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Biphasic Reactions in Emergency Department Anaphylaxis Patients: A
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Highlights

- What is already known about this topic? Rates of biphasic anaphylaxis are variable, and associated risk factors are unclear.
- What does this article add to our knowledge? This prospective study showed that biphasic anaphylaxis reactions occurred in 7.2% of patients in the emergency department, and clinically significant biphasic reactions occurred in 5.1%. Biphasic reactions were associated with delayed epinephrine administration.
- How does this study impact current management guidelines? These results support current guidelines, which recommend prompt epinephrine administration for the management of anaphylaxis.

Abstract

Background: Biphasic reaction rates and potential associated risk factors are not well understood.

Objective: To evaluate biphasic reaction rates and associated risk factors.

Methods: We prospectively enrolled patients with anaphylaxis at 2 Midwestern academic emergency departments (EDs). We gathered data using patient and ED provider surveys and a structured health record review. Biphasic reaction rates and clinically significant biphasic reaction rates, defined as recurrent reactions that met anaphylaxis diagnostic criteria or were treated with epinephrine, were calculated. Characteristics associated with biphasic reactions were assessed with logistic regression and reported with odds ratios (ORs) and 95% CIs.

Results: Of 430 ED anaphylaxis visits, 31 (7.2%) patients had biphasic reactions; 22 (5.1%) had clinically significant biphasic reactions. The median time from anaphylaxis onset to first epinephrine dose was longer for patients with biphasic (78 minutes) than uniphasic courses (45 minutes) ($P=.005$). A biphasic course was associated with an ED setting of first epinephrine dose (OR, 3.72 [95% CI, 1.36-10.14]) and a delay of more than 30 minutes from symptom onset to first epinephrine dose (OR, 3.39 [95% CI, 1.13-10.18]), and was inversely associated with arrival by ambulance (OR, 0.18 [95% CI, 0.05-0.61]). A clinically significant biphasic reaction was associated with an ED setting of first epinephrine dose (OR, 3.32 [95% CI, 1.08-10.25]) and inversely associated with arrival by ambulance (OR, 0.08 [95% CI, 0.01-0.61]).

25 **Conclusion:** Biphasic reactions and clinically significant biphasic reactions
26 occurred in 7.2% and 5.1% of ED anaphylaxis patients, respectively.
27 Delayed epinephrine administration was associated with biphasic reactions.

28

29 Keywords: anaphylaxis; biphasic reaction; emergency department;
30 epinephrine

31

Abbreviations

- 32
- 33 ED, emergency department
- 34 EDOU, emergency department observation unit
- 35 EHR, electronic health record
- 36 ICU, intensive care unit
- 37 IQR, interquartile range
- 38 NIAID/FARE, National Institutes of Allergy and Infectious Disease/Food
- 39 Allergy Research and Education
- 40 OR, odds ratio
- 41 REP, Rochester Epidemiology Project
- 42

Introduction

Anaphylaxis is an acute, potentially life-threatening systemic allergic reaction that is commonly treated in the emergency department (ED).¹⁻³ Biphasic reactions are defined as a recurrence of anaphylaxis symptoms after resolution of the initial anaphylactic reaction, without re-exposure to the inciting trigger. Contemporary studies incorporating the National Institute of Allergy and Infectious Diseases/Food Allergy Research and Education (NIAID/FARE) criteria⁴ or similar diagnostic criteria have found widely variable rates of biphasic reactions—from 0.4% to 14.7% among patients with anaphylaxis in the ED.⁵⁻¹⁰

Because biphasic reactions can be life-threatening or fatal,^{11, 12} some authors recommend patients be observed for up to 24 hours,¹³⁻¹⁵ while current guidelines in the United States recommend an individualized period of observation based on patient risk factors and reaction severity.¹⁶ A better understanding of biphasic reaction incidence, potential severity, and associated risk factors may assist emergency providers in assessing the need for observation after an anaphylactic reaction and decrease unnecessary health care utilization. The objectives of this study were to evaluate biphasic reactions among prospectively enrolled ED patients in 2 tertiary care centers to 1) investigate the incidence and management of biphasic reactions and 2) determine risk factors associated with biphasic reactions.

Methods

Study Design and Setting

This prospective cohort study took place at 2 EDs located in the US Midwest: Mayo Clinic Hospital — Rochester, Saint Marys Campus, Rochester, Minnesota, a quaternary care academic ED with 77,000 annual

69 patient visits; and the ED of the University of Iowa Hospitals and Clinics,
70 Iowa City, Iowa, with 65,000 annual patient visits. The institutional review
71 boards at both sites approved the study protocol. The study adhered to
72 Strengthening the Reporting of Observational Studies in Epidemiology
73 (STROBE) guideline.¹⁷

74 ***Participants and Data Collection***

75 Patients of all ages who came to the ED during the study period
76 with potential anaphylactic reactions were prospectively enrolled. At Mayo
77 Clinic Hospital, the study period was between April 23, 2010, and
78 September 14, 2018. At the University of Iowa Hospitals and Clinics, the
79 study period was between April 5, 2017, and May 31, 2018. Study
80 coordinators at both sites identified patients whose chief concern at
81 registration included “allergic,” “reaction,” “anaphy-,” “angio-,” “sting,” or
82 “hives.” If their initial reaction met NIAID/FARE diagnostic criteria for
83 anaphylaxis, informed consent was obtained and they were included in the
84 study.

