


# Pediatric Anaphylaxis: Etiology and Predictive Factors in an Emergency Setting

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## Abstract

Anaphylaxis is a serious allergic life-threatening condition that needs immediate treatment to prevent unfavorable outcomes. The present study revealed that the prevalence of anaphylaxis in children increased with age and the adolescent group has the most frequent anaphylaxis events. Food-induced anaphylaxis was the most common cause of anaphylaxis in pediatric population. This etiology revealed a significant correlation with a known history of food allergy in the study population,  $P = .029$ . Anaphylaxis from insect stings associated with cardiovascular symptoms,  $P < .001$  and inclined to be severe. Univariate analysis showed predicted probability of severe anaphylaxis increased with age with an odds ratio of 1.1. This finding strengthens and supports the view that physicians should be aware of severe anaphylaxis reactions in older age group when there is a documented history of insect sting. The overall pediatric anaphylaxis patients in the study population had favorable outcomes. The authors recommended at least 24 hours hospital observation in order to observe biphasic reaction in pediatric anaphylaxis especially in adolescent age group.

## Keywords

anaphylaxis, epidemiology, pediatric, treatment

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## Introduction

Anaphylaxis is a serious allergic life-threatening condition.<sup>1</sup> This condition is unpredictable and has various allergic triggers. Several etiological mechanisms of anaphylaxis were described including; immunologic mechanism from Immunoglobulin E (IgE)-dependent (foods, insect stings, drugs, aeroallergens, etc.) and IgE-independent (Non-Steroidal Anti-Inflammatory Drugs), non-immunologic mechanism (direct mast cell stimulation-exercise, ethanol, opioids), and idiopathic anaphylaxis.<sup>2</sup> Anaphylaxis has several manifestations such as rashes (typically urticaria),<sup>3</sup> angioedema, respiratory symptoms (wheezing, shortness of breath), gastrointestinal symptoms (abdominal pain, diarrhea), and cardiovascular symptoms (hypotension, tachycardia, syncope). Even though there are many faces of its presentation, diagnosis of anaphylaxis can be made by the consensus clinical criterions.<sup>2-5</sup> However, in an emergency context with a limitation of patient history taking to find out the causative triggering

allergens, some anaphylaxis cases were misdiagnosed.<sup>6</sup> This can cause morbidity and mortality consequences since this condition needs an immediate specific treatment.<sup>5,7-11</sup> Anaphylaxis in children has various allergic triggers. The European Anaphylaxis Registry confirmed food as the major elicitor of anaphylaxis in children, specifically hen's egg, cow's milk and nuts.<sup>12</sup> However, the study of anaphylaxis in different geographic areas may have different characteristic and raises the need of awareness to improve prevention and

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**Table 1.** Incidence of Pediatric Anaphylaxis During 2016 to 2019 in the Study Population.

Year	Pediatric emergency visits (N)	Pediatric anaphylaxis (n)	Incidence/1000person-year	95% CI
2016	10689	11	1.03	5.10-1.84
2017	9688	16	1.65	9.40-2.68
2018	9983	32	3.21	2.19-4.52
2019	10323	17	1.65	9.60-2.64

medical care. This became the objective of our study to determine the incidences, causes, characteristics, treatments and outcomes of anaphylaxis in pediatric population in an emergency context of a tertiary care university hospital in Thailand.

## Material and Methods

### Data Collection

Retrospective data from the official electronic medical record (Health Object<sup>®</sup> program) used for statistical analysis. All diagnosed anaphylaxis patients at the Emergency Department, tertiary care pediatric referral center, Faculty of Medicine, Khon Kaen University, Thailand, between January 2016 and December 2019 were included in the study. Diagnosis of anaphylaxis based on recorded diagnosis from ICD-10 and confirmed meeting criteria of anaphylaxis evaluated by certified pediatricians.

