Pediatric anaphylaxis: triggers, clinical features, and treatment in a tertiary-care hospital

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Summary

Background: **Anaphylaxis is a life-threatening condition. There are limited data about its etiology and clinical characteristics in Asian children with anaphylaxis.**

Objective: **To investigate triggers, presenting symptoms, treatment and clinical course of anaphylaxis in Thai children.**

Method: **Medical record of children who were diagnosed with anaphylaxis between 2004 and 2013 at Ramathibodi Hospital, Bangkok, Thailand were reviewed.**

Results: **One hundred-seventy two episodes of anaphylaxis occurred in 160 children (91 boys, 69 girls) aged 3 months to 18 years. Anaphylaxis increased from 2.7 cases/1000 pediatric admission to 4.51 cases/1000 pediatric admission between 2004-2008 and 2009-2013. The main causes were food (34.92%), drug (33.1%), blood components (23.8%), insect sting (9%), and unidentified causes (2.8%). Allergy to the triggers was known prior to anaphylaxis in 42 episodes (24.6%). Treatment consisted of epinephrine intramuscularly (93.8%), corticosteroids (92.5%), H_1 antihistamines (96%), H_2 antihistamines (50%), and β_2 agonists nebulization (35.1%). Biphasic anaphylaxis occurred in 8.7% of the documented episodes and severe anaphylaxis in 34.3% of the documented episodes. Biphasic anaphylaxis and severe anaphylaxis were associated with fewer administrations of intramuscular epinephrine (OR 0.08 [95%CI0.014-0.43]; *p* =0.01and OR 9.36 [95%CI2.5-34.7]; *p* <0.001 respectively). There were no fatality cases. There were associations between triggers of anaphylaxis and atopic histories, patients with severe anaphylaxis and cardiovascular involvement (*p* <0.01).**

Conclusions: **The incidence of anaphylaxis in Thai children is increasing. Anaphylaxis in children commonly occurred without the histories of prior reaction to the causative agent. Less frequent treatment with intramuscular epinephrine was associated with biphasic and severe anaphylaxis. A better knowledge of patterns and causes of anaphylaxis might contribute to a better management. *(Asian Pac J Allergy Immunol 2015;33:281-8)***

Keywords: *anaphylaxis, biphasic anaphylaxis, blood component allergy, children, drug allergy, epidemiology, food allergy*

Introduction

Anaphylaxis is an acute severe systemic hypersensitivity reaction with symptoms of an immediate allergic reaction and is potentially life threatening.[1] There are several studies on the clinical features, cause of anaphylaxis and management of anaphylaxis in adult or general population.[2-8] However, it was shown that triggers of anaphylaxis in children and adult were different. Food has been reported as the leading trigger of pediatric anaphylaxis[6,9-13] while drug is the major cause of anaphylaxis in several adult or general population studies.[2,3,5] In addition, studies on pediatric anaphylaxis are mostly carried out in Western countries such as the United States, European countries and Australia.[6,9,11-13] Due to the differences in culture and life styles, findings from the previous studies may not be applicable to children from South East Asian countries. The purpose of the present study was thus to evaluate triggers, clinical course and treatment of anaphylaxis in children

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Submitted date: 29/12/2014
Accepted date: 2/3/2015

hospitalized in a major tertiary care hospital in Thailand.