85 At the time of their initial ED evaluation, patients or their
86 caregivers completed an anaphylaxis patient questionnaire that included data
87 on allergic history, presenting signs and symptoms, and prehospital
88 management. A questionnaire on physical examination findings was
89 completed by the primary provider caring for the patient. Additional data
90 were extracted from the electronic health record (EHR) using a standardized
91 extraction procedure. Patient records were reviewed after the initial
92 anaphylactic reaction for any documentation of a recurrent reaction. In
93 addition, patients in the Iowa cohort were contacted by telephone
94 approximately 3 days after the index ED visit. To assess for a possible

95 biphasic reaction, we used a structured interview format that included
96 questions about any recurrent symptoms; use of epinephrine, steroids, or
97 antihistamines; ED return visits; and hospitalizations. The inpatient record
98 was reviewed if the patient was admitted. Return ED visits and outpatient
99 follow-up visits were also reviewed to determine if a patient had a recurrent
100 reaction.

101 Vital status was assessed to ensure that no patients died within 7
102 days after their ED visit by reviewing the EHR and the Rochester
103 Epidemiology Project (REP) Death Registry.¹⁸ Patients were considered to
104 have survived if there was proof of survival in the EHR or if there was no
105 proof of death (ie, absence of a death certificate) in the REP death registry
106 for patients with a current address in Minnesota. Patients who did not have
107 proof of life or death in the EHR or in the REP death registry and lived
108 outside of Minnesota were considered lost to follow-up.

109 ***Definition and Outcome Measure***

110 Patients with anaphylaxis were divided into 2 reaction groups:
111 uniphasic and biphasic. Patients who had any recurrent symptoms within 72
112 hours after resolution of their initial symptoms were included in the biphasic
113 reaction group. A clinically significant biphasic reaction was defined as a
114 recurrent reaction that either met NIAID/FARE anaphylaxis criteria or was
115 treated with epinephrine. The 2 main outcomes were 1) incidence and
116 management of biphasic reactions; and 2) risk factors associated with
117 biphasic reactions.

118 ***Statistical Analysis***

119 Continuous variables were summarized with means and SDs if
120 they were normally distributed and with medians and interquartile ranges

(IQRs) otherwise; categorical variables were summarized with frequency counts and percentages. Variables were compared between the Iowa and Minnesota cohorts and between the uniphasic and biphasic groups using the 2-sample t , Wilcoxon rank sum, χ^2 , and Fisher exact tests. Statistically significant differences between the uniphasic and biphasic groups were further characterized with odds ratios (ORs) and 95% CIs obtained from univariable and multivariable logistic regression models. Statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc). All tests were 2-sided, and P values $<.05$ were considered statistically significant.

Results

Participants and Demographic Characteristics

During the enrollment period, 430 patients whose initial reaction met NIAID/FARE anaphylaxis criteria were eligible for study inclusion (Iowa, 64 patients; Minnesota, 366 patients) (Figure). The mean (SD) age of all patients (Table 1) was 34 (22) years, and 110 (26%) were children (<18 years). Of the patients, 250 (58%) were female, and 372 (88%) were white. Patient histories included anaphylaxis in 218 (51%), food allergy in 198 (46%), and asthma in 164 (38%).

The comparison of characteristics of the initial visits of the Iowa and Minnesota cohorts is shown in Table 1. There were no significant differences between the 2 cohorts in suspected trigger, proportion with a known trigger, epinephrine doses to treat initial reactions, and time interval between symptom onset to epinephrine administered. However, there were significant differences in prior anaphylaxis history, widened pulse pressures at evaluation, and presence of presenting cardiovascular symptoms.

Patient Characteristics, Disposition, and Management

Clinical characteristics are shown in Table 1. There was an identifiable trigger in 358 cases (83%). Food was the most common trigger (n=162 [38%]), followed by medications (n=82 [19%]) and insect venom (n=65 [15%]). Mucocutaneous manifestations were the most frequently reported (n=424 [99%]), then respiratory (n=373 [87%]), gastrointestinal (n=207 [48%]), and cardiovascular (n=202 [47%]). At least 1 dose of epinephrine was administered to 305 patients (71%), including to 136 (45%) patients who received epinephrine before ED arrival. Multiple (≥ 2) doses of epinephrine were required for 50 (12%) patients. Of the patients, 215 (50%) were discharged directly from the ED, 73 (40%) were admitted to the ED observation unit (EDOU), and 42 patients (10%) were admitted to the hospital, including 25 (6%) who were admitted to a general ward and 17 (4%) to the intensive care unit (ICU). Fourteen patients from the Minnesota cohort were lost to follow-up, but there were no deaths identified secondary to anaphylaxis in the 7-day follow-up period. No patient in the Iowa cohort was lost to follow-up.

