

Anaphylaxis and Biphasic Phase in Thailand: 4-year Observation

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ABSTRACT

Background: Anaphylaxis, a severe systemic allergic reaction, can be fatal. However, its prevalence has been underestimated especially in biphasic phase, due to a lack of case awareness. This study aimed to determine the rate of anaphylaxis, describe clinical manifestations and management, and identify the causative agents and risk factors of biphasic anaphylactic reaction.

Methods: An observational study was conducted at the Emergency Department of Thammasat University Hospital, Thailand, during the period 2004-2008.

Results: Of total 208 cases of anaphylaxis identified, the median age was 20.67 years; 52.9% were male. The anaphylaxis rate was 49 per 100,000 patient-years. No fatal case was found; 58.7% had a history of atopy, and 38.5% had experienced a previous allergic reaction, of whom 8.8% had had a previous anaphylactic reaction. The causative allergens were identified in 82.2% of cases; food allergy was most common. Urticaria was the most common presentation (87%). Among 6.3% of the patients who developed biphasic reaction, a significantly longer time from onset of symptoms to administration of epinephrine was detected, with a median of 240 minutes for those with biphasic anaphylaxis, versus 70 minutes for those without ($p = 0.002$). The median times from onset to hospital arrival and the arrival to administration of epinephrine were also significantly longer in the biphasic group than the non-biphasic patients ($p = 0.002$ and $p = 0.001$, respectively). In multivariable regression models, the time intervals from onset and hospital arrival to administration of epinephrine continued to predict biphasic phase occurrence ($p < 0.01$).

Conclusions: Anaphylaxis predominantly occurs among children and young adults. Delayed administration of epinephrine was associated with the occurrence of biphasic anaphylaxis.

KEY WORDS

allergen, anaphylaxis, biphasic reaction, occurrence, risk

INTRODUCTION

Anaphylaxis, an acute, serious, potentially fatal systemic allergic reaction, can manifest in a variety of presentations, onsets, appearances, and severities. In the US, 1-3% of the population is estimated to be at risk of anaphylaxis.¹ The incidence of anaphylaxis in the UK was 6.7 per 100,000 person-years in 2001, and increased by 19% to 7.9 per 100,000 in 2005.² This trend implies the emerging incidence and impact of this medical problem. In Thailand, the incidence of anaphylaxis was 21 per 100,000 person-years, with a fatality rate of 0.65% of cases.³ The annual occurrence

of anaphylaxis increased from 9.16 per 100,000 admitted persons in 1999, to 55.45 per 100,000 admitted persons in 2004, and the case fatality rate was 0.19 per 100,000 admitted persons.⁴ Epidemiologic information about anaphylaxis in Thailand is likely to be underestimated.

Many contributing factors masking the actual incidence of anaphylaxis include unawareness;⁵ non-identification,^{5,6} especially in some circumstances such as the perioperative period; emergencies, and life-saving or unconditional management and death with unidentified cause (SUDS); and missed diagnosis⁶ of a case presenting mild symptoms. Using the

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diagnostic criteria for anaphylaxis outlined by the 2006 Symposium on the Definition and Management of Anaphylaxis, sponsored by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network,⁷ few studies have been published demonstrating the incidence and clinical characteristics of anaphylaxis. The objectives of this study were to describe the clinical manifestations and management of anaphylaxis according to the criteria, and to identify the causative agents and risk factors of biphasic anaphylaxis.

METHODS

A cohort study was conducted in Thammasat University Hospital, Prathumthani Province, Thailand, and was approved by the Ethics Committee of the Faculty of Medicine, Thammasat University (Rangsit Campus). All suspected cases seen at the emergency department of the hospital from 1 July 2004 to 30 September 2008 were enrolled into the study. The cases of anaphylaxis were defined by a physician in charge and had to satisfy one of the following diagnostic criteria⁷: 1) acute onset of an illness with involvement of the skin, mucosal tissues, or both, in combination with at least one of the following: respiratory compromise or reduced blood pressure or symptoms associated with terminal organ dysfunction, 2) two or more of the following combinations, which occur rapidly after exposure to a likely allergen: involvement of the skin-mucosal tissues, respiratory compromise, reduced blood pressure, or persistent gastrointestinal symptoms, and 3) reduced blood pressure after exposure to a known allergen for that patient. In addition, all cases sorted by the discharge diagnostic codes using the 9th and 10th version International Classification of Diseases (ICD) and defined as the following terms: anaphylaxis, angioedema, urticaria, shock, syncope, food allergy, drug allergy, insect allergy, insect sting, and allergic reaction, were reviewed by the allergist of the Department of Medicine, Thammasat University, for retrospective recruitment into this study.

