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Anaphylaxis in children: Effect of age and atopic status

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Abstract

Background: Anaphylaxis is a life-threatening allergic reaction with rising incidence worldwide. Young children's limited ability to express symptoms adds unique diagnostic challenges.

Objective: To study on anaphylaxis in children, including triggers, symptoms, treatment, atopic status impact, and adrenaline injection time intervals.

Methods: In-patient medical records of children who were diagnosed with anaphylaxis during 2014-2021 were reviewed.

Results: One hundred thirty-three anaphylaxis events were identified. Food (47%) was the most common trigger, followed by drugs (31%), blood components (17%), insects (3%), and idiopathic causes (2%). Ten cases of refractory anaphylaxis, 2 cases of biphasic reactions, and 1 case of persistent anaphylaxis were found. There were no reported fatalities. The most common presentations involved the skin (94%), followed by the respiratory (73%), gastrointestinal (47%), and cardiovascular (42%) systems. In atopic patients, wheezing was more prominent than in those without atopy (p-value = 0.017). In the non-atopic patients, there was a higher incidence of cardiovascular symptoms, particularly hypotension (p-value = 0.001), compared to individuals with atopy. Children under 5 years old with mild-moderate anaphylaxis required more time to reach the hospital (147.0 vs. 45.0 minutes, p = 0.033) and to receive adrenaline injections (35.0 vs. 9.0 minutes, p-value = 0.017) than those with severe anaphylaxis.

Conclusion: Childhood anaphylaxis is prevalent. Children with mild-moderate anaphylaxis experienced delays in hospital visits and adrenaline administration. Education on allergies is needed to improve the identification and prompt response to anaphylactic reactions, especially in young children.

Key words: anaphylaxis, young, children, atopy, adrenaline

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Introduction

Anaphylaxis is a potentially fatal systemic allergic reaction. The widely used diagnostic criteria are based on the 2006 National Institute of Allergy and Infectious Diseases (NIAID) guidelines.[1] Furthermore, there has been standardization in defining the clinical courses of anaphylaxis, including persistent, biphasic, and refractory anaphylaxis.[2]

The incidence of anaphylaxis in the pediatric population has increased worldwide.[3-8] In Asia, its incidence of anaphylaxis in children is less frequent compared to Western countries. A study in Hongkong reported an incidence of 6.63 per 100,000 person-years,[4] while a study in US reported an incidence of 24.9 per 100,000 person-years.[9] A Swedish study based on parent-reported questionnaires demonstrated the highest incidence at 761 per 100,000 person-years.[10]

However, studies from Western countries have revealed that among patients with anaphylaxis, Asian children constitute the majority and are more likely to experience severe reactions.[11-13] A study based on the Korean national database from 2008 to 2014 found a continuous increase in Asian pediatric anaphylaxis, rising from 6 to 21.26 episodes per 100,000 person-year.[5] Another study conducted in a tertiary hospital from 2004 to 2013 showed an increasing trend in anaphylaxis rates throughout the study period, from 2.67 to 4.51 cases per 1,000 pediatric admissions.[3]

Regarding anaphylaxis severity, previous studies have demonstrated that patients with asthma or atopy are more likely to develop severe anaphylactic symptoms.[14,15] However, due to differences in study designs, comprehensive data representing the Asian pediatric population in terms of incidence, triggers, and clinical course cannot be conclusively determined.[16]

Transitioning to the critical topic of treatment, it's important to highlight that adrenaline administration is the first-line medication in the treatment of anaphylaxis. Delayed administration of adrenaline can lead to more complications, severe reactions, and even death.[17] Additionally, anaphylaxis in young children presents unique challenges as they may have difficulty expressing their symptoms and recognizing them, making diagnosis challenging.[15]

Building on these considerations, our study has two primary objectives. First, we aim to investigate various aspects of anaphylaxis in children, including triggers, symptoms, treatment, and clinical courses of this condition. Second, we intend to examine whether atopic status influences clinical outcomes. Additionally, we would assess the timing of adrenaline injection in children experiencing anaphylaxis. By exploring these interconnected aspects, we aim to gain a comprehensive understanding of anaphylaxis in the pediatric population, which would help future treatment approaches.