Biphasic Reactions

Thirty-one patients (7.2% [95% CI, 5.0%-10.2%]) had a biphasic reaction, and 22 (5.1% [95% CI, 3.3%-7.8%]) had a clinically significant biphasic reaction, defined as a biphasic reaction that met NIAID/FARE anaphylaxis criteria or was treated with epinephrine. There was no significant difference in rates of biphasic reactions in the 2 cohorts (7.8% vs 7.1%; $P=.80$) or clinically significant biphasic reaction rates (3.1% vs 5.5%; $P=.76$). A comparison of characteristics between initial visits of patients who did and did not have a biphasic reaction is shown in Table 2.

172 Table 3 summarizes patient characteristics and anaphylaxis
173 management for the 31 biphasic reactions. The mean (SD) age of patients
174 who had biphasic reactions was 34 (25) years. Of these patients, 16 (52%)
175 were female, and 12 (39%) were children. The median (IQR) time between
176 the resolution of initial symptoms and onset of the biphasic reaction was 6
177 (2-23) hours (range, 0.5-45 hours) for 29 patients for whom data were
178 available: 16 patients (55%) had reactions within 6 hours of initial symptom
179 resolution; 7 (24%) patients between 7 and 24 hours; and 6 (21%) patients
180 over 24 hours. Nineteen (61%) patients experienced the onset of a biphasic
181 reaction after ED or EDOU discharge. Mucocutaneous manifestations were
182 most common in biphasic reactions (n=30 [97%]), followed by respiratory
183 (n=15 [48%]), gastrointestinal (n=8 [26%]), and cardiovascular (n=3 [10%]).
184 Epinephrine was administered during 19 visits (61%) for management of
185 biphasic reactions. Six (19%) patients required 2 doses of epinephrine.
186 Eleven (35%) patients were admitted to a hospital ward, and 4 patients
187 (13%) were admitted to the ICU after the biphasic reaction. Table 4 shows
188 the details of individual characteristics and management of patients with
189 biphasic reactions.

190 Based on univariable analysis, a biphasic course was inversely
191 associated with a prior history of food allergy (26% vs 48%; OR, 0.38 [95%
192 CI, 0.17-0.88]; $P=.02$) and arrival by ambulance (10% vs 37%; OR, 0.18
193 [95% CI, 0.05-0.61]; $P=.002$). A biphasic course was also associated with
194 administration of the first dose of epinephrine in the ED rather than in the
195 prehospital setting (81% vs 53%; OR, 3.72 [95% CI, 1.36-10.14]; $P=.007$)
196 and a delay of more than 30 minutes from symptom onset to first
197 epinephrine dose (83% vs 60%; OR, 3.39 [95% CI, 1.13-10.18]; $P=.02$).

198 More specifically, the median time to the first epinephrine dose was longer
199 for patients with a biphasic course (78 minutes) than for those with a
200 uniphasic course (45 minutes) ($P=.005$). After adjusting for over 30 minutes
201 from symptom onset to epinephrine administration, a history of food allergy
202 and ED setting of first epinephrine dose were no longer significantly
203 associated with the development of a biphasic reaction (OR, 0.49 [95% CI,
204 0.19-1.24]; $P=.13$ and OR, 2.32 [95% CI, 0.72-7.49]; $P=.16$, respectively).
205 However, arrival by ambulance continued to be inversely associated with a
206 biphasic course (OR, 0.26 [95% CI, 0.08-0.91]; $P=.04$).

207 A clinically significant biphasic course was inversely associated
208 with adulthood (≥ 18 years old) (55% vs 75%; OR, 0.39 [95% CI, 0.16-0.93];
209 $P=.029$) and arrival by ambulance (5% vs 37%; OR, 0.08 [95% CI, 0.01-
210 0.61]; $P=.002$) as well as with ED setting of first epinephrine dose (79% vs
211 53%; OR, 3.32 [95% CI, 1.08-10.25]; $P=.03$). We were unable to perform
212 multivariable adjustment for the time of first epinephrine dose because there
213 were insufficient patients with adequate timing data who developed a
214 clinically significant biphasic reaction. There were nonstatistically
215 significant tendencies toward an increased rate of clinically significant
216 biphasic reactions with increased epinephrine doses used to treat the initial
217 reaction ($P=.052$) and a widened pulse pressure at initial presentation
218 ($P=.08$).