Methods

A retrospective medical chart review was performed including all pediatric patients who were admitted to Ramathibodi Hospital, Mahidol University, Bangkok, Thailand between January 1, 2004 and December 30, 2013 using the ICD-10 code system. The ICD-10 codes used to search for the medical records were as follow: T78.0, anaphylactic shock due to adverse food reaction; T78.1, adverse reaction to food not else classified; T78.2, anaphylactic shock, unspecified; T78.3, angioneurotic edema, laryngeal edema, Quincke edema, urticaria-larynx; T78.4, Allergy, unspecified; T 78.9, Adverse effect, unspecified; T80.5, anaphylactic shock due to serum; T80.9, unspecified complication following infusion, transfusion and therapeutic injection; T88.6, anaphylactic shock due to adverse effect of correct drug of medicament properly administered. Patients who fulfilled 1 of the 3 diagnostic criteria published in 2006 by the National lnstitute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) were diagnosed as having anaphylaxis.[14] Data were collected using a standard questionnaire including (1) demographic data; (2) atopic status of the child; (3) cause of anaphylaxis; (4) previous allergic reactions from the same triggers; (5) the symptoms of anaphylactic event; (6) severity of anaphylaxis using grading system for generalized hypersensitivity reactions[15]; (7) biphasic reaction as defined by the occurrence of symptoms after complete resolution of the primary reaction;[16] (8) the level of serum tryptase; (9) location; (10) the treatment; (11) outcome; (12) epinephrine auto-injector or prefilled epinephrine prescription. The study was reviewed and approved by the human rights and ethic committee of Faculty of medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

Statistical analysis

All analyses were performed using SPSS statistical software version 18.0 (SPSS Inc., Chicago, IL, USA). A descriptive analysis was used for the characterization of the study population. Results were expressed as the mean ± SD (age) or percentages (gender, atopic status, symptoms of anaphylaxis, severity of anaphylaxis, presence of biphasic course, settings of anaphylaxis, cause of anaphylaxis, treatment of anaphylaxis). To compare different groups, t-test, one way ANOVA, Kruskal-Wallis test, chi-squared test or Fisher's exact test were used as appropriate. A p-value of < 0.05 was considered to be statistically significant.

Results

During the study period, a total of 172 episodes occurred in 160 children predominantly male (56.9%). The minimum age was 3 months and the maximum age was 18 years with a mean age of 8.66 years. Seventy two percent of the children had histories of allergic diseases. Half of anaphylaxis episodes occurred in community settings. Previous allergic reactions from the same triggers of anaphylaxis were known only in 24.6% of the patients. Baseline characteristics are provided in table 1.

Clinical characteristics of anaphylaxis reactions

The clinical manifestations during anaphylaxis in order of frequency were cutaneous (n = 161, 91%), followed by respiratory (n = 140, 79.1%), cardiovascular (n = 66, 37.3%), gastrointestinal (n = 52, 29.4%), and neurological (n = 3, 1.7%). There was no fatality case. H1 antihistamine (96%) was the most common drug administered during anaphylaxis episodes, followed by epinephrine intramuscularly (93.8%), systemic corticosteroids (91%), H2 antihistamine (49.2%), and salbutamol nebulization (34.5%) (Table 1). However, epinephrine prefilled syringe or epinephrine auto-injector was prescribed only in 72 cases (40.2%) after discharged from the hospital.

Incidence, triggers and management of anaphylaxis between 2004-2008 and 2009-2013

There was an increase in the incidence of anaphylaxis in our pediatric patients from 2.67 cases per 1,000 pediatric admissions to 4.51 cases per 1,000 pediatric admissions between 2004-2008 and 2009-2013. There was a significant increase in anaphylaxis from foods, drugs, blood components and insects ($p < 0.05$) (Figure 1). However, we did not observe any significant difference in age, gender, settings of anaphylaxis episodes, histories of allergic disease, treatment received and epinephrine prefilled syringe prescribed between these two periods.

Predictor of biphasic anaphylaxis and severe anaphylaxis

Biphasic anaphylaxis occurred in 15 patients (8.5%). Patients with biphasic tended to be younger than those with uniphasic anaphylaxis (6.47 ± 4.65 years vs 8.87 ± 4.59 years, $p = 0.055$). There was no