### Statistical Methods

At the end of the study, the collected data were analyzed using STATA software version 10 (StataCorp LP). Descriptive statistical methods-means, standard deviations (SDs), medians, and frequencies-were used to analyze the demographic data. Values of  $P < .05$  are considered to indicate statistical significance. Multinomial logistic regression and post hoc analysis used to test for the association between etiologic factors of anaphylaxis.

**Ethical Approval and Informed Consent.** The study was approved by the institutional review board of Faculty of Medicine, Khon Kaen University, Thailand (IRB no. #HE631544) before enrolling any participants.

## Results

There were 76 anaphylaxis pediatric patients in total at the Emergency Department during the study period. The incidence ranged 1.03 to 3.21/1000-person-year. Table 1 showed incidence of pediatric anaphylaxis during 2016 to 2019 in the study population. The age ranged from

5 months to 18 years old. The median age was 14.54 years, IQR 12.04 to 16.83. The mean age was 13.72, SD 3.88. There were 49 (64.47%) boys and 27 (35.53%) girls. Making male to female ratio was 1.8: 1.

The authors classified patients into 4 different age groups as follows; (i) Infant (<1 year old), (ii) Pre-school age (1-6 years old), (iii) School age (7-12 years old), and (iv) Adolescent (13-18 years old). The most prevalent age group of anaphylaxis patients in the study population was found in adolescent group (52 cases, 68.42%), followed by school age group (19 cases, 25%), pre-school age group (3 cases, 3.95%), and infantile age group (2 cases, 2.63%).

Causes of anaphylaxis identified. Anaphylaxis from food was recorded as the most frequent cause in the present pediatric population (28 cases, 36.8%), followed by idiopathic anaphylaxis, insect stings, drugs, infection-induced, and exercise-induced anaphylaxis. Table 2 describes demographic information of anaphylaxis cases from various different etiologies.

There were 46 cases with underlying atopic diseases. These included asthma (19 cases, 25%), atopic dermatitis (9 cases, 11.84%), allergic rhinitis (8 cases, 10.53%), and known food allergy (10 cases, 13.16%). History of known food allergy significantly correlated to the causes of anaphylaxis from food in the study population,  $P$ -Value .029, Table 2.

Presenting symptoms of anaphylaxis patients in the study population included urticaria, angioedema, respiratory symptoms, gastrointestinal symptoms, and cardiovascular symptoms. Majority of cases (75 cases, 98.68%) had urticaria. Sixty-seven cases (88.16%) had respiratory symptoms, mostly with the presentation of wheezing, dyspnea, and chest discomfort symptoms. Twenty-four cases (31.58%) had angioedema. Sixteen cases (21.05%) had gastrointestinal symptoms such as abdominal pain, abdominal cramp, and diarrhea. Seven cases (9.21%) had cardiovascular symptoms.

All patients received intramuscular adrenaline as an emergency treatment of anaphylaxis. Seventy-four cases (97.37%) had this treatment at the emergency room. Only 2 cases received the treatment after the hospital admissions. There were 3 cases (3.94%) of biphasic anaphylaxis whom received second doses of intramuscular adrenaline.

