Original Article

Anaphylaxis in Children: Experience of 485 Episodes in 1,272,482 Patient Attendances at a Tertiary Paediatric Emergency Department from 2007 to 2014

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Abstract

Introduction: Anaphylaxis is a predominantly childhood disease. Most of the literature on anaphylaxis has emerged from Western countries. This study aimed to describe the incidence, triggers and clinical presentation of anaphylaxis among children in Singapore, look for predictors for anaphylaxis with severe outcomes, and study the incidence of biphasic reactions. Materials and Methods: We retrospectively reviewed records of children presenting with anaphylaxis to our paediatric emergency department from 1 January 2007 to 31 December 2014. Results: We identified 485 cases of anaphylaxis in 445 patients. Cutaneous symptoms (urticaria/angio-oedema) were the most common across all age groups (481 cases, 99%), followed by respiratory (412, 85%), gastrointestinal (118, 24%) and cardiovascular (35, 7.2%) symptoms. Central nervous system symptoms (drowsiness/irritability) were rare across all age groups (11, 2.2%). Food was identified as the most common trigger across all age groups (45% to 63%). Seafood was the most common food trigger (57, 25%). A total of 420 (86.6%) children were treated with adrenaline, 451 (93%) received steroids and 411 (85%) received antihistamines. Sixty-three (13%) children fulfilled the criteria of severe anaphylaxis. There was no statistically significant association between severe anaphylaxis and the type of trigger ($P = 0.851$), nor an overall past history of atopy ($P = 0.428$). The only independent predictor for severe anaphylaxis was a previous drug allergy ($P = 0.016$). A very low prevalence of biphasic reactions (0.6% of study population) was noted in our study. Conclusion: We described the presentation and management of anaphylaxis in the Singapore population. A history of drug allergy is associated with severe presentation. Biphasic reactions are rare in our population.

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Introduction

Anaphylaxis is a severe and potentially fatal allergic reaction that occurs rapidly after exposure to an allergen.[1] There have been reports that the incidence of paediatric anaphylaxis is on the rise in the industrialised world.[2-4] There is, however, limited data confirming these trends in the Asian population.

Anaphylaxis is a predominantly childhood disease.[5,6] Young children with anaphylaxis present differently from adults. They have difficulty describing symptoms such as pruritus, throat tightness, or feelings of impending doom. Potential signs of anaphylaxis often occur in young children for a variety of other reasons. These include behavioural changes, irritability, drooling, regurgitation, and incontinence of urine and stool.

Because of the variable and non-specific nature of presentation, there are often delays between the child's arrival in the emergency department (ED) and the institution of definitive management.[4,7,8] A recent study concluded that the paediatric ED treatment and management of patients with anaphylaxis fell short of standard recommendations. Only 54% of patients who met the diagnostic criteria were treated with epinephrine despite current clear guidelines.[9]

In an earlier Singapore study, it was reported that hypotensive episodes are more likely to be due to drug triggers than food triggers. Among the food triggers causing

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anaphylaxis, there is an increasing number of peanut-related anaphylaxis episodes as compared to the previous decade.[10] The diet of Asian children differ from their counterparts in Western countries. Unique allergens such as bird's nest are not commonly consumed in the West and they have been reported to be significant allergens.[10]

Moving beyond the initial presentation, others have studied the incidence of biphasic reactions among children with anaphylaxis. The reported incidences are highly variable, ranging from 1% to 20% of all anaphylactic reactions.[11]

In view of the above, we set out to: i) describe the incidence, triggers and clinical presentation of anaphylaxis among children in Singapore, primarily an Asian population; ii) look for discriminatory predictors for anaphylaxis with severe outcomes; and iii) study the incidence of biphasic reactions in this population of children.

