
1587 chemotherapy desensitization would also provide valuable insight, in addition to understanding
1588 the role of premedication in patients in situations with very high risks of anaphylaxis.

1589

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APPENDIX

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2201 **Studies Not 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

2202 **Method Used for Appraisal and Synthesis**

2203 The Cochrane Collaborative computer program, Review Manager (Higgins & Green, 2011)^a was
2204 used to synthesize the 32 included studies. [GRADEpro GDT \(Guideline Development Tool\)](#) is
2205 the tool used to create the Summary of Findings Tables for this analysis.

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2207 ^aHiggins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of*
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2211

2212 **EBP Scholar's responsible for analyzing the literature**

2213 Teresa Bontrager, RN, BSN, MSNed, CPEN

2214 Jennifer Foley, RT(R)(N), CNMT

2215 Becky Frederick, PharmD

2216 Ferdaus Hassan, PhD

2217 Kori Hess, PharmD

2218 Kelly Huntington, RN, BSN, CPN

2219 David Keeler, RN, BSN, CPN

2220 Erin Lindhorst, MS, RD, LD

2221 Helen Murphy, BHS RRT AE-C

2222 Nicole Ratliff BS RT(R)

2223 Robert Rhodes, MHA, RRT-NPS

2224 Kim Robertson, MBA, MT-BC

2225 Hope Scott, RN CPEN

2226 Audrey Snell, MS, RD, CSP, LD

2227 Rhonda Sullivan, MS, RD, LD

2228 Azadeh Wickham MS, FNP-BC

2229 **EBP Team Member Responsible for Reviewing, Synthesizing, and Developing this**

2230 **Document**

2231 Jarrod Dusin, MS, RD, LD

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2234 **Table eQ1-1**2235 **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]

2236 Notes

2237 *Significant OR

2238 ^aRetrospective data, Included studies with no reported follow up or follow up limited to 24hours, moderate heterogeneity I²=45

2239 ^bRetrospective data, definition of cutaneous was not standard, included studies with no reported follow up or limited to 24hours, low

2240 number of events, moderate heterogeneity I²=43%

2241 ^cRetrospective data, substantial heterogeneity I²=71%, low number of events

2242 ^dRetrospective data, low number of events

2243 ^eRetrospective data, low number of events, follow up not reported or limited to 24hours, different definitions of severity

2244 ^fRetrospective data, low number of events, follow up not reported or limited to 24hours, substantial heterogeneity I²= 89%

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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-anantawat 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, Lubner 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

2246 **Table eQ1-2**

2247 **Risk of Bias (Quality in Prognosis Studies)**

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2251 Additional Q1 References

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2347 Q2a(1) Included Studies and Methodologic Notes:

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2349 **Scholars responsible for analyzing the literature**

2350 Natlie Riblett, MD

2351 Marcus Shaker, MD, MS

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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	≥ 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

			<p>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</p>			
Poachanukoon	2006	Comparison tx across two groups	<p>Anaphylaxis defined as symptoms of generalized mediator release including flushing; pruritus / parathesias of lips, axilla, hands, or feet</p>		<p>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</p>	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 sx's 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
Veziir	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	Patients 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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2358 **METHODOLOGICAL NOTES:**

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2360 *Methodological decision re: the analysis of the findings from Michelson and Grunau et al.*

- 2361 a. Studies were conducted in a prospective manner whereby they evaluated a cohort of patients presenting with allergy/anaphylaxis,
2362 divided them up by exposure/non-exposure (i.e. steroid vs no steroid) and then assessed the subjects for the development of several
2363 outcomes including a biphasic reaction.
- 2364 b. Data was analyzed by comparing the frequency of steroid use among patients who experienced a biphasic vs those who experienced a
2365 monophasic reactions, because the majority of studies included in our review analyzed findings in this manner. Of note, a summary
2366 estimate of these two studies in isolation suggested that there was no significant difference in the incidence of biphasic events between
2367 patients prescribed steroids and those not prescribed steroids. Overall with Grunau and both Michelson Subgroups OR was 0.86 (95%CI:
2368 0.71 – 1.04). When the analysis was limited to only patients seen in the ED and discharged (i.e. Grunau and Michelson Discharged
2369 Subgroup) the OR was 1.26 (95%CI: 0.85 – 1.85)

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2371 *Measurement of Treatment Effect and Data Synthesis*