Method

Patients

We conducted a retrospective study in the Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol university, Bangkok, Thailand. The study was reviewed and approved by the human rights and Ethics Committee of the Faculty of Medicine Ramathibodi Hospital, Mahidol University (ID MURA2021/224).

The in-patient Electronic Medical Records (EMR) of patients aged 18 years and under, from January 1, 2014, to December 31, 2021, coded with the following ICD-10: T780 anaphylactic reaction to food, T781 adverse reaction to food not else classified, T782 anaphylactic shock, unspecified, T783 angioneurotic edema, T784 allergy, unspecified, T789 adverse effect, unspecified, T805 anaphylactic reaction to serum, T809 unspecified complication following infusion, transfusion, and therapeutic injection, and T886 anaphylactic shock due to drug, were reviewed. Only events that met the 2006 NIAID diagnostic criteria1 were included in the study, while referred patients with a diagnosis of anaphylaxis from other hospitals were excluded, as managing patient information for referred cases presented challenges. Clinical criteria based on recently developed consensus definitions[2] were used to classify anaphylaxis into persistent, refractory, and biphasic types. In brief, persistent anaphylaxis occurs when symptoms meet the 2006 NIAID anaphylaxis criteria and last for at least 4 hours. Refractory anaphylaxis is when anaphylaxis persists despite treatment and initially requires 3 or more doses of epinephrine or intravenous epinephrine infusion. Biphasic anaphylaxis is likely when specific criteria are met: new symptoms match the 2006 NIAID anaphylaxis criteria, initial symptoms fully resolve before new ones appear, with no allergen reexposure, and this happens within 1 to 48 hours of initial symptom resolution.

Collected data

The collected data included baseline demographics, comorbidities, triggers, clinical courses (biphasic, persistent, and refractory anaphylaxis), treatment, and outcomes. The timing of anaphylaxis symptom onset, hospital arrival, and adrenaline injection was based on statements recorded in EMRs. The time intervals for hospital visits were defined as the duration from the onset of anaphylaxis to the arrival at the hospital, while the time intervals for adrenaline injection were defined as the duration from hospital arrival to the administration of adrenaline. Atopic patients were defined as individuals diagnosed with asthma, allergic rhinitis, or atopic dermatitis by a physician.

Severity grading

Anaphylaxis events were stratified using the grading system for generalized hypersensitivity reactions[18] into mild-moderate and severe reactions. Severe anaphylaxis was classified if at least one of the following conditions was present: cyanosis (SpO_2 ≤ 92%), hypotension, confusion, collapse, loss of consciousness, or incontinence. Mild-moderate anaphylaxis included skin, respiratory, cardiovascular or gastrointestinal involvement such as urticaria, dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness.

Statistical analysis

We performed all analyses using STATA statistical software version 17.0 (StataCorp, College Station, TX, USA). Comparisons of discrete variables across different groups were assessed using the chi-square test or Fisher's exact test. The Mann-Whitney U test was used for continuous nonparametric variables within each sub-grouped. A p-value of less than 0.05 was considered statistically significant.

Results

Anaphylaxis events' characteristics

A total of 222 in-patient EMRs were coded using the above ICD-10 codes. Three EMRs that belonged to referred patients and 87 charts that did not meet the criteria for anaphylaxis were excluded. We identified 133 anaphylaxis events, involving 125 individuals. Of these events, 78 (59%) occurred in males, with a median age of 8.8 years (interquartile range 4.1-13.0). The community setting was the location for 74 (56%) anaphylactic events. Notably, 10 cases of refractory anaphylaxis were found among those with severe anaphylaxis, while none were observed in cases of mild-moderate anaphylaxis. Additionally, among patients with mild-moderate anaphylactic events, two cases of biphasic anaphylaxis and one case of persistent anaphylaxis were identified, as shown in **Table 1**. We did not find any associations between severe anaphylaxis and age, sex, or onset location.

