

## Original Article

# Epidemiology of anaphylaxis and biphasic reaction in Japanese children

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**Aim:** Anaphylaxis is common, but can sometimes be fatal. However, data on the epidemiology and characteristics of anaphylaxis are limited. Although 0.9%–14.7% of anaphylactic reactions in children are biphasic, it is unclear what the characteristics of biphasic reaction are and how long patients with this reaction should be observed. The present study aimed to investigate the epidemiology of anaphylaxis and biphasic reactions and identify the characteristics of the latter.

**Methods:** We conducted an observational study of patients who visited the pediatric emergency department (PED) and were hospitalized for anaphylaxis between March 2010 and March 2017.

**Results:** Of the 264,689 children who visited our PED, 353 (1.3 per 1,000 patient) were hospitalized for anaphylaxis, and six (1.7%) had a biphasic reaction. Of the patients with a biphasic reaction, the median time from initial anaphylaxis to the biphasic reaction was 5.9 (interquartile range [IQR] = 3.3–7.6) hours. Symptoms of the initial episode and the biphasic reaction varied. One (0.3%) of the 353 patients developed a clinically important biphasic reaction that required epinephrine administration.

**Conclusions:** The rate of biphasic reactions was 1.7%, and that of clinically important biphasic reactions was 0.3%. Patients with anaphylaxis need to be carefully monitored because of the regular occurrence of biphasic reactions.

**Key words:** Anaphylaxis, biphasic reaction, children, epidemiology, food allergy

## INTRODUCTION

**A**NAPHYLAXIS IS A systemic allergic reaction with rapid onset and is potentially fatal.<sup>1</sup> Its incidence among children has been increasing in recent years.<sup>2–4</sup> In North America, the incidence of anaphylaxis is reportedly 2–4 per 1,000 patients visiting the pediatric emergency department (PED).<sup>5</sup> Although anaphylaxis is common, the data on its epidemiology and characteristics are limited, especially with respect to the Asian pediatric population.

A biphasic reaction is defined as the recurrence of symptoms following the initial anaphylactic episode in the absence of re-exposure to the causative agent. Cases that are as severe as the initial anaphylactic episode are called “clinically

important biphasic reactions.”<sup>6</sup> A recent study has shown that biphasic reactions occur in 0.9%–14.7% of pediatric anaphylaxis cases,<sup>5,7–12</sup> but the rate of clinically important biphasic reactions in children has not yet been reported. Observation of patients hospitalized with anaphylaxis is recommended in case a biphasic reaction should occur. However, the recommended observation time differs among the guidelines<sup>13,14</sup> because the time from the initial episode to the occurrence of a biphasic reaction is not well understood. Furthermore, predicting and preventing a biphasic reaction is difficult because its characteristics are not known.

The aim of the present study was to investigate the epidemiology of anaphylaxis and biphasic reactions and the characteristics of the latter.

## METHODS

### Study design and participants

**T**HE PRESENT, RETROSPECTIVE cohort study enrolled patients who visited the PED at Tokyo Metropolitan Children Medical Center, the main tertiary care

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center in Tokyo, Japan, which receives ~35,000 visits annually, including 3,000 by ambulance. Approximately 520,000 children live in the area served by our hospital. All patients presenting with anaphylaxis to the study center are admitted for at least one night. The present study reviewed the medical records of pediatric patients who were hospitalized for anaphylaxis between March 2010 and March 2017.

### Definition of anaphylaxis and biphasic reaction

The definition and treatment of anaphylaxis at our hospital are based on the World Allergy Organization guidelines.<sup>1</sup> The following are the criteria for a biphasic reaction: (i) recurrence of symptoms without re-exposure to the trigger; (ii) lapse of 1 h or less following the resolution of the initial anaphylactic episode; (iii) occurrence of a second reaction up to 72 h after the initial anaphylactic reaction; and (iv) a second reaction of sufficient severity to require therapeutic intervention or extended hospitalization.<sup>5,15</sup> A clinically important biphasic reaction was defined as a biphasic reaction that is fatal or requires epinephrine administration.<sup>16,17</sup>

### Data collection and outcome measures

Data on age, sex, symptoms, treatment, and historical details of the anaphylactic event were collected. In addition, the following data were collected if a biphasic reaction developed: the causative agent, time between the initial episode and the biphasic reaction, signs, severity, relationship with exercise, and treatment given.