**Table 2.** Demographic Information of Anaphylaxis Cases from Different Etiologies.

Variable	Total (n=76)	Cause of anaphylaxis						P-value
		Idiopathic (n=24)	Infection (n=1)	Foods (n=28)	Insect stings (n=11)	Exercise (n=1)	Drugs (n=11)	
<b>Gender</b>								
Male	49 (64.47)	15 (62.5)	1 (100)	20 (71.43)	9 (81.82)	1 (100)	3 (27.27)	.080
Female	27 (35.53)	9 (37.5)	0 (0)	8 (28.57)	2 (18.18)	0 (0)	8 (72.73)	
<b>Age (years)</b>								
Mean ± SD	13.72 (3.88)	15.46 (2.21)	8.17	12.68 (4.77)	13.51 (3.46)	14.08	13.24 (3.79)	
<b>Age</b>								
≤1 year	2 (2.63)	0 (0)	0 (0)	2 (7.14)	0 (0)	0 (0)	0 (0)	.737
1-6 years	3 (3.95)	0 (0)	0 (0)	1 (3.57)	1 (9.09)	0 (0)	1 (9.09)	
7-12 years	19 (25)	4 (16.67)	1 (100)	8 (28.57)	3 (27.27)	0 (0)	3 (27.27)	
13-18 years	52 (68.42)	20 (83.33)	0 (0)	17 (60.71)	7 (63.64)	1 (100)	7 (63.64)	
<b>Underlying disease</b>								
Known food allergy	10 (13.16)	0 (0)	1 (100)	6 (21.43)	1 (9.09)	0 (0)	2 (18.18)	.029*
Atopic dermatitis	9 (11.84)	3 (12.5)	0 (0)	4 (14.29)	1 (9.09)	0 (0)	1 (9.09)	.988
Allergic rhinitis	8 (10.53)	2 (8.33)	1 (100)	1 (3.57)	2 (18.18)	0 (0)	2 (18.18)	.042
Asthma	19 (25)	5 (20.83)	0 (0)	9 (32.14)	0 (0)	0 (0)	5 (45.45)	.169
<b>Fever</b>								
No	69 (90.79)	21 (87.5)	0 (0)	27 (96.43)	10 (90.91)	1 (100)	10 (90.91)	.045
Yes	7 (9.21)	3 (12.5)	1 (100)	1 (3.57)	1 (9.09)	0 (0)	1 (9.09)	
<b>Length of stay (hours)</b>								
Median (Min-max)	24 (8-72)	24 (8-48)	72	24 (24-72)	24 (24-48)	24	24 (24-48)	.054
Median (IQR)	24 (24-24)	24 (24-24)	72	24 (24-48)	24 (24-24)	24	24 (24-48)	
Mean ± SD	29.89 (14.57)	24.67 (12.46)	72	34.29 (16.56)	26.18 (7.24)	24	30.55 (11.21)	
<b>Presenting symptoms</b>								
Urticarial rash	75 (98.68)	24 (100)	1 (100)	28 (100)	11 (100)	1 (100)	10 (90.91)	.307
Angioedema	24 (31.58)	4 (16.67)	0 (0)	6 (21.43)	7 (63.64)	0 (0)	7 (63.64)	.010*
Respiratory	67 (88.16)	22 (91.67)	0 (0)	23 (82.14)	10 (90.91)	1 (100)	11 (100)	.065
Gastrointestinal	16 (21.05)	3 (12.5)	1 (100)	10 (35.71)	1 (9.09)	0 (0)	1 (9.09)	.060
Cardiovascular	7 (9.21)	2 (8.33)	0 (0)	0 (0)	4 (36.36)	1 (100)	0 (0)	<.001*

\*Value of  $P < .05$  indicates statistical significance.

Various types of systemic corticosteroids used to treat anaphylaxis patients in the study population. There were intravenous dexamethasone (72.37%), intravenous hydrocortisone (40.79%), and oral prednisolone (56.58%). Antihistamines were put-to-use in the present population. H1-blockers (chlorpheniramine, ceterizine) prescribed in most of the patients. H2-blocker (ranitidine) was prescribed in 77 cases (88.16%).

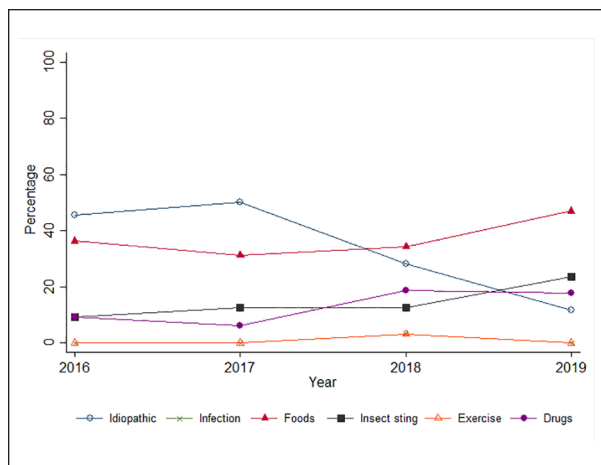
The outcome of anaphylaxis in pediatric population in the present study was good. The mean length of hospital stay was 29.89 hours (SD=14.57). There was no mortality case recorded in the present study population.