In terms of rising serum tryptase levels, the proportion of events with a significant increase in tryptase did not differ significantly between the severe and mild-moderate groups. The primary treatment for anaphylaxis was adrenaline injections (98%). Alongside adrenaline, anti-H1 antihistamines were given in 98% of the events during anaphylaxis episodes, followed by corticosteroids (95%).

Trends of anaphylaxis

The occurrence of anaphylaxis exhibited variation annually from 2014 to 2021, as depicted in **Figure 1**. The rates per 1000 pediatric hospitalized patients were as follows: 2.01, 1.03, 2.59, 1.28, 1.34, 1.43, 1.62, and 1.15, respectively. When examining the data in 4-year intervals, it showed that anaphylaxis rates experienced a downward trend over the course of this study. Specifically, the rates decreased from 1.73 to 1.39 per 1000 pediatric hospitalizations during the periods of 2014-2017 and 2018-2021.

Table1. Anaphylaxis events' characteristics.

	Total (n = 133)	Mild-moderate anaphylaxis (n = 90)	Severe anaphylaxis (n = 43)	*P* value*
Male, n (%)	78 (59)	57 (63)	21 (49)	0.112
Age, years, median (IQR)	8.8 (4.1, 13.0)	7.9 (4.0, 12.8)	11.5 (5.2, 13.5)	0.081
Location of anaphylaxis onset				
Hospital, n (%)	59 (44)	36 (40)	23 (53)	0.190
Community, n (%)	74 (56)	54 (60)	20 (47)	
Clinical courses				
Refractory anaphylaxis, n (%)	10 (8)	0 (0)	10 (23)	< 0.001**
Biphasic anaphylaxis, n (%)	2 (2)	2 (2)	0 (0)	1.000
Persistent anaphylaxis, n (%)	1 (1)	1 (1)	0 (0)	1.000
Significant rising tryptase level, n (%) ***	26 (20)	12 (52)	14 (58)	0.671
Treatment				
Adrenaline, n (%)	130 (98)	89 (99)	41 (95)	0.240
Salbutamol nebulization, n (%)	72 (54)	54 (60)	18 (42)	0.063
Anti-H1 antihistamine, n (%)	131 (98)	90 (100)	41 (95)	0.100
Anti-H2 antihistamine, n (%)	82 (62)	53 (59)	29 (67)	0.450
Corticosteroid, n (%)	126 (95)	83 (92)	43 (100)	0.096

*Comparison between mild-moderate and severe anaphylaxis
**Statistically significant
***Level exceeded 2 ng/mL + 1.2 × (baseline tryptase level), % from 47 events

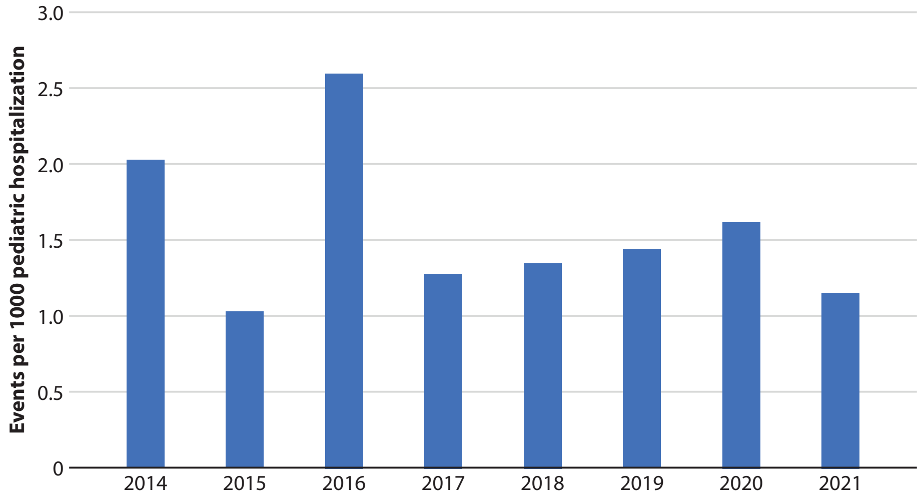

Figure 1. Episode number of anaphylaxis during 2014-2021.