219 Discussion

220 *Main Findings*

221 This prospective study, which included patients from 2 academic
222 medical centers in the Midwestern United States, showed that 7.2% of ED
223 patients with anaphylaxis experienced a biphasic reaction, and 5.1% of those

224 had a clinically significant biphasic reaction. The time intervals from
225 resolution of the initial event to onset of recurrence of symptoms ranged
226 from 0.5 to 45 hours. Epinephrine was administered for 61% of biphasic
227 reactions, and 19% of patients with biphasic reactions required 2 doses of
228 epinephrine. Four patients (13%) were admitted to the hospital after the
229 biphasic reaction. A biphasic course was associated with a delay of more
230 than 30 minutes from symptom onset to epinephrine administration and
231 inversely associated with arrival by ambulance.

232 ***Interpretation of Study Findings***

233 Although other observational studies have been conducted to
234 elucidate the characteristics of biphasic reactions, the true incidence of
235 biphasic reactions is not well understood and varies considerably. The
236 incidence of biphasic reactions in our cohort is consistent with that in several
237 prior studies that have reported rates of 4.5%-6.3%.^{1, 7, 19, 20} However, a few
238 studies have reported substantially higher or lower rates.^{5, 13, 21} Ellis and
239 Day²¹ reported a biphasic reaction rate of 19.4% in a cohort study of
240 pediatric and adult ED patients who were contacted by telephone after their
241 ED visit to assess the initial reaction as well as the presence of a biphasic
242 reaction. Brazil and MacNamara¹³ reported 6 (18%) biphasic reactions in a
243 retrospective review of 34 patients admitted over an 18-month period for
244 observation after anaphylactic reactions that required treatment with
245 epinephrine. In another retrospective review of 496 consecutive adult ED
246 patients with anaphylaxis, Grunau et al⁵ reported only 2 patients with
247 clinically important biphasic reactions (0.40% [95% CI, 0.07%-1.6%]).

248 The rate of epinephrine administration for treatment of biphasic
249 reactions in our cohort was also similar to that reported in several studies.^{6,}

250 ²⁰⁻²² Mehr et al,²² Alqurashi et al,⁶ Lee and Greenes,²⁰ and Ellis and Day²¹
251 showed that 42%, 49%, 50%, and 55% of biphasic reactions were treated
252 with epinephrine, respectively. Grunau et al⁵ reported that both of the
253 patients who experienced clinically important biphasic reactions in their
254 study required epinephrine. In contrast, Rohacek et al⁷ reported that 20% of
255 biphasic reactions required epinephrine.

256 Importantly, we showed that patients with a biphasic reaction
257 course were less likely to have received the first dose of epinephrine in a
258 prehospital setting and had a longer median time to first epinephrine dose.
259 Several prior studies have suggested that early epinephrine administration
260 may reduce the risk of a biphasic reaction.^{6, 19, 20, 23, 24} Alqurashi et al⁶
261 reported that a delay to epinephrine treatment longer than 90 minutes from
262 the onset of the initial reaction was significantly associated with a biphasic
263 reaction in children. In an observational study, Lertnawapan and Maek-a-
264 nantawat¹⁹ showed that the median time interval from onset to
265 administration of epinephrine was significantly longer in a biphasic group
266 than a nonbiphasic group (240 vs 70 minutes). In a cohort study of children,
267 Lee and Greenes²⁰ also reported that the time interval between onset of
268 symptoms and the initial dose of epinephrine was significantly longer for
269 patients who had biphasic reactions.

270 Although we did not show that biphasic reactions were
271 significantly associated with higher doses of epinephrine for management of
272 the initial reaction as other studies have reported,^{6, 13, 22, 25} we did show a
273 tendency toward an association of increased epinephrine doses with
274 clinically significant biphasic reactions. Brazil and MacNamara,¹³ Mehr et
275 al,²² and Alqurashi et al⁶ all found that biphasic reactions were more likely in

276 patients who required more than 1 dose of epinephrine to treat the initial
277 anaphylactic reaction. Increased epinephrine doses for the management of
278 the initial reaction may be a marker of increased reaction severity, which has
279 been hypothesized to be associated with a biphasic course. This may explain
280 why some studies that included patients with more severe anaphylaxis and
281 were conducted before the adoption of the NIAID/FARE clinical diagnostic
282 criteria reported higher rates of biphasic reactions.^{11, 12}

283 Although the rate of biphasic reactions among patients with an
284 unknown trigger was higher than among those with a known trigger (11% vs
285 6%), we did not find a significant association, which is in contrast to our
286 previous studies.^{9, 10} The cohort described in this study includes 207 patients
287 from our previous study that included patients enrolled both prospectively
288 and retrospectively.¹⁰ Compared with patients in our previous study, patients
289 in this study had a similar rate of biphasic reactions, but the sample size was
290 about 50% smaller, as was the proportion of patients with an unknown
291 trigger (16% vs 22%, respectively). Thus, with a smaller overall number of
292 outcomes of interest, we have less power to detect statistically significant
293 associations. A potential explanation for the difference we previously
294 observed may be that patients with an unknown trigger were less likely to
295 rapidly identify the onset of anaphylaxis and more likely to have received
296 delayed epinephrine, an explanation based on our current finding of an
297 association between delayed epinephrine administration and increased risk
298 of biphasic reaction. In addition, patients with an unknown trigger may have
299 been re-exposed to the trigger, resulting in a recurrent reaction rather than a
300 true biphasic reaction. Further prospective evaluation is needed.