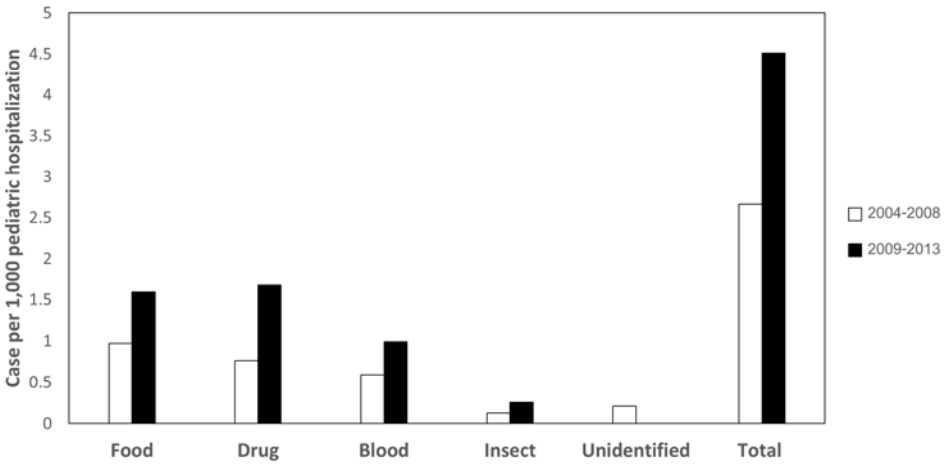
Table 1. Characteristics of all episodes of anaphylaxis reactions

	Overall n =172	Biphasic n =15	Uniphasic n =157	*P* *value
Age, years mean (SD)	8.66 (4.63)	6.47 (4.65)	8.87 (4.59)	0.055
Female sex, n (%)	74 (43)	5 (33.3)	69 (43.9)	0.58
History of allergic disease n (%)	123 (71.5)	9 (60)	114 (72.6)	0.36
Previous allergic reaction to the same triggers n (%)	42 (24.6)	0	42 (26.9)	0.02
Location n (%)				
Community	90 (52.3)	3 (20)	87 (55.4)	0.013
Hospital	82 (47.7)	12 (80)	70 (44.6)	
Triggers n (%)				
Foods	60 (34.9)	2 (13.3)	58 (36.9)	0.09
Drugs	57 (33.1)	10 (66.7)	47 (29.9)	
Blood components	41 (23.8)	3 (20)	38 (24.2)	
Insect	9 (5.2)	0	9 (5.7)	
Unknown	5 (2.9)	0	5 (3.2)	
Serum tryptase ng/mL median (min,max)	3.23 (0-72)	3.72 (1.48-35)	3.72 (0-72)	0.98
Clinical manifestations n (%)				
Cutaneous system	161 (91)	13 (86.7)	144 (91.7)	0.62
Respiratory system	140 (79.1)	11 (73.3)	124 (79)	0.74
Cardiovascular system	66 (37.3)	8 (53.3)	56 (35.7)	0.26
Gastroinstestinal system	52 (29.4)	4 (26.7)	48 (30.6)	1
Neurological system	3 (1.7)	0	3 (1.9)	1
Severe anaphylaxis n (%)	62 (35)	12 (80)	47 (29.5)	<0.001
Therapy n (%)				
Adrenalin IM	166 (93.8)	12 (80)	152 (98.1)	0.01
Antihistamine H1	170 (96)	15 (100)	150 (96.8)	0.62
Antihistamine H2	87 (49.2)	10 (68.7)	76 (49)	0.41
Systemic corticosteroids	161 (91)	14 (93.3)	142 (92.3)	0.62
Salbutamol nebulization	61 (34.5)	8 (53.3)	50 (32.2)	0.23

*comparison between biphasic and uniphasic anaphylaxis

significant difference in the level of serum tryptase between patients with biphasic and uniphasic episodes. Sex, histories of allergic disease, clinical manifestations of biphasic anaphylaxis compared with uniphasic anaphylaxis were similar. There were less frequent administration of intramuscular epinephrine in biphasic anaphylaxis compared to uniphasic anaphylaxis (80% vs 98%, OR 0.08 [95% CI0.014-0.43]; $p = 0.01$) and more severe anaphylaxis (80% vs 29.5%, OR 9.36 [95%CI2.5-34.7]; $p < 0.001$). All patients with biphasic episode had no history of allergic reaction to the same triggers (Table 1). Sixty two patients (35%) had severe anaphylaxis. There was no significant association between sex, age

Figure 1. Episodes number of anaphylaxis comparing between 2004-2008 and 2009-2013. The y axis represents



group, history of allergic diseases and severe anaphylaxis. Similar to what we observed for biphasic anaphylaxis, severe anaphylaxis was associated with less frequent administration of intramuscular epinephrine (91.5% vs 99.1%, OR 0.1[95%CI0.01-0.86]; p =0.005) and less frequent knowhistory of previous allergic reaction from the same triggers (11.9% vs 31.3%, OR 0.3 [95%CI0.12-0.71]; p <0.001).