Data collection included demographic data, history of atopic disease and allergic disease, food allergy and drug allergy, previous anaphylaxis, family history of atopy, underlying disease and medication, time from allergen contact to onset of symptoms, type of culprit allergen, and clinical manifestations. In all patients, skin reactivity was tested on the volar surface of the forearm by the same trained and experienced person. The results were read at 15 min. A positive result yields a wheal at least 3 mm in diameter larger than the negative control (glycerinated phenol-saline). The studied allergens (Alk-Abello; Lincoln Diagnostics, Dallas, TX, USA), included 13 food allergens: egg white, egg yolk, cow's milk, beef, pork, mixed fish (Flounder, Cod, Halibut), wheat, mixed shellfish (crab, shrimp, lobster, oyster), peanut, soy-

bean, cocoa bean, green pea and yeast; and 12 aero-allergens composed of molds (*Aspergillus*, *Penicillium*, *Cladosporium*), pollens (paragrass, bermuda grass, careless weed), house dust, mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), cat hair, dog epithelium and cockroaches.

Sample size estimation using Epi Info 6 was 138, based on acceptable biphasic-phase occurrence range of 5-15%, with 95% confidence interval. All data was entered and analyzed using the statistical software SPSS version 17. Qualitative data were expressed as percent. Chi-square testing was performed for univariate analysis of the relationship between dichotomous clinical variables and outcome variables of biphasic reactions. The unpaired t-test was used for univariate analysis of continuous clinical predictor variables and outcome variables of biphasic reactions. The Mann-Whitney U test was used to analyze correlations in nonparametric data. Logistic regression was used for multivariate analysis to determine the independent association of factors related to occurrence of biphasic phase of anaphylaxis. A *p*-value < 0.05 was considered statistically significant.

RESULTS

A total of 208 cases of anaphylaxis were identified and fulfilled the diagnostic criteria. We calculated the occurrence from the total attendances of all patients during that period; the rate of anaphylaxis in the emergency department was 49 per 100,000 patients per year. No fatal cases were reported.

DEMOGRAPHIC DATA

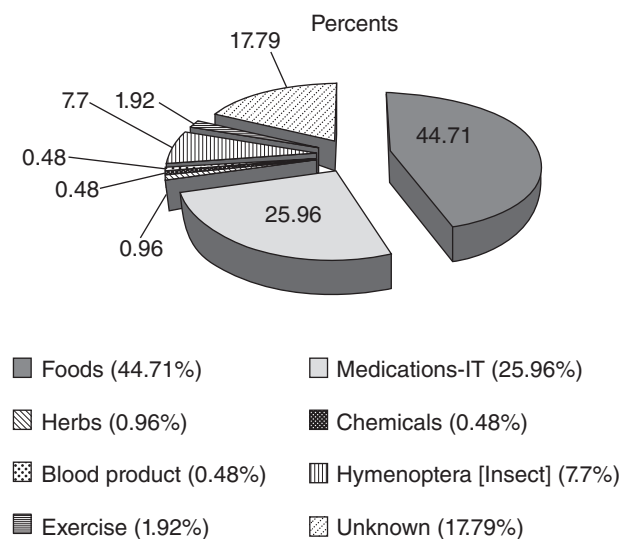
Demographic data and underlying atopy are presented in Table 1. There were 110 (52.9%) male cases and 98 (47.1%) female cases. The median (range) age of patients was 20.67 (1 month to 70 years). Most patients were children and young adults. Fifty-eight point seven percent of patients had a positive atopic history. Associated atopy was classified into allergic rhinitis (24.5%), atopic dermatitis (2.9%), asthma (16.3%), urticaria (4.8%), drug allergy (17.3%), and food allergy (22.6%). Previous allergic reactions were reported in 83 (39.9%) patients. Seven cases (3.4%) had previous anaphylactic reactions. Surprisingly, all of these had developed anaphylaxis from the same cause as the previous anaphylactic reaction.