Materials and Methods

This was a retrospective chart review. We reviewed electronic records of children presenting with anaphylaxis to the KK Women's and Children's Hospital (KKWCH) paediatric ED from 1 January 2007 to 31 December 2014. This is 1 of the 2 tertiary hospitals in Singapore with a dedicated paediatric ED, and sees an annual attendance of about 170,000 children. Records of all children with a free text discharge diagnosis containing the words "anaphylaxis", "anaphylactic shock", "anaphylactic reaction", "anaphylactoid reaction" as well as International Classification of Diseases, 9th Revision (ICD-9) coding of "anaphylaxis" (995.0), "anaphylactic reaction" (995.0), "anaphylactic shock" (995.0) and "anaphylactic shock or reaction to adverse food reaction" (995.6) were obtained and reviewed.

We included all patients younger than 16 years old who met the definition of anaphylaxis.[12] This is defined as: i) acute onset of illness with involvement of skin, mucosal tissue, or both, and at least 1 other system involved (respiratory compromise, or cardiovascular compromise/associated end organ dysfunction); ii) two or more of skin-mucosal, respiratory, reduced blood pressure/associated end organ dysfunction, gastrointestinal symptoms, and occurring rapidly after exposure to a likely allergen for that patient; and iii) reduced blood pressure minutes to hours after exposure to a known allergen for that patient.

We evaluated the severity of anaphylaxis with a 3-grade scale according to the criteria proposed by Huang et al.[13] Mild anaphylaxis was defined as those with skin involvement (flushing, urticarial and angio-oedema), mild respiratory (minimal dyspnoea, wheeze and upper respiratory tract symptoms) and gastrointestinal symptoms (mild abdominal pain and/or emesis). Moderate anaphylaxis included those who had mild symptoms and features suggesting moderate respiratory (dysphagia, shortness of breath, hoarseness, and/or stridor, wheezing and retractions), cardiovascular or gastrointestinal (recurrent vomiting and/or diarrhoea, crampy abdominal pain) symptoms. The definition of severe anaphylaxis included patients with severe respiratory compromise resulting in cyanosis or hypoxia (SpO_2 <92%), hypotension or neurological compromise (confusion, collapse, loss of consciousness or incontinence).[13]

Each record was hand searched and patients who did not fulfill the above criteria were excluded from the study.

We recorded information on the demographics, presenting complaints, suspected triggers, risk factors, vital signs, and physical examination findings. The risk factors that we studied for an overall history of atopy included: a history of asthma, eczema, allergic rhinitis, food or drug allergies. We divided the symptoms and signs based on systems involved: cutaneous (urticarial, angio-oedema), respiratory (wheeze, stridor), cardiovascular (hypotension), gastrointestinal (abdominal pain, vomiting, diarrhoea) and central nervous system (drowsiness, irritability), but these were not mutually exclusive. We reviewed the ED management—specifically the use of adrenaline, antihistamines and steroids—and followed up all admitted patients for biphasic reactions by reviewing their inpatient notes, re-attendances to the ED and clinic notes.

The study was approved by the Singhealth Institutional Review Board (E, Paediatrics), with a waiver of informed consent.

Data Analysis

Categorical variables were described in frequencies and percentages while continuous variables were described with means and standard deviations (SD). Univariable logistic regression was performed to search for discriminatory predictors for severe outcomes, consistent with previous reported definitions for severe anaphylaxis.[13] Statistical significance was established at P <0.05. The data was analysed using IBM SPSS statistics 19.

Results

There were a total of 1,272,482 attendances in our ED from 2007 to 2014. Our initial search identified 639 cases with ICD codes related to anaphylaxis. Nineteen patients (3%) were aged 16 years and older, and 135 patients (21%) were excluded because they did not meet the criteria for anaphylaxis on a detailed chart review (Fig. 1). The total number of patients excluded were 154 (24%). We identified 485 cases of anaphylaxis in 445 patients. The number of