Triggers of anaphylaxis reactions

Among the different causes of anaphylaxis, food was the most common trigger of anaphylaxis (34.9%), followed by drugs (33.1%), blood components (23.8%), insect bites (5.2%) and a set of non-identified triggers in 2.8% of the cases (Table 2). Among those who developed anaphylaxis from food, seafood was the most common trigger for anaphylaxis followed by wheat, hen's egg and cow's milk. Antibiotic was the most common cause of drug induced anaphylaxis, followed by chemotherapy agents, and allergen immunotherapy. Platelet transfusion was the most common cause of blood component-induced anaphylaxis, followed by packed red cell and fresh frozen plasma transfusions (Table 2).

Characteristics of anaphylaxis by triggers

There was no differences in age, sex among triggers of anaphylaxis. However, there was an association between location of anaphylaxis and triggers of anaphylaxis (p < 0.001). Almost all children with food or insect-induced anaphylaxis developed anaphylaxis in community settings. While anaphylaxis from drug or blood components were occurred more frequently in hospital. Furthermore, atopic status was associated with triggers of anaphylaxis (p = 0.001). Seventy to one hundred percent of patients who developed anaphylaxis from food, blood components and insect had atopic diseases. In contrast, only 53% of patients with drug-induced anaphylaxis had atopic diseases (Table 3). Triggers of anaphylaxis was significantly associated with the incidence of severe anaphylaxis and cardiovascular involvement (p <0.03). Approximately 15% of insect or food-induced anaphylaxis were severe anaphylaxis whereas half of drug, blood component or unidentified cause were severe anaphylaxis. Similarly, cardiovascular involvement occurred significantly less in children with food or insect string induced anaphylaxis than those from other cause of anaphylaxis. Biphasic anaphylaxis occurred in 18%, 7% and 3% of drug, blood component and food induced anaphylaxis respectively but this trend was not statistically significant (Table 3).

Discussion

Anaphylaxis is an increasingly common severe life threatening allergic reaction in children. Report from South Australia has shown that approximately 5 out of 1,000 children experience anaphylaxis episodes.[17] In Thailand, the incidence of anaphylaxis in hospitalized patients varies between 10 to 50 cases per 100,000 hospitalized patients.[2, 3] However, there are no reports focusing on the incidence of pediatric anaphylaxis in Thailand. Our study shows that the incidence of anaphylaxis increased from 2.67 to 4.51 per 1,000 hospitalized pediatric patients

Table 2. Triggers of 172 anaphylaxis episodes

Triggers	n (%) of children	Specific agent	n (%) of children
Food	60 (34.9)	Seafood	32 (53.3*)
		Wheat	11 (18.3*)
		Hen's egg	7 (11.7*)
		Cow's milk	1 (1.7*)
		Other food	9 (15.1*)
Drug	57 (33.1)	Antibiotic	17 (29.8*)
		Chemotherapy	15 (26.3*)
		Immunotherapy	8 (14*)
		Peri-operative	6 (10.5*)
		Radio-contrast media	3 (5.3*)
		NSAID	3 (5.3*)
		Other drug	5 (8.8*)
Blood component	41 (23.8)	Platelet	21 (51.2*)
		Packed red cells	9 (22.0*)
		Fresh frozen plasma	5 (12.2*)
		Other	6 (14.6*)
Insect	9 (5.2)	Fire ant	4 (42.8*)
		Wasp	5 (57.2*)

*percentage in each trigger

between 2004-2008 and 2009-2013, a trend matching world-wide patterns of incidence.[5,18] Such a trend may be the result of the overall rising of allergic disease in association with ongoing livelihood changes and/or due to an increased attention to and recognition of anaphylaxis by physicians.