CAUSATIVE ALLERGEN

One hundred seventy-one patients (82.2%) could identify the culprit (Fig. 1). By medical history, food was the most common causative allergen. Of the 93 cases (44.7%) for whom food was the trigger, the most common was seafood (45.2%), including shrimp (24.7%) and crab (9.7%), followed by seafood (unspecified or mixed) (8.6%), and squid (4.3%). Fried-insect-(such as grasshoppers) induced anaphylaxis was noted in 23.6% of cases. Other causes of food-trigger anaphy-

Table 1 Baseline characteristics, clinical manifestations and initial treatment of 208 anaphylactic patients

Characteristics	Non-biphasic anaphylaxis N = 195	Biphasic anaphylaxis N = 13	P-value
Male (%)	106 (54.4)	4 (30.8)	0.173
Median age, years	22	18.5	0.564
Atopy (%)	118 (60.5)	4 (30.8)	0.069
- Allergic rhinitis (%)	47 (22.6)	4 (30.8)	0.526
- Asthma (%)	31 (15.9)	3 (23.1)	0.771
- Food allergy (%)	45 (23.1)	2 (15.4)	0.764
Drug allergy (%)	36 (18.5)	0	0.13
Previous allergic reactions (%)	78 (40)	5 (38.5)	0.855
Underlying disease (%)	87 (44.6)	5 (38.5)	0.885
Presenting symptoms:			
· Urticaria/angioedema (%)	169 (86.7)	12 (92.3)	1.00
· Bronchospasm (%)	100 (51.3)	4 (30.8)	0.252
· Abdominal pain (%)	57 (29.2)	7 (53.8)	0.121
· Hypotension (%)	63 (32.3)	5 (38.5)	0.879
· Shock (%)	56 (28.7)	5 (38.5)	0.665
· Unconsciousness (%)	7 (3.6)	1 (7.7)	0.409
Treatment:			
· Intramuscular injection of epinephrine (%)	170 (87.2)	13 (100)	0.467
· Epinephrine use (%)	192 (98.5)	12 (92.3)	0.229
· Injected H1 antagonist (%)	180 (92.3)	11 (84.6)	0.288
· Injected H2 antagonist (%)	114 (58.5)	9 (69.2)	0.636
· Steroid use (%)	169 (86.7)	10 (76.9)	0.398
· Beta-agonist use via nebulizer (%)	59 (30.3)	4 (30.8)	1.00
Time Interval (from onset to treatment)	Median (IQR)	Median (IQR)	
· Time from Contact – Onset (min.)	30 (17.5-107.5)	120 (10-240)	0.501
· Time from Onset – Hospital Arrival (min.)	60 (30-120)	180 (105-360)	0.002
· Time from Onset – Epinephrine (min.)	70 (40-135)	240 (122.5-380)	0.002
· Time from Hospital Arrival – Epinephrine (min.)	15 (10-15)	25 (16.5-30)	0.001


Fig. 1 Possible causes of anaphylaxis (N = 171).

laxis included fish (11 cases), wheat (7 cases), and cow's milk (4 cases). Medications and herbs were the second-most common groups of allergens. 55 cases (26.4%) of anaphylaxis caused by medications were classified into drugs (49 cases), herbs (2 cases), vaccine (1 case), and immunotherapy (3 cases). The types and names of the medications causing anaphylaxis are grouped in Table 2. Insect stings were also detected as a cause of anaphylaxis in 16 cases (7.7%). Exercise-induced anaphylaxis was noted in 4 cases (1.9%). Other identified causes were chemicals (1 case) and blood product (1 case). However, 37 patients (17.8%) could not identify their possible triggers.