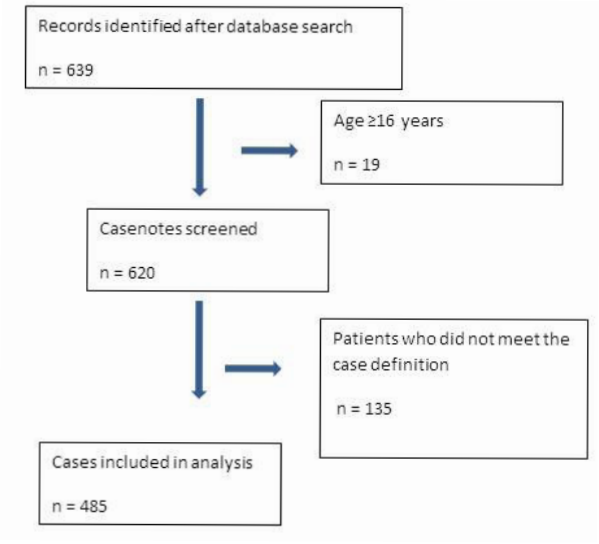

Fig. 1. Flowchart of patients included for the analysis in the study.

Table 1. Patient Demographics

Characteristics	n (%)
Age, mean (SD)	8.2 (4.3)
Males (%)	297 (61.2)
Patients receiving adrenaline (%)	420 (86.6)
Patients receiving prehospital adrenaline (%)	31 (6.4)
Patients receiving repeat adrenaline (%)	4 (0.8)
Patients receiving antihistamines (%)	411 (84.7)
Patients receiving steroids (%)	451 (93.0)
Patients with biphasic reactions (%)	3 (0.6)
Disposition	
Admitted to GW (%)	434 (89.5)
Admitted to HD/ICU (%)	29 (6.0)
Discharged (%)	10 (2.1)
Discharged against medical advice (%)	11 (2.3)

GW: General ward; HD/ICU: High dependency/Intensive care unit

patients diagnosed with anaphylaxis increased from 23 cases in 2007 to 84 in 2014. Over these 8 years, there was an average increase in 7.6 patients (or 33.0%) per year. The frequency of anaphylaxis in our ED appears to be 1 event in 2624 attendances, equivalent to a risk level of 38 events in 100,000 emergency visits.

The mean age of the children was 8.4 years (SD: 4.3). Of the 485 presentations, 297 (61.2%) were males (Table 1). A total of 284 patients (58.6%) in our cohort had a past history of atopy, specifically asthma (105, 21.6%), food allergy (139, 28.7%), drug allergy (46, 9.4%), eczema (39, 8.0%) and allergic rhinitis (33, 6.8%).

Based on the system of involvement (Table 2), cutaneous symptoms (urticaria/angio-oedema) were the most common across all age groups (97.8% to 100%) followed by respiratory symptoms (65.2% to 93.7%), gastrointestinal symptoms (19.4% to 47.8%) and cardiovascular symptoms (3.1% to 12.6%). Central nervous system symptoms

Table 2. System(s) of Involvement

Systems Affected*	0 to <2 Years n = 46	2 to <5 Years n = 89	5 to <10 Years n = 159	10 to <16 Years n = 191
Respiratory, n (%)	30 (65.2)	78 (87.6)	149 (93.7)	155 (81.2)
Wheeeze‡	28 (60.9)	74 (83.1)	144 (90.6)	147 (77.0)
Stridor‡	2 (4.3)	5 (5.6)	15 (9.4)	18 (9.4)
Cardiovascular†, n (%)	2 (4.3)	4 (4.5)	5 (3.1)	24 (12.6)
Cutaneous, n (%)	45 (97.8)	89 (100.0)	156 (98.1)	191 (100.0)
Urticaria	25 (54.3)	37 (41.6)	49 (30.8)	59 (30.9)
Angioedema	3 (6.5)	14 (15.7)	52 (32.7)	52 (27.2)
Both	17 (37.0)	38 (42.7)	55 (34.6)	80 (41.9)
Gastrointestinal, n (%)	22 (47.8)	23 (25.8)	36 (22.6)	37 (19.4)
Vomiting‡	20 (43.5)	16 (18.0)	17 (10.7)	16 (8.4)
Diarrhoea‡	2 (4.3)	1 (1.1)	0 (0.0)	4 (2.1)
Abdominal pain‡	0 (0.0)	6 (6.7)	20 (12.5)	19 (9.9)
Central nervous system§, n (%)	1 (2.2)	2 (2.2)	1 (0.6)	7 (3.7)

*Not mutually exclusive, as per anaphylaxis definition.
†Evidenced by hypotension.
‡Not mutually exclusive.
§Evidenced by drowsiness and irritability.