301 The time period for observation after an anaphylactic reaction
302 remains controversial, and there is no universally agreed upon duration of
303 observation.²⁶ Because most patients do not have biphasic reactions, the
304 benefits of observation must be considered against the longer stay in the
305 EDOU. It is interesting that even though a substantial number of patients had
306 a biphasic reaction after ED or EDOU discharge, we did not find any
307 subsequent morbidity or mortality. Therefore, it seems reasonable to
308 customize observation rates and periods on the basis of the patient's reaction
309 severity, access to epinephrine, and patient reliability because reliable
310 clinical predictors for biphasic reactions have not been consistently
311 identified, and there have been a wide range of times to onset reported.^{16, 27}
312 Patients should be educated regarding the risk of a biphasic reaction, and it
313 is critical that they have ready access to self-injectable epinephrine and an
314 appropriate action plan.²⁸

315 ***Study Limitations***

316 This study has several limitations. First, the number of biphasic
317 reactions is relatively small, prohibiting robust statistical analysis of
318 associations. Second, estimation of the time of resolution of the initial
319 symptoms is imprecise, and it is possible that the biphasic reaction was
320 actually the ongoing initial reaction that manifested when the initial
321 treatment was "wearing off." Third, the use of the NIAID/FARE criteria for
322 identification of anaphylaxis cases is imperfect because the criteria have
323 been shown to be very sensitive (95%) but to have a specificity of 71%,
324 which could result in the inclusion of cases that were not truly anaphylaxis.²⁹
325 Fourth, the cohorts at the 2 study sites had differences in allergic history and
326 some presenting symptoms, which could have impacted our findings.

327 Additionally, only the patients in the Iowa cohort were contacted after their
328 ED visit to determine if symptoms had recurred. Thus, some biphasic
329 reactions, particularly mild reactions that did not require any interventions,
330 in the Minnesota cohort may have been missed. However, the similar rates
331 of biphasic reactions as well as clinically significant biphasic reactions in the
332 2 cohorts make it unlikely that this had a substantial impact on our results.
333 Fifth, although there are 2 academic centers included in this study, they are
334 both located in the upper Midwest and have a predominance of white
335 patients, which could reduce the generalizability of the results. Sixth, the
336 prospective design may have resulted in exclusion of some patients with
337 anaphylaxis who had chief concerns other than those used to identify
338 patients for inclusion in the study or other patients who developed
339 anaphylaxis during their ED evaluation that was attributed to medication or
340 contrast dye. However, prospective data collection generates more reliable
341 information regarding time of symptom onset as well as prehospital
342 management, which is frequently not well documented in the EHR. Seventh,
343 26% of the patients with a biphasic reaction in this study did not have an
344 identifiable trigger; thus, we cannot exclude the possibility of re-exposure to
345 the trigger. Finally, 14 patients in the Minnesota cohort were lost to follow-
346 up; therefore, it is possible that biphasic reactions were overlooked in this
347 group.

348 **Conclusions**

349 We report a 7.2% incidence of biphasic reactions and a 5.1% rate
350 of a clinically significant biphasic reaction in patients with anaphylaxis. Our
351 findings add to the mounting evidence that early epinephrine administration
352 may reduce the risk of biphasic reactions.