Table 2. Culprit allergens.

Culprit allergen	Events (%) n = 133
Food	63 (47)
Shellfish	20 (15)
Wheat	20 (15)
Mite	5 (4)
Egg	4 (3)
Cow milk	4 (3)
Fish	2 (2)
Other*	10 (8)
Drug	41 (31)
Chemotherapy	14 (11)
Antibiotics	8 (6)
Immunotherapy	7 (5)
Contrast media	3 (2)
Biologic agents	3 (2)
Other**	6 (5)
Blood components	23 (17)
Platelet	15 (11)
Cryo-removed plasma	4 (3)
Packed red cell	2 (2)
Fresh frozen plasma	2 (2)
Insect	4 (3)
Vespidae	2 (2)
Idiopathic	2 (2)

*Other food allergens included food additives, fried insect, mushroom, unspecified food
**Other drug allergens included paracetamol, codeine, vitamin K, drug additives, propofol, omeprazole, unspecified drug

Allergens

The triggers for the 133 anaphylaxis events are presented in **Table 2**. Among the cases, food was identified as the most common causative agent, accounting for 47% of the events. This was followed by drug-induced anaphylaxis at 31%, blood components at 17%, insect triggers at 3%, and cases where the allergen was unknown at 2%.

Within the food-induced anaphylaxis category, shellfish and wheat were the top two allergens, each accounting for 15% of the events. In drug-induced anaphylaxis, chemotherapy was identified as the leading cause, responsible for 11% of the cases, followed by antibiotics at 6%. Platelet transfusions were found to be the primary blood component triggering anaphylaxis, accounting for 11% of the cases.

Clinical manifestations

The clinical manifestations of anaphylaxis are presented in **Table 3**. Cutaneous symptoms were the most frequently observed (94%), followed by symptoms affecting the respiratory system (73%), gastrointestinal system (47%), cardiovascular system (42%), and central nervous system (6%). Among the cases, 44 events (33%) were classified as severe anaphylaxis. Throughout the study, 10 refractory anaphylaxis, 2 biphasic anaphylaxis, and 1 persistent anaphylaxis events were observed. Fortunately, there were no reported fatalities among the patients experiencing anaphylactic events.

Comparison of clinical features regarding the atopic status

The presence of atopy significantly influenced the occurrence of wheezing. Children who had atopy experienced more prominent wheezing compared to those without atopy (p-value = 0.017). In the non-atopic group, there was a higher incidence of cardiovascular symptoms, particularly hypotension (p-value = 0.001), compared to individuals with atopy, as shown in **Table 3**. Furthermore, children without atopy had a higher frequency of severe anaphylaxis (p-value = 0.007) and refractory anaphylaxis (p-value = 0.030) compared to those with atopy.

Table 3. Anaphylaxis clinical manifestations and clinical courses regarding atopic status.

	Atopy (n = 42)	Non-atopy (n = 91)	*P* value*
Clinical manifestations, n (%)			
Cutaneous system	42 (100)	83 (90)	0.057
- Urticaria	29 (69)	64 (70)	0.881
- Angioedema	15 (36)	31 (34)	0.853
Respiratory system	35 (83)	62 (67)	0.056
- Wheezing	22 (52)	28 (31)	0.017*
- Chest tightness	13 (31)	23 (25)	0.493
Gastrointestinal system	20 (48)	42 (46)	0.830
- Vomiting	10 (24)	30 (33)	0.284
- Diarrhea	4 (10)	8 (9)	0.891
Cardiovascular system	9 (21)	47 (51)	0.001*
- Hypotension	2 (5)	30 (33)	< 0.001*
- Tachycardia	7 (17)	24 (27)	0.218
Clinical course			
Severe anaphylaxis	7 (17)	37 (40)	0.007*
Refractory anaphylaxis	0 (0)	10 (11)	0.030*
Biphasic anaphylaxis	1 (2)	1 (1)	0.530
Persistent anaphylaxis	0 (0)	1 (1)	1.000