Table 3. Identifiable Trigger, by Age

	0 to <2 years n = 46	2 to <5 years n = 89	5 to <10 years n = 159	10 to <16 years n = 191
Food, n (%)	29 (63.0)	46 (51.7)	72 (45.3)	87 (45.5)
Seafood	4 (13.7)	5 (10.9)	13 (18.0)	35 (40.2)
Peanut	3 (10.3)	10 (21.7)	10 (13.8)	10 (11.5)
Tree nut	0 (0.0)	9 (19.6)	9 (12.5)	9 (10.3)
Egg	18 (62.0)	1 (2.1)	1 (0.1)	2 (2.2)
Cow's milk	3 (10.3)	6 (13.0)	3 (4.1)	0 (0.0)
Drugs, n (%)	5 (10.9)	11 (12.4)	28 (17.6)	38 (19.9)
Insects, n (%)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.5)
Others, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.6)
Unknown, n (%)	12 (26.1)	32 (36.0)	58 (36.5)	62 (32.5)

(drowsiness/irritability) were rare across all age groups (0.6% to 3.7%). Gastrointestinal symptoms predominated in the younger age groups (47.8% in children aged 0 to 2 years old as compared to 19.4% in children aged 10 to 16 years old). Cardiovascular symptoms predominated in the older age group (10 to 16 years old), affecting 12.6% of patients in this age group.

Identifiable triggers divided by age strata are described in Table 3. Food was identified as the most common trigger across all age groups (45.3% to 63.0%). Among those with food triggers (Table 4), seafood was the most common food trigger, causing 25% of all food triggered anaphylaxis presenting to the ED. This was followed by peanuts (14.5%), tree nuts (11.9%), egg (9.6%) and bird's nest (6.6%). Drugs were the second most common trigger (10.9% to 19.9%) and were noted to be more common among older children aged 10 to 16 years,involving 38 (19.9%) patients. Ibuprofen was the most common trigger (47.6%) among anaphylaxis cases triggered by medication and it was followed by paracetamol (13.4%) and antibiotics (11.9%) (Table 5). We had 2 cases of insect bite-induced anaphylaxis and 2 cases of exercise induced anaphylaxis (both in the 10- to 16-year-old range). No specific triggers were identified in 164 (33.8%) of all patients.

A total of 420 patients (86.6%) were treated with adrenaline. Thirty-one (6.4%) patients received pre-hospital adrenaline, the majority of which was administered by a caregiver. Among those given steroids (n = 451), 447 (99.1%) were given in the hospital and 4 (0.9%) were given at home. Among those with antihistamines (n = 411), 356 (86.7%) of them were given in the hospital while 55 (13.4%) were given at home.

Sixty-three (13%) of all anaphylaxis cases fulfilled the criteria of severe anaphylaxis. The mean age of severe cases was slightly higher at 9.6 years with similar male predominance as compared with non-severe cases. A higher percentage of severe cases (56, 89%) received adrenaline

Table 4. Details of Specific Food Triggers

Food Trigger*	Number	Percentage
Seafood	57	25.0%
Peanuts	33	14.5%
Tree nuts	27	11.9%
Egg	22	9.6%
Bird's nest	15	6.6%
Commercially packed food	14	6.1%
Cow's milk	12	5.3%
Fruits/vegetables	10	4.4%
Herbal drink	9	4.0%
Wheat	7	3.0%
Honey	7	3.0%
Meat/poultry	6	2.6%
Baked goods	6	2.6%
Chocolate	4	1.8%
Goat's milk	3	1.3%

*More than 1 food trigger may be involved in a case of anaphylaxis.