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448

Table 1. Comparison of Iowa and Minnesota Cohorts

Characteristic	All (N=430)	IA (n=64)	MN (n=366)	P Value
		Mean (SD)		
Age at visit, y	34 (22)	31 (21)	35 (22)	.14
		Median (IQR)		
Symptom onset to epinephrine administration, min (n=289, 42, 247)	48 (15-101)	60 (20-90)	46 (15-104)	.72
		No. (%)		
Age at visit, y				.46
<18	110 (26)	14 (22)	96 (26)	
≥18	320 (74)	50 (78)	270 (74)	
Sex				.74
Female	250 (58)	36 (56)	214 (58)	
Male	180 (42)	28 (44)	152 (42)	
Race (n=425, 62, 363)				.16
White	372 (88)	50 (81)	322 (89)	
Black/African American	19 (4)	5 (8)	14 (4)	
Other	34 (8)	7 (11)	27 (7)	
Medical history				
Anaphylaxis	218 (51)	25 (39)	193 (53)	.04
Food allergy	198 (46)	28 (44)	170 (46)	.69
Asthma	164 (38)	23 (36)	141 (39)	.69
Prior SIE prescription	209 (49)	26 (41)	183 (50)	.17
Prior SIE use	115 (27)	17 (27)	98 (27)	.97
Suspected allergen				.09
Food	162 (38)	28 (44)	134 (37)	
Medication	82 (19)	9 (14)	73 (20)	
Venom	65 (15)	6 (9)	59 (16)	
Latex	4 (1)	2 (3)	2 (1)	
Contrast	26 (6)	3 (5)	23 (6)	
Other	19 (4)	1 (2)	18 (5)	
Unknown	72 (17)	15 (23)	57 (16)	
Arrival by ambulance	151 (35)	18 (28)	133 (36)	.20
Widened pulse pressure (n=388, 61, 327)	48 (12)	2 (3)	46 (14)	.02
Signs and symptoms of initial reaction				
Mucocutaneous	424 (99)	62 (97)	362 (99)	.22
Respiratory	373 (87)	56 (88)	317 (87)	.85
Gastrointestinal	207 (48)	23 (36)	184 (50)	.03
Cardiovascular	202 (47)	15 (23)	187 (51)	<.001
Epinephrine administered	305 (71)	48 (75)	257 (70)	.44
Setting of first epinephrine dose				.09

(n=305, 48, 257)				
Self/caregiver/other/EMS	136 (45)	16 (33)	120 (47)	
ED	169 (55)	32 (67)	137 (53)	
Symptom onset to epinephrine, min (n=289, 42, 247)				.83
≤30	111 (38)	15 (36)	96 (39)	
>30 to ≤60	57 (20)	7 (17)	50 (20)	
>60 to ≤90	40 (14)	10 (24)	30 (12)	
>90	81 (28)	10 (24)	71 (29)	
Symptom onset to epinephrine, min (n=289, 42, 247)				.70
≤30	111 (38)	15 (36)	96 (39)	
>30	178 (62)	27 (64)	151 (61)	

Abbreviations: ED, emergency department; EMS, emergency medical services; IA, Iowa; IQR, interquartile range; MN, Minnesota; SIE, self-injectable epinephrine.

Table 2. Comparison of Uniphasic and Biphasic Groups

Characteristic	Group			P Value ^a	P Value ^b
	Uniphasic (n=399)	Biphasic (n=31)	Clinically Significant Biphasic (n=22)		
	Mean (SD)				
Age at visit, y	34 (22)	34 (25)	30 (25)	.99	.36
	Median (IQR)				
Symptom onset to epinephrine, min (n=265, 24, 18)	45 (15-100)	78 (53-338)	60 (24-167)	.005	.07
	No. (%)				
Age at visit, y				.08	.03
<18	98 (25)	12 (39)	10 (45)		
≥18	301 (75)	19 (61)	12 (55)		
Sex				.44	.97
Female	234 (59)	16 (52)	13 (59)		
Male	165 (41)	15 (48)	9 (41)		
Medical history					
Anaphylaxis	204 (51)	14 (45)	11 (50)	.52	.92
Food allergy	190 (48)	8 (26)	6 (27)	.02	.06
Asthma	155 (39)	9 (29)	8 (36)	.28	.82
Prior SIE prescription	195 (49)	14 (45)	11 (50)	.69	.92
Prior SIE use	108 (27)	7 (23)	6 (27)	.59	.98
Suspected trigger				.31	.23
Food	152 (38)	10 (32)	8 (36)		
Medication	74 (19)	8 (26)	7 (32)		
Venom	62 (16)	3 (10)	2 (9)		
Latex	3 (1)	1 (3)	1 (5)		
Contrast	25 (6)	1 (3)	0		
Other	19 (5)	0	0		
Unknown	64 (16)	8 (26)	4 (18)		
Suspected trigger				.16	.77
Known	335 (84)	23 (74)	18 (82)		
Unknown	64 (16)	8 (26)	4 (18)		
Arrival by ambulance	148 (37)	3 (10)	1 (5)	.002	.002
Widened pulse pressure (n=360, 28, 20)	41 (11)	7 (25)	5 (25)	.065	.08
Signs and symptoms of initial reaction					
Mucocutaneous	393 (98)	31 (100)	22 (100)	1.0	1.0
Respiratory	345 (86)	28 (90)	19 (86)	.78	1.0
Gastrointestinal	191 (48)	16 (52)	13 (59)	.69	.31
Cardiovascular	191 (48)	11 (35)	8 (36)	.18	.29