## Discussion

The average lifetime prevalence of anaphylaxis is estimated at 0.05% to 2% in the USA and ~3% in Europe.<sup>13</sup> However, the pooled community-based prevalence of

anaphylaxis in the general Asian population remains unknown. In Thailand, a study in Bangkok during 2008 to 2013 revealed a prevalence of pediatric anaphylaxis at 2.7 to 4.51 cases/1000 pediatric admissions.<sup>14</sup> A recent study from the north part of Thailand showed an incidence of pediatric anaphylaxis at 3.0 to 4.9 episodes/100 000 visits during 2007 to 2016.<sup>15</sup> The present study had data that are more recently collected during 2016 to 2019. We found a higher incidence of pediatric anaphylaxis in our setting at 1.03-3.21/1000-person-year. This higher incidence in the more recent years had a correlation to the overall world data that have found an increase in incidences of anaphylaxis over the years.

Anaphylaxis is more common in adults compared to young children. Guidelines from the World Allergy Organization (WAO) have reported that teenagers, pregnant women, and elderly are at higher risk for anaphylaxis due to various reasons.<sup>15,16</sup> The present study



**Figure 1.** Yearly percentage of anaphylaxis with the different etiologies.

revealed a similar pattern that the rate of anaphylaxis increased with age. The highest prevalence found in pediatric population was in adolescent group (68.42%), however, the present data did not show a statistical difference compared to the other age groups.

The causes of anaphylaxis described and thought to vary among different age groups. Anaphylaxis from food was the most prevalent in pediatric population.<sup>10,18-20</sup> The findings correlated to the present study that found food-induced anaphylaxis as the most frequent cause. This etiology has found to increase during the following years. Figure 1 showed yearly percentage of anaphylaxis with the different etiologies.

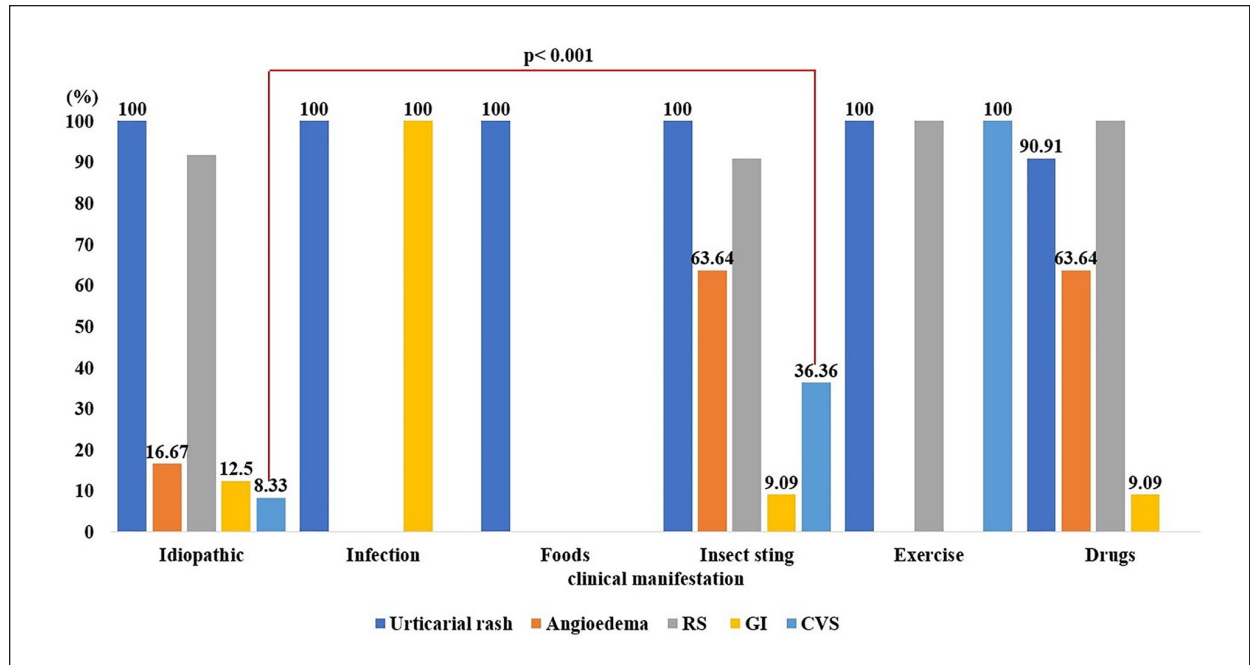
Incidence of food anaphylaxis in people with food allergy was low at all ages.<sup>21</sup> This may be because people tend to avoid contact with food that they are allergic to. However, food anaphylaxis in people with food allergy still appeared to be high in young children. This finding is correlated to the present study in pediatric population that revealed a significant difference of the food-induced anaphylaxis when patients had a known history of food allergy compared to the other causes of anaphylaxis,  $P = .029$ , Table 2. This finding strengthens supports that food-induced anaphylaxis is still a common cause of anaphylaxis in children and pediatricians should look for this trigger allergen especially in young age groups.