### Data analysis

The background characteristics of all the patients were analyzed using the median and interquartile range (IQR) for continuous variables and frequency distribution and percentages for categorical variables. Data analysis was performed using SPSS 25 (IBM Corp., Armonk, NY).

### Ethical considerations

This study was conducted in accordance with the ethical principles set out in the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Ministry of Health, Labor and Welfare of Japan. The study was approved by the ethics board of our institution (ID: H30b-108).

Because the data were collected retrospectively from patients' medical records, the requirement for written informed consent was waived.

## RESULTS

### Demographics

**B**ETWEEN MARCH 2010 and March 2017, 264,689 children visited the PED at Tokyo Metropolitan Children's Medical Center. Of these, 353 (1.3 per 1,000 patient) were hospitalized for anaphylaxis. Their median age was 4.1 years (IQR = 1.6–7.8), and 216 (61.2%) were male.

### Anaphylaxis features

Table 1 shows the symptoms of anaphylaxis. Skin and mucocutaneous symptoms were the most frequently observed symptoms ( $n = 321$ , 90.9%), followed by respiratory symptoms in 286 (81.0%) patients. Epinephrine, including via auto-injector ( $n = 56$ , 18.8%), and steroids were administered as treatment for anaphylaxis to 298 patients (84.4%) and 309 patients (87.5%), respectively.

The median time between the intake of the causative agent and the appearance of symptoms was 30.0 min (IQR = 5.0–60.0), and the median time between the intake of the causative agent and arrival at the emergency department

**Table 1.** Characteristics of patients with anaphylaxis visiting the ED

Demographics	
Age (y), median, IQR	4.1, 1.6–7.8
Male, $n$ (%)	216 (61.2)
Symptoms $n$ (%)	
Skin and mucocutaneous	321 (90.9)
Respiratory	286 (81.0)
Gastrointestinal	140 (39.7)
Neurological	90 (25.5)
Cardiovascular	70 (19.8)
Treatment $n$ (%)	
Epinephrine	298 (84.4)
Epinephrine before ED arrival	56 (18.8)
Steroids	309 (87.5)
H1-antihistamines	245 (69.4)
H2-antihistamines	118 (33.4)
$\beta$ 2 stimulant	118 (33.4)
Time	
From intake to symptoms (min), median, IQR	30.0, 5.0–60.0
From intake to arrival at ED (min), median, IQR	110.0, 70.0–169.0
From symptoms to epinephrine (min), median, IQR	70.0, 43.0–110.0

ED, emergency department; SD, standard deviation.

(ED) was 110.0 min (IQR = 70.0–169.0). The median time from the appearance of symptoms to the administration of epinephrine was 70.0 min (IQR = 43.0–110.0).

## Biphasic reactions

Six of the patients with anaphylaxis (1.7%) had a biphasic reaction after resolution of the initial episode. Tables 2 and 3 show the characteristics of the initial and biphasic episode, respectively. The median age of this group was 5.3 years (IQR = 2.8–6.4), and four of the patients were male (66.7%). The median time from the initial anaphylactic episode to the biphasic reaction was 5.9 hours (IQR = 3.3–7.6) (Table 3). During the biphasic reactions, skin and

mucocutaneous symptoms were most frequently observed ( $n = 5$ , 83.3%), followed by respiratory symptoms in three patients (50.0%) and gastrointestinal symptoms in one patient (16.7%). One patient (0.3%) experienced a clinically important biphasic reaction and received epinephrine.