Food (34.9%) and drug (33.1%) were shown to be the two most common causes of anaphylaxis in the present study. The causative agent of anaphylaxis in children thus is suggested to be different from those involved in adult anphylaxis. Food was reported to be the most common trigger of anaphylaxis in children[11, 13, 19] and drug was the most common cause in adult.[2, 3] However, specific causes of anaphylaxis may be different from countries to countries. A recent study in German-speaking countries has shown that insect stings were the most common cause of anaphylaxis, followed by food and drug.[4] In Thailand, it has been demonstrated that drug is the most common cause of anaphylaxis in hospitalized patients including children and adult.[2,3] However, there are no reports focusing in hospitalized children. In addition, the locations where the anaphylaxis cases were recorded tend to determine the kind of anaphylaxis observed. Food has been reported to be the leading cause of anaphylaxis in patients presenting themselves at the emergency department in Thailand.[7,8] The present study has shown that the majority of drug and blood component-induced anaphylaxis occurred in hospital while anaphylaxis from food and unidentified causes occurred more frequently in community settings. Blood component induced anaphylaxis is the third common cause of anaphylaxis in the present study with the frequency of 23.8% of total anaphylaxis cases. A recent study from Taiwan in adult and children has demonstrated that blood transfusion is a cause of anaphylaxis only in 4% of the cases, but there was no blood transfusion induced anaphylaxis in the pediatric group.[5] Previous studies has reported the frequencies of transfusion associated anaphylaxis as 1 per 170,000 to as high as 1 per 18,000 blood products transfused.[20] As a result, anaphylaxis from blood transfusion is not uncommon and physicians should be aware of this possible clinical risk while prescribing patients with blood components.

Seafood and antibiotic have been demonstrated to be the most common cause of food and drug induced anaphylaxis in the present study. A recent study from Singapore has demonstrated differences in the common food and drug that caused anaphylaxis in children. Peanut and ibuprofen were the most common cause of anaphylaxis in Singaporean children.[10] However, there was no peanut anaphylaxis case in the present study. This finding is in line with studies from Thailand which demonstrated the absence of peanut allergy.[21, 22] The differences in type of food consumed and the method of food processing may have an impact on food allergy trends in different countries. In this context, each countries should have its own information on specific cause of anaphylaxis. Due to the difference in cultural behaviors, common causes of anaphylaxis may vary even in the same geographic area.

Association between severe anaphylaxis and triggers of anaphylaxis was demonstrated in the present study. Approximately 50% of patients who developed anaphylaxis from drug or blood had severe anaphylaxis. Medication (drug and blood components) related anaphylaxis has been demonstrated to be the most common cause of fatal anaphylaxis in a recent study in the United States.[23] History of allergic diseases has been shown to be associated with cause of anaphylaxis. Seventy to one hundred percent of patients with food, insect and

Table 3. Characteristics of anaphylaxis episodes categorized by triggers

Factor		Trigger					*P* value
		Food N=60	Drug N=57	Insect N=9	Blood component N=41	Unidentified N=5	
Age, years	mean (SD)	8.82 (4.9)	8.09 (5.1)	8.78 (3.2)	9.17 (4.1)	9 (2.3)	0.83
Sex n (%)	Male	35 (58.3)	28 (49.1)	8 (88.9)	25 (61)	2 (40)	0.18
	Female	25 (41.7)	29 (50.9)	1 (11.1)	16 (39)	3 (60)	
Location n (%)	Community	58 (97.6)	16 (28.1)	9 (100)	2 (4.9)	5 (100)	<0.001
	Hospital	2 (3.3)	41 (71.9)	0	39 (95.1)	0	
Atopic disease n (%)	yes	46 (76.7)	30 (52.6)	9 (100)	33 (80.5)	5 (100)	0.001
	No	14 (23.3)	27 (47.4)	0	8 (19.5)	0	
Clinical symptoms n (%)							
Cutaneous system		57 (95.0)	51 (89.5)	9 (100)	36 (87.8)	4 (80)	0.16
Respiratory system		51 (85.0)	42 (73.7)	9 (100)	28 (68.3)	5 (100)	0.08
Cardiovascular system		13 (21.7)	23 (40.4)	2 (22.2)	24 (58.5)	2 (40)	0.03
Gastroinstestinal system		19 (31.7)	17 (29.8)	3 (33.3)	13 (31.7)	0	0.75
Neurological system		0	1 (1.8)	0	1 (2.4)	1 (20)	0.07
Severe anaphylaxis n (%)		9 (15.0)	26 (45.6)	1 (11.1)	21 (51.2)	2 (40)	<0.001
Biphasic n (%)		2 (3.3)	10 (17.5)	0	3 (7.3)	0	0.09