Table 5. Details of Specific Drug Triggers

Drug Trigger	Number	Percentage
Ibuprofen	39	47.6%
Antibiotics*	27	11.9%
Paracetamol	11	13.4%
Traditional Chinese medicine	4	4.8%
Cough syrup	3	3.6%

*Antibiotics refer to the following: amoxicillin, cephalexin, bactrim, erythromicin, clarithromicin.

Table 6. A Detailed Description of the 3 Biphasic Reactions

Reaction	Age	Trigger	System	ED Management	Time of Reaction	Ward Management
1	6.3	Food: crab	Respiratory and skin – wheeze, periorbital and lip swelling.	IM adrenaline, IV dyphenhydramine and hydrocortisone.	Wheeze, pruritus and periorbital swelling 12 hours after first reaction.	Continued on steroids and antihistamine.
2	3.6	Unknown	Respiratory and skin – hoarse voice, urticaria and periorbital swelling.	IM adrenaline, IV dyphenhydramine and hydrocortisone, and ventolin puffs.	Developed worsening urticaria and periorbital oedema 18 hours after first symptoms.	Repeat IM adrenaline and IV dyphenhydramine.
3	12.8	Food: egg	Respiratory and skin – chest tightness, periorbital swelling and urticaria.	IM promethazine and prednisolone.	Developed wheeze, stridor, worsening pruritus, abdominal pain and vomiting 14 hours after first symptoms.	Treated with IM adrenaline, IV hydrocortisone and IV dyphenhydramine.

ED: Emergency department; IM: Intramuscular; IV: Intravenous

and steroids (59, 95%) compared to the non-severe cases. A significantly higher number of severe cases were also admitted to the high dependency or intensive care unit (ICU) (18 out of 63 patients, 28.5%) as compared to non-severe cases (11 out of 422 patients, 2.6%). There was no statistically significant association between the severity of cases and types of triggers ($P = 0.851$), nor an overall past history of atopy ($P = 0.428$). Specifically, a previous drug allergy was found to be the only predictor of a severe episode of anaphylaxis.($P = 0.016$)

Only 3 cases of biphasic reaction were recorded, representing a very low proportion (0.6%) of all cases of anaphylaxis. Table 6 describes these 3 patients in detail.

Forty (8.9%) patients had repeat attendances for anaphylaxis, of which 4 patients were seen 3 times and 2 other patients were seen 4 and 5 times each. Of these 6 patients who were seen 3 times or more, 3 of them had a positive history of atopy and 3 had multiple known food allergies. The severity of their anaphylactic reactions were all mild.

Discussion

To our knowledge, this is the largest report of the incidence, clinical presentation, triggers and management of anaphylaxis presenting to an Asian paediatric ED.

There had been an increasing trend of anaphylaxis cases presenting to our ED over the duration of our study. This trend is consistent with other studies worldwide.[11,12,14,15] Apart from a possible true increase in the incidence of anaphylaxis, we postulate that this trend may be contributed by increased awareness and recognition of anaphylaxis amongst ED physicians. Others have suggested that a change in physician practices may have resulted in increased hospitalisations.[16]

We observed certain age-related patterns in our cohort of patients with anaphylaxis. Gastrointestinal symptoms were more prevalent in the younger age groups whereas cardiovascular symptoms were primarily seen in the older age groups. Our results mirrors the results of Rudders et al from Boston. In this study, cardiovascular symptoms, while noted among adolescents, were rarely reported among the younger children.[17] In another study performed among children with anaphylaxis presenting to the Mount Sinai pediatric ED between 2004 and 2008, the authors identified that infants are less likely to have a blood pressure measurement obtained in the ED compared with older children.[13] This could potentially confound the true numbers of hypotension seen in younger age groups.