The causes, symptoms, and severity of the initial anaphylaxis varied, and no relationship to exercise was observed (Table 2). In the initial episode, no neurological or cardiovascular symptoms were observed, and epinephrine and steroids were administered to three patients (50.0%) and five patients (83.3%), respectively.

Table 4 summarizes the background factors of the patients with and without a biphasic reaction. The proportion of patients receiving an adrenaline injection for the initial

**Table 2.** Characteristics and management of the initial anaphylactic episode in patients with a biphasic reaction

No.	Sex	Age (y)	Com	Initial anaphylaxis				Treatment			
				Causes	Symptoms	Exer	Grad <sup>‡</sup>	Ad	St	H1	β2
1	M	2.8	(–)	Soy milk	Facial redness, cough, pharyngeal discomfort	(–)	3	●	●	●	
2	F	2.8	(–)	Sea urchin Salmon roe	Cough, vomiting, salivation	(–)	3		●	●	
3 <sup>†</sup>	M	4.9	(–)	Cashew nuts	Erythema, swelling of eyelids, sore throat, vomiting	(–)	3	●	●	●	
4	M	5.8	(–)	Egg	Erythema, cough, stomachache, vomiting, diarrhea	(–)	3		●		●
5	F	6.0	(–)	Egg	Wheals, cough, wheezing	(–)	4	●			●
6	M	7.5	(–)	Milk	Wheals, swelling of eyelids and lips, dyspnea	(–)	4		●	●	

Ad, adrenaline; β2, β2 stimulant; Com, comorbidity; Exer, exercise; Grad, grading; H1, H1 antihistamines; St, steroid.

<sup>†</sup>Patient 3 (male) had a clinically important biphasic reaction.

<sup>‡</sup>Anaphylaxis was graded using Sampson's criteria.<sup>21</sup>

**Table 3.** Characteristics and management of biphasic reactions

No.	Sex	Age (y)	Biphasic reaction						
			Time to biphasic reaction (h)	Symptoms	Treatment				
					Ad	St	H1	β2	Others
1	M	2.8	6.8	Wheals, salivation				●	
2	F	2.8	7.6	Desaturation					Inhaled adrenaline
3 <sup>†</sup>	M	4.9	2.7	Wheals, wheeze, desaturation	●				
4	M	5.8	5.0	Erythema, cough, dyspnea				●	
5	F	6.0	15.5	Wheals					Delayed discharge
6	M	7.5	3.3	Wheals, vomiting		●	●		

Ad, adrenaline; β2, β2 stimulant; St, steroid.

<sup>†</sup>Patient 3 (male) had a clinically important biphasic reaction.

**Table 4.** Differences in background factors between patients with and without a biphasic reaction

	Without BR (n = 347)	BR (n = 6)
Age (y)	4.0 (1.6–8.1) <sup>†</sup>	5.3 (2.8–6.4) <sup>†</sup>
Sex (male)	212 (61.1) <sup>‡</sup>	4 (66.7) <sup>‡</sup>
Symptoms		
Skin	316 (91.0) <sup>‡</sup>	5 (83.3) <sup>‡</sup>
Respiratory	281 (81.0) <sup>‡</sup>	5 (83.3) <sup>‡</sup>
Gastrointestinal	136 (39.2) <sup>‡</sup>	4 (66.7) <sup>‡</sup>
Neurological	90 (25.9) <sup>‡</sup>	0
Cardiovascular	70 (20.2) <sup>‡</sup>	0
Hypotension	12 (3.5) <sup>‡</sup>	0
Treatment		
Adrenaline	295 (85.0) <sup>‡</sup>	3 (50.0) <sup>‡</sup>
Steroids	304 (87.6) <sup>‡</sup>	5 (83.3) <sup>‡</sup>
H1 antihistamines	241 (69.5) <sup>‡</sup>	4 (66.7) <sup>‡</sup>
H2 antihistamines	118 (34.0) <sup>‡</sup>	0
β2 stimulant	116 (33.4) <sup>‡</sup>	2 (33.3) <sup>‡</sup>

BR, biphasic reaction.