blood component anaphylaxis had histories of allergic diseases, while only half of patients with drug induced anaphylaxis had histories of allergic disease. While the association between histories of allergic disease and severe anaphylaxis was not found in the present study (data not shown), physicians should be aware of this clinical risk factor when treating a patient with anaphylaxis.

Guidelines for management of anaphylaxis recommend administering intramuscular epinephrine at thigh as a first line treatment for anaphylaxis.[24,25] Intramuscular epinephrine was given in 93.8% of the cases in the present study. This contrasts with previous reports which have found that intramuscular epinephrine was administered less frequently, as low as 2.2%[26] to 30% of the cases.[4,11,12] The high percentage of intramuscular epinephrine administration in the present study may result from the fact that the personnel in charge of treating analphylaxis patients are tertiary care hospital, medical school and university hospital personnel. Even with a high percentage of received intramuscular epinephrine, biphasic anaphylaxis was demonstrated in 8.5% of cases in the present study which is higher than previous studies targeting children[11] In contrast to the findings from previous studies,[16, 28] drug induced anaphylaxis were associated to an increased rate of biphasic anaphylaxis than food-induced anaphylaxis in the present study. The difference might be explained by the high percentage of chemotherapy drugs and immunotherapy-induced anaphylaxis found in the present study. Almost all of chemotherapy-induced anaphylaxis cases were resulting from L-asparaginase intramuscular administration and subcutaneous immunotherapy. As a result of these mode of administration, the blood level of the drugs were slowly declining over time, resulting in the re-occurrence of clinical anaphylaxis.

Treatment with intramuscular epinephrine has been demonstrated to be protective for biphasic anaphylaxis in the present study. Delayed administration of epinephrine has been proposed to increase the risk of a biphasic anaphylaxis.[27] However, we did not evaluate the timing of epinephrine administration relative to onset of symptom. In contrast to previous study,[28] history of previous allergic reaction from the same triggers has also been demonstrated to be a protective effect for biphasic anaphylaxis in the present study. Patients with history of prior allergic reaction may lead to an

early diagnosis of anaphylaxis, leading to an early treatment with intramuscular epinephrine and in consequence a better clinical outcome. In addition, severe anaphylaxis has been demonstrated to associate with biphasic anaphylaxis in the present study. As a result, patients with severe anaphylaxis (hypotension or hypoxemia) should be closely monitored for clinical of biphasic anaphylaxis.

There are several limitations in our study. First, this study is a retrospective study. There may be some incomplete data. While cases were recruited using the ICD-10 code system which may constrain somehow cases selection, we have used all codes seemingly compatible with clinical cases of anaphylaxis insuring the exhaustiveness or our selection. In addition, anaphylaxis was diagnosed by extensive medical recorded review with the clinical symptoms matching anaphylaxis diagnosis criteria.[4] Further prospective data collection is required to better reflect the incidence, cause and management of anaphylaxis for Thailand.

In conclusion, the incidence of anaphylaxis in children is increasing. Anaphylaxis in children commonly occurred without known history of prior reaction to the causative agent. Less frequent administration of intramuscular epinephrine was associated with biphasic and severe anaphylaxis. Food and drug were the most common triggers of anaphylaxis in children. A better knowledge of patterns and cause of anaphylaxis might contribute to a better management.

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