CLINICAL MANIFESTATIONS AND MANAGEMENT

The median time (range) of the latent period, from allergen culprit exposure to first presenting symptom, was 69.5 (5-4200) minutes. The common signs and symptoms are also shown in Table 1. Anaphylactic

Table 2 Drug-induced anaphylaxis (*N* = 49)

Causative Agent	Patient number	Percent
NSAIDS	17	34.7
Beta-lactams	12	24.5
Quinolones	4	8.2
Paracetamol	3	6.15
Cephalosporin (ceftriaxone)	2	4.1
Sulfa	2	4.1
Tolperisone	1	2.05
Desferrioxamine	1	2.05
Nicotinamide	1	2.05
Omeprazole injection	1	2.05
Streptokinase	1	2.05
Aminoglycoside	1	2.05
Xylocaine	1	2.05

shock was identified in 29.3% of cases. Dermatologic symptoms, including urticaria (87%), angioedema (70.7%), and pruritus (69.7%), were most commonly detected symptoms among anaphylactic cases. Oral pruritus and flushing were noted in 19.7 and 26.4% of cases, respectively. Respiratory symptoms included dyspnea (50%), wheezing (39.4%), and hoarseness of voice (3.8%). Abdominal cramps, nausea and diarrhea were noted commonly, at 30.8, 42.8, and 19.2%, respectively. Syncope and hypotension could be found in 18.8 and 32.7% of cases, respectively. Neurological symptoms, including seizure and unconsciousness, were uncommon. Skin prick tests (SPT) were performed in 46 cases (22.1%), of which 82.6% were SPT-positive with clinically confirmed for causative allergen. A negative SPT result was found in 8 cases (17.4%). Specific IgE by RAST test or Immunocap were performed in only 2 cases (1%), and showed positive results in both patients. An oral food-challenge test was performed with one patient, with a positive result. No exercise-challenge test was performed.

Two hundred and four patients (98.1%) were given epinephrine. The median time interval from onset of symptom to first administration of epinephrine was 75 minutes (IQR 40-137.5). The routes of injection were intramuscular (88%), subcutaneous (9.6%), and intravenous (0.5%). Other drugs prescribed included steroids (86.1%), H1-receptor antagonist (91.8%), H2-antagonist (59.1%), and beta-adrenergic agonist (30.3%) (Table 1). Only 8 patients (3.8%) received self-administered epinephrine or auto-injection epinephrine (Epipen) at the time of discharge. The mean length of hospitalization was 1.2 days.

BIPHASIC REACTION

Anaphylaxis resolved acutely for every patient. However, biphasic reactions were detected in 13 patients (6.25%), 9 females and 4 males. The time from initial

event to onset of second reaction ranged from 2 to 13 hours, with a mean of 7.84 hours. One case was documented as protracted anaphylactic reaction. The allergens involved in the biphasic-reaction group were shrimp/seafood (30.8%), fried insect as food (15.4%), immunotherapy (15.4%), insecticide (7.7%), and unknown cause (30.8%). Five of 13 patients had a history of previous allergic reaction caused by the same culprit allergen. Atopic disease and documented anaphylactic shock were detected in 30.8 and 38.5% of cases, respectively. All biphasic patients had symptoms and signs involving organ systems similar to their presentation in their initial phase.

There was no significant difference in baseline characteristics between patients with and without biphasic anaphylaxis. In addition, other clinical parameters, such as atopic disease, triggers, precipitating factors (i.e. food, exercise, and medication), clinical manifestations and treatment, were not significantly different between the two groups (Table 1). There was no significant difference in time from initial exposure of the presumptive culprit to onset of reaction between patients with and without biphasic anaphylaxis ($p = 0.5$). Regarding treatment of initial anaphylaxis, intramuscular epinephrine and steroid were administered in 92.3 and 76.9% of cases, respectively. Steroid administration was not statistically significantly different between biphasic and non-biphasic patients. The median time interval (minutes) from onset to administration of epinephrine was significantly longer in the biphasic group than the non-biphasic patients, at 240 (IQR 122.5-380) vs 70 (IQR 40-135) minutes, $p = 0.002$ (Table 1, Fig. 2). Also the median time interval (minutes) from hospital arrival to administration of epinephrine was significantly longer in the biphasic group than the non-biphasic patients, at 25 (IQR 16.5-30) vs 15 (IQR 10-15) minutes, $p = 0.001$. Furthermore, the median time interval (minutes) from onset to hospital arrival was longer in the biphasic group than the non-biphasic group, at 180 (IQR 105-360) vs 60 (IQR 30-120), $p = 0.002$. However, there was no statistical difference between the median time interval from contact to onset of symptoms (Table 1). In multivariable regression models, the time intervals from reaction onset to hospital arrival and the onset and arrival to administration of epinephrine continued to predict biphasic phase occurrence ($p < 0.01$).