*Statistically significant

Time Intervals for Hospital Visit and Adrenaline Administration: Impact of Age

We conducted an investigation involving children under 5 years of age, regardless of anaphylaxis severity, and found that there was a tendency for them to take a longer time to reach the hospital compared to those aged 5 years and above (146.0 vs. 21.0 minutes, *p*-value = 0.839). However, there was a similar duration of adrenaline injection between the two groups (21.0 vs. 20.0 minutes, *p*-value = 0.529).

To further analyze the data, we classified the children into two groups based on anaphylaxis severity: mild-moderate and severe anaphylaxis. Among children under 5 years of age (n = 25) with mild-moderate anaphylaxis, it was observed that they significantly required a longer time to reach the hospital compared to those with severe anaphylaxis (147.0 vs. 45.0 minutes, *p*-value = 0.033) (**Table 4**). A similar pattern was observed when focusing on children under 2 years of age (n = 19) with mild-moderate anaphylaxis, taking 65 minutes to reach the hospital compared to 45 minutes for severe anaphylaxis (*p*-value = 0.043).

Furthermore, we found a longer duration of adrenaline injection in the mild-moderate anaphylaxis group compared to those with severe anaphylaxis. For children under 5 years old, the duration of adrenaline injection was 35.0 minutes for mild-moderate anaphylaxis and 9.0 minutes for severe anaphylaxis (*p*-value = 0.017) (**Table 4**). In the subgroup of children under 2 years old, the duration was 38.5 minutes for mild-moderate anaphylaxis and 9.0 minutes for severe anaphylaxis (*p*-value = 0.055).

Table 4. Time Intervals for Hospital Visit and Adrenaline Administration.

Age	Onset to hospital visit, minutes, median (IQR)		*p* value	Hospital visit to adrenaline, minutes, median (IQR)		*p* value
	Mild-moderate Anaphylaxis	Severe Anaphylaxis		Mild-moderate Anaphylaxis	Severe Anaphylaxis	
Age < 5 years old n = 25	147.0 (60.0, 180.0)	45.0 (22.5, 61.0)	0.033*	35.0 (14.0, 53.0)	9.0 (4.0, 11.0)	0.017*
Age ≥ 5 years old n = 49	115.0 (60.0, 180.0)	57.5 (30.0, 150.0)	0.510	23.5 (10.5, 35.5)	4.5 (2.5, 17.5)	0.013*

* Statistically significant
IQR, interquartile range

Discussion

During the period from 2014 to 2021, a total of 133 anaphylaxis events occurred. Non-atopic patients had more cardiovascular symptoms and anaphylactic shock than atopic patients, while atopic patients had more wheezing. Children with mild-moderate anaphylaxis, especially less than 5 years old, experience longer delays in hospital visits and adrenaline administration compared to severe cases.

Compared to the previously published study,[3] our investigation indicates a seemingly reduced frequency of pediatric anaphylaxis. In the earlier study, 172 anaphylaxis cases were observed, with rates of 2.64 and 4.51 per 1000 hospitalized children during the periods 2004-2008 and 2009-2013, respectively.[3] However, in this study encompassing the years 2014-2021, we identified 133 anaphylaxis events, corresponding to a rate of 1.78 per 1000 hospitalized patients. Notably, our study reveals a declining trend in anaphylaxis incidence among pediatric hospitalizations over time, with rates decreasing from 1.73 per 1000 hospitalizations during 2014-2017 to 1.39 per 1000 hospitalizations during 2018-2021. Similarly, a study from Northeast Thailand during 2016-2019 showed an increase in pediatric anaphylaxis emergency department visits from 1.03 to 3.01 per 1000-person-year in the first 3 years, but it decreased to 1.65 per 1000-person-year in 2019.[19] It is worth considering that the observed decrease in anaphylaxis cases during 2018-2021 might be partially attributed to the COVID-19 pandemic. Furthermore, there has been a notable decrease in anaphylaxis cases among Canadian children during the COVID-19 pandemic.[20] Specifically, the total number of anaphylaxis cases has significantly dropped by 24 cases per month ($p < 0.05$).[20] As a result of pandemic-related measures, parents and children tend to spend more time at home and adhere to quarantine guidelines. Consequently, the reduced chance of exposure to allergens and social gatherings during this period could have contributed to the decline in anaphylactic events among pediatric patients.