- 2372 • Analysis was performed using an odds ratio because the included studies approximated case-control methodology. The population was
2373 asses as either having the outcome (biphasic reaction (or equivalent such as ED revisit) or not (i.e. monophasic reaction) and then comparing
2374 steroid usage prior to the development of the outcome. (Cochrane Handbook 9.4.4.1)
- 2375 • In the primary analysis, data was pooled using the Mantel-Haenszel (MH) fixed effect method. This method tends to be preferred by the
2376 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
2377 efficient when there are few events or studies are small (Cochrane Handbook 9.4.4.1).
- 2378 • Meaningful heterogeneity was seen during the primary analysis, so the analysis using a random effects model. In order to conduct the
2379 confirmatory analysis, the Cochrane’s recommended DerSimonian and Laird (DL) method was used This DL method makes use of inverse-
2380 variance (IV) whereby the model adjusts study weight according to the extent of heterogeneity reflected in the different effect estimates
2381 reported by included studies (Cochrane Handbook 9.4.3.1). The standard errors of the effect measures are modified to account for degree of
2382 heterogeneity across the included studies (i.e. τ^2) (Cochrane Handbook 9.4.3.1).The random effects model is considered to be a more
2383 conservative approach in the event of substantial and meaningful heterogeneity because the random effect method will result in wider
2384 confidence intervals than reported using the Mantel-Haenszel fixed effect method (Cochrane Handbook 9.4.3.3).

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2386 *Assessment of heterogeneity*

- 2387 • Heterogeneity across included studies was assessed by performing a chi-squared test and calculating a corresponding Cochran Q statistic
2388 and p-value. A p-value <0.10 was considered to be statistically significant. In addition, inconsistency was calculated across included studies
2389 and an $I^2 >50\%$ was considered to be reflective of substantial and meaningful heterogeneity (Cochrane Handbook 9.5.2). Finally, because

2390 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
 2391 sample sizes, this test was used in addition to the Cochran Q statistic during the primary analysis in order to evaluate whether there were
 2392 notable differences depending on the approach taken to the analysis. (Bagheri, Z. et al)
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 2404 Q2a2 Included Studies and Methodologic Notes
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2406 **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	<p>Anaphylaxis defined as multisystem allergic reaction with clinical features including respiratory and/or cardiovascular involvement per NIAID guidelines.</p> <p>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-</p>	≥ 6 hours	<p>Rate of steroid use between groups not significantly different. Biphasic reactions associated with > 1 dose of epinephrine and fluid bolus. One death reported.</p>	Moderate
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			anaphylactic allergic reaction, not caused by antigen re-exposure			
Lee	2013	Comparison tx across two groups	Biphasic reaction defined as recurrence of sx's 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 in 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

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2410 **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*

- 2416 • Findings were pooled using an odds ratio because the included analyses approximated case-control studies. Data was analyzed by outcome
2417 (biphasic reaction or equivalent such as ED revisit) or comparator (i.e. monophasic reaction) with comparison of H1/H2 usage prior to the
2418 development of the outcome. (Cochrane Handbook 9.4.4.1)
2419 • In the primary analysis the data were pooled together using the Inverse Variance (IV) fixed effect method. Meaningful heterogeneity was
2420 not encountered.
2421

2422 *Zero Cell Correction*

- 2423 • A zero cell correction was used for studies that reported zero cells (i.e. either no patients provided with H1 or all patients received
2424 H1). As discussed in the Cochrane Handbook (16.9.2), it is common for meta-analytic software correct for zero counts by adding
2425 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
2426 method because the Mantel-Haenszel method only applies the correction if the same cell is zero in all the included studies. While
2427 there are benefits to applying a “fixed correction method” to a meta-analysis, there are also risks including the possibility that it
2428 may bias estimates towards no difference or overestimate variance of study estimates. There is also concern for bias in one
2429 direction if the sizes of the study arms are unequal. The Peto Method avoids these problems because it doesn’t require a zero cell
2430 correction (only exception is if no events occur in all arms of all studies). However, the Peto Method was not appropriate for our
2431 analysis because the Peto Method is at risk for bias if the study arms are highly unbalanced which was the case in this analysis.
2432 To minimize introducing additional bias into our current study, we applied a more conservative correction factor of 0.2.
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2434 *Assessment of heterogeneity*

- 2435 • Heterogeneity across included studies was assessed by performing a chi-squared test and calculating a corresponding Cochran Q statistic
2436 and p-value. A p-value <0.10 was considered to be statistically significant. In addition, inconsistency was calculated across included studies
2437 and considered an $I^2 >50\%$ to be reflective of substantial and meaningful heterogeneity (Cochrane Handbook 9.5.2).
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2439 **References:**

- 2440 1. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Collaboration 5.1.0 [updated March 2011]. Higgins JPT, Green S
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2443 unequal sample sizes within and among centers. *BMC Medical Research Methodology*, 11, 58. <http://doi.org/10.1186/1471-2288-11-58>.
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2446 Q2b Included Studies and Methodologic Notes

2447 **Scholars responsible for analyzing the literature**

2448 E Fregene

2449 P Kasireddy
 2450 F McEnany
 2451 AK Patel
 2452 V Trivedi
 2453 Natlie Riblett, MD
 2454 Marcus Shaker, MD, MS
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2456 **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 clinical 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, fluorouracil, 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
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METHODOLOGICAL NOTES:

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2462 *Data synthesis*

2463 Data synthesis was performed using random effects model because this model assumes that the different studies are estimating
 2464 different, yet related, intervention effects which is consistent with the variable study designs among the studies included in this meta-
 2465 analysis.