DISCUSSION

The prevalence of anaphylaxis is increasing, as found in this study and previous studies.^{2,8} Age distribution predominated in child and young adult groups; however, being elderly might be a risk factor contributing to anaphylaxis-related death, for which the likelihood increases with increasing age.⁹ The lack of fatal cases in this study may be explained with the young study population with the mean age of 20.67 years. This

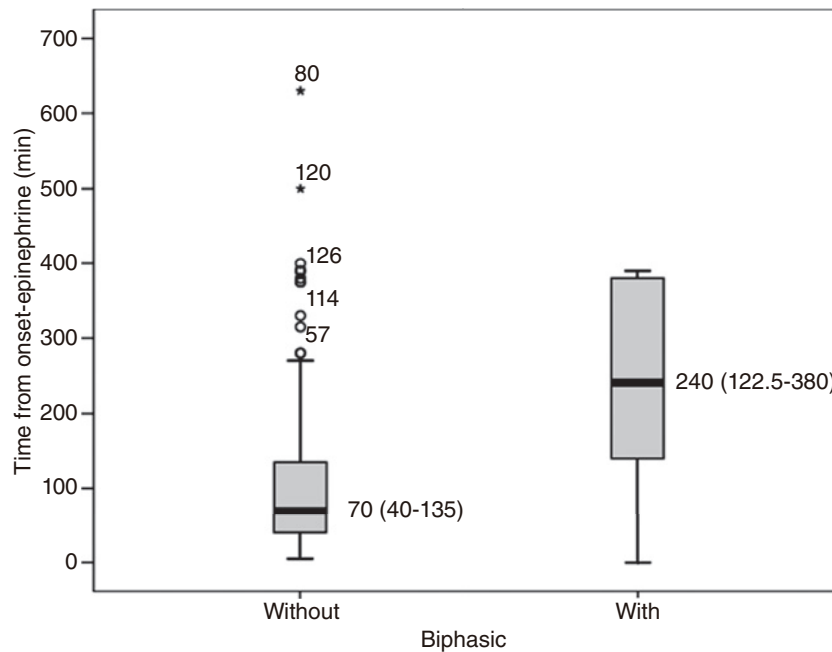


Fig. 2 Time from onset to administration of epinephrine in patients with and without biphasic phase, $p = 0.002$ ($N = 208$).

study was also conducted in a hospital remote from surrounding communities, so it is possible that severe cases might not reach the hospital in time. Also, some anaphylactic events during hospitalization, related to operations or medical interventions, were not included in this study. Other recent studies have detected low to rare anaphylaxis-associated death rates, with mortality at 0.0001%¹⁰ and 0.19 per 100,000.⁴ Over two thirds of the patients had previous atopic history, which was similar to other studies.¹¹ Surprisingly, the previous allergic and previous anaphylactic reactions were detected at lower rates than a previous study.¹¹ This finding might be related to a lack of recognition in a case of mild reaction.

Like previous studies,^{1,3,10,12-14} the most commonly identified allergen was food. This is consistent with the increasing incidence of food allergy, which is 3-4% in the general population and 5% in children.¹² However, the kinds of food causing anaphylaxis differ from country to country; e.g., peanuts in Western developed countries.¹⁵ Peanut allergy is found among 1% of Western populations,¹⁶ but scarcely among Asian populations.¹⁷ We found the food most commonly inducing anaphylaxis was seafood, which caused nearly half of all food-related anaphylaxis, and one-quarter of all cases. These findings are supported by other studies,^{8,11} but contrast with a study from Japan¹⁸; this might be explained by the lifestyles in the developed world or a history of high seafood exposure in an affected area. A history of food anaphylaxis related to fried insects, which has never been reported from other countries, was also detected. Fried

insects caused anaphylaxis in about one-quarter of food-related anaphylaxis, which is relatively higher than has been reported in the USA.¹⁹