<sup>†</sup>Values are expressed as the median and IQR.<sup>‡</sup>Values are expressed as the number and percentage.

treatment in the non-biphasic group was slightly higher than in biphasic group whereas age, sex, and symptoms of the initial episode did not differ between the groups.

## DISCUSSION

THE PRESENT STUDY demonstrated the frequency and characteristics of anaphylaxis and biphasic reactions. Of the 353 patients with a diagnosis of anaphylaxis who were admitted to our hospital, six patients (1.7%) experienced a biphasic reaction.

The incidence of biphasic reactions among anaphylaxis cases was 1.7% in the present study, and their characteristics and symptoms varied. The incidence of biphasic reactions is lower in Asia (0.9%–3.6%)<sup>7–9</sup> than in other areas (5.2%–14.7%),<sup>5,10–12</sup> which may explain the low incidence observed in the present study although, again, the incidence among different ethnicities has not been studied in children. Previous studies have reported that rapid adrenaline administration can prevent biphasic reactions.<sup>5,10,18</sup> Our study demonstrated a higher proportion of cases of adrenaline administration (84.4%) in Japan than the global figure of 45%–54%,<sup>3,19</sup> which may account for the exceptionally low incidence in our study. The summary of the characteristics of patients with and without a biphasic reaction in Table 4 also demonstrates the ability of adrenaline administration to prevent biphasic reactions. Three of six patients (50%) with

a biphasic reaction received adrenaline for their initial anaphylactic episode, and more patients in the non-biphasic reaction group (85.0%) than in the biphasic reaction group received adrenaline.

Our study also found that the median time to the onset of a biphasic reaction following the resolution of the initial anaphylactic episode was 5.9 h (IQR = 3.3–7.6). Previous studies in children have reported widely varying intervals (median interval = 1.5–15 h).<sup>7,9–12</sup> Our results fell within this range; therefore, the actual onset of a biphasic reaction can vary considerably, making it difficult to establish an appropriate observation period.

The present study, the first to report the incidence of clinically important biphasic reactions in children, found the incidence in this population to be 0.3%. A previous study of adults reported an incidence of 0%–0.4%,<sup>16,20</sup> which is close to our own. Because the frequency of clinically important biphasic reactions is low, it may not be necessary to hospitalize all patients with anaphylaxis. In fact, the American and European guidelines recommend an observation period of 4–8 h, and not all patients are hospitalized.<sup>13,14</sup> If the patient has fast and easy access to a hospital, observation at home after an initial emergency department visit may suffice.

None of the patients in the present study with hypotension or anaphylaxis because of an unknown antigen had a biphasic reaction. Additional, prospective studies are needed to investigate the risks and preventive factors of biphasic reactions.

Our study has several limitations. First, it was retrospective; therefore, the reliability of the data may be limited. However, most cases of biphasic reaction were likely to have been correctly identified because most patients with anaphylaxis were observed during hospitalization until the day after the initial anaphylactic episode. Second, all the data were collected from a single center, therefore, possibly limiting their external validity. However, our PED also serves as a primary to tertiary emergency medical facility, mitigating this limitation. Third, our study enrolled only a small number of patients with biphasic reaction, possibly reducing its internal validity. A multi-institutional study enrolling a larger cohort is necessary to verify our results.

In conclusion, the rate of biphasic reactions was 1.7%, and that of clinically important biphasic reactions was 0.3%. Patients with anaphylaxis need to be carefully monitored in view of the regular occurrence of biphasic reactions following an initial anaphylactic episode. Further prospective studies are warranted to identify the characteristics of biphasic reactions and to establish an appropriate observation period for patients with anaphylaxis.

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## DISCLOSURES

**A**PPROVAL OF THE Research Protocol: The study was approved by the ethics board of our institution (ID: H30b-108).

Informed Consent: Not applicable.

Registry and Registration No. of the study/Trial: Not applicable.

Animal Studies: Not applicable.

Conflicts of Interest: None declared.

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