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2467 *Assessment of heterogeneity.* The heterogeneity of the studies used in this review was assessed using Revman and the I^2 and p-values
 2468 were computed.

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2470 *Limitations*

2471 The analysis was limited to English-speaking adult populations who had not previously experienced a hypersensitivity reaction to
 2472 chemotherapy. Variation existed in premedication protocols used in various studies. (i.e. glucocorticoids vs. antihistamines, or a
 2473 combination of both).

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2476 **Q2b Included Studies and Methodologic Notes**

2477 **Scholars responsible for analyzing the literature**

2478 AMP Bobrownicki
 2479 S Hellerstedt
 2480 B Kim
 2481 J Milbank
 2482 O Pando
 2483 Natlie Riblett, MD
 2484 Marcus Shaker, MD, MS
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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.

2492 Included Studies

Author Year	Sample Size (n)	Procedure	Intervention	Control	Risk of Bias
Abe 2016	751	†CT, 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

2493 †CT: Computed tomography, MRI: Magnetic resonance imaging, DSA: Digital subtraction angiography

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2497 **METHODOLOGICAL NOTES:**

2498 *Data synthesis*

2499 Risk ratios were analyzed as dichotomous outcome - adverse reaction - for subjects with pretreatment and subjects without
2500 pretreatment. Data was abstracted using a standardized, predefined data extraction form and entered into RevMan, with the primary
2501 outcome was summarized using a random effects model, due to the heterogeneity of our sample. This analysis produced a pooled risk
2502 ratio and 95% confidence interval.

2503

2504 *Assessment of heterogeneity*

2505 We utilized RevMan to synthesize our abstracted data and produce forest plots with assessments of heterogeneity. ur complete meta-
2506 analysis of all 6 included studies without media change yielded an I² of 94% and suggests a high amount of variation between studies.
2507 Additional analyses were conducted across studies with and without media change.
2508

2509 *Limitations*

2510 The Newcastle-Ottawa scale to was used to assess the methodological quality of the included studies since all included studies were
2511 retrospective cohort studies. According to this scale, all studies were found to be “good quality” (out of options poor, fair, and good).
2512 Despite this result, there are several limitations to the included studies. The included studies were primarily retrospective studies and
2513 none of the studies were randomized or blinded. Since retrospective studies relied on existing medical records, test subjects were
2514 assigned to test vs control groups based on physician choice, introducing selection bias. There was a high level of methodological
2515 variation within and between studies.

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2518 **Q2d Included Studies and Methodologic Notes:**

2519 **Scholars responsible for analyzing the literature**

2520 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 sx's, 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

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2527 **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 reactions	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 levocetirizine 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	ferumoxitol + 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 antivenom 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

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METHODOLOGICAL NOTES:

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Measurement of Treatment Effect and Data Synthesis

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- 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.

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- 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 used. 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

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2545 not unexpected, because the populations grouped together had important differences with respect to both condition and exposures of
2546 interest.

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2548 *Zero Cell Correction*

2549 • Some studies that reported zero cells. Unfortunately, the Inverse variance fixed effect and the DerSimonian and Laird random
2550 effects methods are unable to handle these situations and will not be able to perform the calculation. As discussed in the Cochrane
2551 Handbook (16.9.2), it is common for meta-analytic software such as Revman to correct for zero counts by adding a fixed value
2552 (typically 0.5) to all zero cells. While there are benefits to applying a “fixed correction method” to a meta-analysis, there are also
2553 risks including the possibility that it may bias estimates towards no difference or overestimate variance of study estimates. There
2554 is also concern for bias in one direction if the sizes of the study arms are unequal. To minimize introducing additional bias into
2555 our current study, a more conservative correction factor of 0.2 was applied.

2556

2557 *Assessment of heterogeneity*

2558 • Heterogeneity across included studies was assessed by performing a chi-squared test and calculating a corresponding Cochran Q statistic
2559 and p-value. A p-value <0.10 was considered to be statistically significant. In addition, inconsistency across included studies was calculated
2560 and considered an $I^2 >50\%$ to be reflective of substantial and meaningful heterogeneity (Cochrane Handbook 9.5.2).

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2563 **References:**

2564 1. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Collaboration 5.1.0 [updated March 2011]. Higgins JPT, Green S
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