Medication-associated anaphylaxis is important among adults and children. Antibiotics and analgesics are the most common culprits of anaphylaxis. Although immunotherapy-related anaphylaxis is possible, it rarely occurs; it is safe for selected atopic cases.^{20,21} We did not find any case of food-dependent exercise-induced anaphylaxis, which is a rare and easily underestimated disease. Among the skin-prick-test cases, we found the test yielded positive results among 82.6% of patients. This conclusion should encourage physicians to perform skin-prick tests to confirm a diagnosis and to improve further management.

This study emphasized the assessment of early detection, management, and short-term outcomes of anaphylaxis. We found the latent periods from contact with the allergen to onset of symptom were 5 minutes to 70 hours (median 30 minutes, mean 123.94 minutes). The mean duration was double that of a previous study.¹¹ This could be related to the study setting and recall bias in a study using a questionnaire. Regarding the clinical manifestations of anaphylaxis in our study, the most common presentation was cutaneous symptoms, especially urticaria, which is similar to previous studies.^{22,23} In our institution, the treatment of anaphylaxis, by giving intramuscular epinephrine, following published guideline⁷ was 87.5%. The overall usage of epinephrine in all routes of injection (intramuscular, intravenous, and subcutaneous) was 98.1% of cases. This finding con-

trasts with other studies showing lower rates of epinephrine use.^{4,24} The high rate of epinephrine use in the treatment of anaphylaxis might result from recent intensive emergency training for medical staff. One patient was given intravenous epinephrine due to circulatory collapse. However, steroids, H1 and H2 antagonists, and beta-adrenergic agonists, were prescribed in 86, 91.8, 86, and 30.8% of cases, respectively, which is comparable with previous studies.^{25,26}

Biphasic reaction was detected in 6.25% of cases, which is similar to previous studies.²⁷⁻²⁹ Its incidence ranges from 1 to 20% of all episodes.³⁰ The severity could be less severe, equally severe, or more severe than the initial reaction, ranging in degree from mild symptoms to fatal reactions.³¹ The occurrence of biphasic reaction might be affected by early management and early recognition of cases. Although 30% of biphasic anaphylactic cases had a history of atopy, it could not be identified as a risk factor. The latent period, from initial phase to biphasic phase in our study, ranged from 2 to 13 hours. The reaction may even occur later, up to 72 hours after resolution of the primary event,³⁰ so that anaphylactic patients should be observed for at least 24 hours.^{28,32,33} Although steroid administration was detected, it seemed that its use did not prevent biphasic reaction.^{28,29,34}

From our study, the time from onset to the administration of epinephrine is the predisposing determinant of biphasic reaction, in which there was a significantly longer median time from onset to administration of epinephrine than for the non-biphasic group ($p = 0.002$). The median time from hospital arrival to administration of epinephrine was also significantly longer in the biphasic group than the non-biphasic patients ($p = 0.001$). Of interest, Smit *et al.* observed that the time interval from onset to presentation was three times longer in biphasic than the non-biphasic patients.³⁵ Our study confirmed the association between the time interval from onset to presentation at hospital was longer in biphasic patients. We postulate that the slowly progressive symptoms in the patients might delay their recognition and hospital arrival. The delayed time intervals could predispose them to have biphasic reaction and receive delayed administration of epinephrine. These findings support the early administration of epinephrine to prevent late-phase anaphylaxis.²⁹ The delayed administration of epinephrine, caused by delayed hospital arrival or delayed recognition for treatment, was associated with a higher rate of complications and mortality.³³ We recommend giving epinephrine as early as possible, to prevent morbidity and mortality. Patients at risk or with a previous history of anaphylaxis should be educated to use self-administered epinephrine. Training the patient to use auto-injected epinephrine using the correct method and at the correct time is beneficial and will reduce mortality from anaphylaxis.^{36,37}

Food-related anaphylaxis is common. Early admini-

stration of epinephrine is critical and significantly associated with lower morbidity from anaphylaxis. Physicians should be more aware of the emergence of anaphylaxis, for prompt recognition and immediate management.

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