The present study also found that different age groups revealed different anaphylaxis etiologies. Anaphylaxis from insect stings and drugs found to be more frequent in adolescent age group. A different common cause of anaphylaxis in a different age group may help physicians to narrow down for a history taking during the emergency visit.

Urticaria was the most common presentation of anaphylaxis in the study population (98.68%), followed by respiratory symptoms (88.16%), angioedema (31.58%), gastrointestinal symptoms (21.05%), and cardiovascular symptoms (9.21%). Having cardiovascular symptoms such as hypotension and tachycardia may indicate severe anaphylaxis.<sup>22</sup> The present study revealed that cardiovascular symptoms found were more frequent in anaphylaxis from insect stings compared to other causes,  $P < .001$ , Figure 2. Anaphylaxis to insect stings has occurred in 3% of adults and can be fatal even on the first reaction.<sup>23</sup> Thus, physicians should be aware of severe anaphylaxis reaction when a history of insect sting is documented. For future prevention of sting anaphylaxis, venom immunotherapy is 75% to 98% effective.<sup>23</sup>

All patients in the study population received intramuscular adrenaline as an emergency treatment of anaphylaxis according to a standard recommendation guideline.<sup>5,7,9,16,18</sup> Seventy-four cases (97.37%) had this treatment at the emergency room. Only 2 cases received the treatment after the hospital admissions. The number of proper intramuscular adrenaline for anaphylaxis treatment at the emergency room in the study population was high compared to some other previous reports.<sup>11</sup> This is because of the present study retrospectively included patients diagnosed with anaphylaxis in a tertiary care setting. Physicians at the emergency department had proper standard guideline for anaphylaxis treatment. Moreover, in those controversial cases, physicians were able to consult on call pediatricians who were available for 24 hours at all time. However, there might have some anaphylaxis misdiagnosed, or under recorded as a limitation in a retrospective study design.

There were 3 cases (3.94%) of biphasic anaphylaxis whom received second doses of intramuscular adrenaline. All 3 cases found were in adolescent age and all cases were caused from food-induced. The prevalence of biphasic anaphylaxis in the study population was relatively low as compared to adult population. Regarding the development of biphasic reactions, symptoms, the number of systems of symptoms and severity of the initial reactions, and treatment with adrenaline and corticosteroid were not clearly related with biphasic reactions.<sup>24</sup> Biphasic anaphylaxis can occur in a variety of times after the first episode. The traditional recommended emergency department observation time is 4 to 6 hours after complete resolution of symptoms for every anaphylaxis patient.<sup>25</sup> However, 3 cases in the present study had biphasic reaction at 10, 12, 18 hours after the first episode respectively. There has been great controversy regarding whether the standard of care to observe 4 to 6 hours is evidence-based. From the present findings,



**Figure 2.** Clinical presentation of pediatric anaphylactic patients among different etiologies. Cardiovascular symptoms found were more frequent in anaphylaxis from insect stings compared to other causes,  $P < .001$ .