Atopic patients with anaphylaxis experienced more wheezing symptoms compared to those without atopy. Our finding aligns with a study conducted in Hongkong, which also showed that anaphylaxis patients with asthma and atopic dermatitis usually presented with wheezing.[21] Furthermore, a study from Sweden reported that anaphylaxis children with asthma exhibited symptoms in the lower respiratory tract twice as often as those without asthma.[22] Interestingly, we observed that anaphylaxis patients without atopy showed a higher incidence of cardiovascular manifestations compared to those with atopy. The reason behind this discrepancy remains unknown. One possible explanation could be related to a lack of awareness regarding early allergic symptoms. Further research is needed to fully understand the factors contributing to these differences.

Regarding allergens in food-induced anaphylaxis, shellfish emerged as the primary allergen, consistent with a previous study by Manuyakorn et al.[3] However, there has been a recent increase in wheat-induced anaphylaxis compared to the earlier studies.[3,23] In Northeast Thailand, shellfish accounted for the majority of food triggers (62%), followed by fried insects (10%).[24] However, in the Northern part of Thailand, the ranking differed, with shellfish still at the top (57.3%), followed by fish (5.4%), ant eggs (2.7%), fried insects (2.7%), and wheat (1.35%).[25] This variation in food allergen ranking can be attributed to distinct cultural contexts and food consumption habits in different regions.

In drug-induced anaphylaxis, chemotherapy was the most common trigger, consistent with a multicenter study from 3 tertiary hospitals in Hongkong.[8] But, the global trend indicates a higher occurrence of drug induced anaphylaxis due to antibiotics.[26] As our institute is a tertiary referral hospital, with many patients having underlying diseases such as malignancy, this might explain the difference in causative drug allergen rankings.

Regarding serum tryptase levels, no difference was found in the proportion of cases with rising tryptase level between different anaphylaxis severities. This differs from a former study by De Schryver et al. which reported that tryptase levels during severe anaphylactic reactions exceeded a previously published threshold in 50% cases, but only in 16.2% cases of mild or moderate anaphylaxis cases.[27] One possible explanation for this disparity could be the low number of tryptase level workups in our study (35% of all anaphylactic events).

Young children, especially those with mild-moderate anaphylaxis, were taken to medical personnel later compared to those with severe anaphylaxis. They also had a longer time until adrenaline injection. A study conducted in Korean young children aged less than 2 years old found that epinephrine administration was significantly delayed by more than 60 minutes from symptom onset.[28] A potential explanation is that younger children are less able to describe their symptoms, making the allergic presentation obscure and challenging to detect in smaller children.[29] This information is important in raising public awareness about anaphylaxis reactions and their treatment, especially in caregivers of young children with mild-moderate anaphylaxis.

Our study has some limitations due to its retrospective design, which involved reviewing electronic medical records. This approach might have led to potential inaccuracies in diagnostic coding and missing data. Moreover, we need to be aware of potential referral bias, as our institute is a tertiary hospital specializing in patients with underlying conditions, especially those with malignancies and organ transplants.

In conclusion, this study reveals important insights into pediatric anaphylaxis. Atopy influences clinical presentation and age impacts hospital visit and adrenaline administration intervals. Education on allergies for caregivers is needed in enhancing the identification and prompt response to anaphylactic reactions.

Conflict of interest

The authors declared no conflicts of interest.

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