Epinephrine administered	279 (70)	26 (84)	19 (86)	.10	.10
Epinephrine doses				.11	.052
0	120 (30)	5 (16)	3 (14)		
1	234 (59)	21 (68)	14 (64)		
2	29 (7)	5 (16)	5 (23)		
≥ 3	16 (4)	0	0		
Epinephrine doses				.39	.16
0 or 1	354 (89)	26 (84)	17 (77)		
≥ 2	45 (11)	5 (16)	5 (23)		
Setting of first epinephrine dose (n=279, 26, 19)				.007	.03
Self/caregiver/other/EMS	131 (47)	5 (19)	4 (21)		
ED	148 (53)	21 (81)	15 (79)		
Symptom onset to epinephrine, min (n=265, 24, 18)				.02	.20
≤ 30	107 (40)	4 (17)	4 (22)		
>30 to ≤ 60	51 (19)	6 (25)	6 (33)		
>60 to ≤ 90	37 (14)	3 (13)	1 (6)		
>90	70 (26)	11 (46)	7 (39)		
Symptom onset to epinephrine, min (n=265, 24, 18)				.02	.13
≤ 30	107 (40)	4 (17)	4 (22)		
>30	158 (60)	20 (83)	14 (78)		
Therapy administered					
Corticosteroid	338 (85)	27 (87)	19 (86)	1.0	1.0
Bronchodilator	94 (24)	8 (26)	5 (23)	.78	.93
H ₁ antihistamines	378 (95)	29 (94)	20 (91)	.68	.34
H ₂ antihistamines	253 (63)	21 (68)	15 (68)	.63	.65
Intravenous fluid	106 (27)	8 (26)	4 (18)	.93	.38

Abbreviations: ED, emergency department; EMS, emergency medical services; IQR, interquartile range; SIE, self-injectable epinephrine.

^a Comparison of uniphasic vs biphasic.

^b Comparison of uniphasic vs clinically significant biphasic.

Table 3. Summary of Characteristics and Management for 31 Biphasic Reactions

Characteristic	No. (%)^a
Resolution of initial to biphasic reaction, median (IQR), h (n=29)	6 (2-23)
Signs and symptoms of biphasic reaction	
Mucocutaneous	30 (97)
Respiratory	15 (48)
Gastrointestinal	8 (26)
Cardiovascular	3 (10)
Epinephrine administered	19 (61)
Epinephrine doses	
0	12 (39)
1	13 (42)
2	6 (19)
Therapy administered	
Corticosteroid	17 (55)
Bronchodilator	7 (23)
H ₁ antihistamines	26 (84)
H ₂ antihistamines	13 (42)
Intravenous fluid	4 (13)
Clinically significant biphasic reaction	22 (71)
Transferred to ICU	4 (13)

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

^a Unless otherwise indicated.

Table 4. Characteristics and Management of Patients With Biphasic Anaphylactic Reactions

Patient	Age, y	Sex	Trigger	Onset After Resolution, h	Disposition After Initial Reaction	Biphasic Reaction Onset Location	Presenting Signs and Symptoms	Biphasic Signs and Symptoms	Management, Initial Reaction	Management, Biphasic Reaction	Disposition After Biphasic Reaction
1	5	M	Food (walnut)	0.5	In ED ^a	ED	MC/GI	MC/GI	Epi, H ₁ , H ₂ , CS	Epi, H ₁	ICU>home
2	1	M	Food (macaroni and cheese)	0.7	In ED ^a	ED	MC/R/GI	MC/R	Epi, H ₁ , CS, B	H ₁ , B	GM>home
3	1	F	Unknown	1.5	In ED ^a	ED	MC/R	MC/R	Epi, H ₁ , H ₂ , CS	Epi	ICU>home
4	63	F	Medication (azithromycin)	1.5	EDOU	EDOU	MC/R	MC	Epi, H ₁ , H ₂ , CS, IVF	Epi	ICU>home
5	7	M	Food (cashews)	2	In ED ^a	ED	MC/R/GI	MC/R	Epi, H ₁ , CS	Epi	GM>home
6	8	F	Unknown	2	Home	Home	MC/R/GI/CV	MC/R/GI/CV	None	Epi, H ₁ , H ₂ , CS	Home
7	68	M	Contrast (gadolinium)	2	In ED ^a	ED	MC/R	MC	H ₁ , CS, B	H ₁ , CS	EDOU>home
8	79	M	Food (peanut)	2	EDOU	EDOU	MC/R/GI/CV	MC	Epi, H ₁ , H ₂ , CS, IVF, B	H ₁ , B	EDOU>home
9	69	F	Medication (aspirin)	2.5	EDOU	EDOU	MC/R/GI/CV	R/GI	Epi, H ₁ , H ₂ , CS, IVF, B	Epi, H ₁ , H ₂	EDOU>home
10	37	M	Food	3	Home	Home	MC/R/GI/CV	MC/R/GI	H ₁ , H ₂ , CS, IVF	Epi, H ₁ , H ₂ , CS	EDOU>home
11	65	F	Medication (sulfamethoxazole /trimethoprim)	3	EDOU	EDOU	MC/R	MC	Epi, H ₁ , H ₂ , CS, IVF	None	EDOU>home
12	1	M	Food (peanut)	4	Home	Home	MC/GI	MC	None	Epi, H ₁ , CS	GM>home
13	46	M	Unknown	4	EDOU	Car	MC/R/CV	MC	Epi, H ₁ , H ₂ , CS, IVF	B	Home
14	40	M	Venom	5.5	EDOU	Home	MC/R/GI/CV	MC/R/GI	Epi, H ₁ , CS	Epi, H ₁ , H ₂ , CS, IVF	Home
15	28	M	Venom	6	EDOU	EDOU	MC/R/GI/CV	MC/R	Epi, H ₁ , H ₂ , CS, IVF	Epi, H ₁ , H ₂	EDOU>GM> home
16	20	F	Environmental (tanning bed)	6	Home	School	MC/R	MC	Epi, H ₁ , H ₂ , CS	H ₁	GM>home