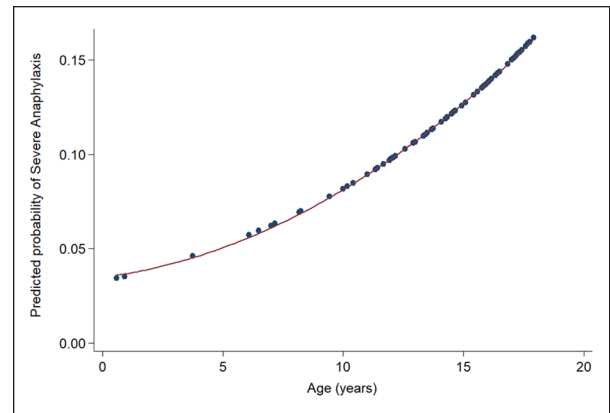
however, we recommended at least 24 hours hospital observation in order to observe biphasic reaction in pediatric anaphylaxis especially in adolescent age groups.

Having cardiovascular symptoms and/or biphasic reactions are defined as severe anaphylaxis. Previous studies revealed that some factors such as having underlying asthma was a predictor of severe presentation.<sup>22,24,25</sup> Nevertheless, the present study did not find any such association regarding patients' underlying diseases. However, from univariate analysis, the association of severe presentation found an odds ratio of 1.1 for every year increase in age. This finding showed a trend of severe presentation in older age group. Figure 3 showed predicted probability of severe anaphylaxis based on patient's age.

The overall pediatric anaphylaxis patients in the study population had favorable outcomes. All patients were hospital admitted. The mean length of hospital stay was 29.89 hours (SD 14.57). No mortality case reported in the present study.

### Limitations

The main limitation of this study was a retrospective study design that may have caused missing of some unrecorded data. One third of the study population (31.57%) documented were idiopathic anaphylaxis in which some of them might have unrecorded specific etiologies. Even



**Figure 3.** Predicted probability of severe anaphylaxis based on patient's age, Crude OR (95% CI) 1.10 (0.88-1.38).

though some factors did not show a significant statistical information, but the present study has shown a trend that correlated to other previous studies from the other geographic regions of the world. Future prospective study with more sample size may reveal a significant information in Asian children population.

### Conclusion

The present study revealed that the prevalence of anaphylaxis increased with age and adolescent group has the

most frequent anaphylaxis events. The most common etiology found was in food-induced anaphylaxis. This etiology revealed a significant correlation with a history of known food allergy in the study population,  $P = .029$ . This finding strengthens supports that food-induced anaphylaxis is still a common cause of anaphylaxis in children and pediatricians should look for this trigger allergen especially in younger age group. Cardiovascular symptoms that indicated severe anaphylaxis found were more frequent in anaphylactic patients from insect stings,  $P < .001$ . Physician should be aware of severe anaphylaxis reactions when there is a documented history of insect sting. The overall pediatric anaphylaxis patients in the study population had favorable outcomes. Three cases of biphasic reactions documented in adolescent age group, all of them had food-induced etiology. The authors recommended at least 24 hours hospital observation in order to observe biphasic reaction in pediatric anaphylaxis especially in adolescent age groups.

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### Authors' Contribution

LT contributed to the conception and design of the study, data analysis, interpretation of findings, drafting the article, revising the article, and final approval of the version submitted. RU, PP, and DM contributed to study conception and data collection. JC contributed to data processing and data analysis, critical revision of the article, and final approval of the version submitted.

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### Availability of Data and Material

Data and material are available up on request via corresponding author, L. Techasatian.

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