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17	55	F	Food (chips and hummus)	9.1	EDOU	EDOU	MC/R/GI/CV	MC/R/GI/CV	Epi, H ₁ , H ₂ , CS	Epi, H ₁ , H ₂ , CS, IVF	MICU>home
18	2	M	Venom	10	Home	Home	MC/R	MC	Epi, H ₁	Epi, H ₁ , CS	GM>home
19	9	F	Unknown	14	Home	Home	MC/R/GI	MC/R/GI	Epi, H ₁ , H ₂ , CS	Epi, H ₁ , H ₂ , CS, B	GM>home
20	49	F	Food (nuts)	16	EDOU	Home	MC/R/CV	MC/R	Epi, H ₁ , H ₂ , CS, B	Epi, H ₁ , H ₂ , IVF, B	GM>home
21	25	F	Medication (allergy shots)	17	EDOU	Home	MC/R/CV	MC/GI	Epi, H ₁ , H ₂ , CS	H ₁ , H ₂	Home
22	17	F	Food (waffles with strawberries)	23	Home	Home	MC/R	MC/R	Epi, H ₁ , H ₂ , CS	Epi, H ₁ , H ₂ , CS	EDOU>GM>home
23	16	M	Unknown	23	Home	School	MC/R	MC	H ₁ , H ₂ , CS	H ₁	Home
24	56	F	Unknown	25	EDOU	Home	MC/R	MC	Epi, H ₁ , H ₂ , CS, IVF	H ₁ , CS	Home
25	63	F	Medication (cefдинир)	32	EDOU	Home	MC/R	MC/R/CV	Epi, H ₁ , H ₂ , CS, B	H ₁ , CS, B	Home
26	47	M	Medication (levofloxacin)	34	EDOU	Home	MC/R/CV	MC	Epi, H ₁ , H ₂ , CS	Epi, H ₁ , H ₂ , CS	GM>home
27	53	F	Medication (cefдинир)	35	EDOU	Hotel	MC/CV	MC	Epi, H ₁ , H ₂ , CS	Epi, H ₁ , H ₂ , CS, IVF	EDOU>GM>home
28	64	F	Medication (sulfamethoxazole/trimethoprim)	37	EDOU	Home	MC/R/GI	MC/R	Epi, H ₁ , H ₂ , CS, B	Epi, H ₁ , H ₂ , CS, B	EDOU>home
29	16	F	Unknown	45	Home	Home	MC/R/GI/CV	MC/R	Epi, H ₁ , CS	Epi, H ₁ , CS	Home
30	9	M	Unknown	Unknown	Home	Home	MC/R/GI	MC	Epi, H ₁ , CS, B	H ₁ , CS	Home
31	47	M	Venom	Unknown	Home	Unknown	MC/R/GI/CV	MC	H ₁ , H ₂ , CS	H ₁	Did not seek care

Abbreviations: B, bronchodilator; CS, corticosteroid; CV, cardiovascular; ED, emergency department; EDOU, emergency department observation unit; Epi, epinephrine; F, female; GI, gastrointestinal; GM, general medical floor; H₁, H₁ antihistamine; H₂, H₂ antihistamine; ICU, intensive care unit; IVF, intravenous fluids; M, male; MC, mucocutaneous; MICU, medical intensive care unit; R, respiratory.

^a Indicates that the biphasic reaction began in the ED before disposition after the initial reaction.

Legend

Figure. Patient Enrollment, Reaction Course, and Management. Uniphasic reaction indicates no recurrence of signs or symptoms after resolution of the initial reaction. Biphasic reactions include all patients with recurrence of any sign or symptom. Clinically significant biphasic reactions include any biphasic reaction that met NIAID/FARE anaphylaxis diagnostic criteria or was treated with epinephrine, or both. IA indicates Iowa; MN, Minnesota; NIAID/FARE, National Institutes of Allergy and Infectious Disease/Food Allergy Research and Education.