This highlights the need to consider the age group of the patient when identifying the symptoms and signs of anaphylaxis in the ED. A low prevalence of central nervous system symptoms in this study is consistent with the findings of other studies.[18,19]

From the 1990s to 2000s, peanut allergy has increased in prominence.[10,20] In our current study, seafood (25.0%) emerged as the most common overall trigger, followed by peanuts (14.5%) and tree nuts (11.9%). The reason for this overall change in food-triggered anaphylaxis remains largely unknown. Firstly, we postulate that our largely cosmopolitan society with changing demographics may have contributed to this evolving landscape of food allergies. Singapore's population demographics has changed significantly in the past 2 decades, with a significant increase of non-residents from 10.2% in 1990 to 18.7% in 2000, and 25.7% in 2010 to 30% in 2015.[21] Secondly, in this study, we obtained the information surrounding the triggers from a detailed clinical history. Seafood consumption is usually obvious and easily reported while peanuts could well be hidden as part of baked products or combined food components. However, the specific food triggers for each age group remains comparable with Liew et al, with egg being the

predominant food trigger for children less than 1 year old, peanut being the predominant food trigger for children between 1 to 5 years old, and seafood in the older children. While milk products have been reported to be the most common cause of food-triggered anaphylaxis among young children aged <2 years old,[17] egg was the most common in our population for this age group. This could be related to different feeding and weaning patterns in different cultures. In our population, it is common to introduce eggs early to weaning infants. We also noted that bird's nest allergy spans most age groups.[10]

Medication-triggered anaphylaxis was less common in the younger age group (10.9%) but gradually rose to 19.9% among the older children. This was similarly reported in 2 previous studies in Singapore.[10,14] This was likely due to increasing medication exposure with age. Ibuprofen-induced anaphylaxis was indeed the most common cause of drug-induced anaphylaxis in our population, comprising up to half of our drug-induced anaphylaxis (39 patients, 47.6%). We also report an increasing trend of antibiotics-induced anaphylaxis (11.9%) as compared to 6% in a previously published series in our population.[10]

One important finding is the very low prevalence of biphasic reactions in our study population. There was no cardiovascular instability noted during the biphasic phase of reactions in all 3 patients. Although biphasic reactions are not as common in the paediatric population when compared to adults, there has been varying reports of its occurrence of between 1% to 20%.[2,11,22] The low rate of occurrence of biphasic reactions in our population is potentially practice changing. Our instititution currently admits all patients presenting with anaphylaxis. However, most paediatric patients with anaphylaxis may not require prolonged monitoring or admission. Our low rates of biphasic reaction could potentially be due to our high use of adrenaline and glucocorticoids in the emergency setting.[23,24] Ellis and Day found that early treatment of the initial anaphylactic reactions with adrenaline was associated with a lower risk of developing biphasic reactions.[25] Due to the geographic proximity of our population to the hospital, most patients present to the ED quite quickly after the onset of symptoms, thus reducing the time delay between the onset of symptoms to the first dose of adrenaline. This may also have contributed to a low rate of biphasic reactions.[24] The findings in this study has the potential to guide a more careful selection of patients who require admission, thus reducing the burden of unnecessary admissions among this group of patients.

The strength of our study lies in our large number of patients seen and treated for anaphylaxis. We have approached our study from the point of view of the initial presentation, highlighting findings that would help ED physicians to understand age-specific triggers and the variable presentations among children presenting with anaphylaxis.

Limitations

We recognise the following limitations of our study. As this was a retrospective chart review, there was potential for incomplete or inadequate documentation in case notes, which may lead to missing data. Secondly, this retrospective work spanned a long period in which the institution's protocols on anaphylaxis and physician practices may have undergone changes. Thirdly, we searched using ICD codes and keywords linked to anaphylaxis, and patients who had wrongly coded in other ICD codes of allergic reactions might have been missed or omitted. Finally, we found only a small number of patients with severe anaphylaxis or biphasic reactions. This could explain why we did not establish statistically significant associations when describing triggers and an overall previous history of atopy.

Conclusion

In this study, we described the paediatric anaphylaxis population presenting to a large tertiary paediatric hospital in Singapore. The estimated frequency of anaphylaxis is 1 event in 2624 attendances, equivalent to a risk level of 38 events in 100,000 emergency visits. Clinical presentations vary depending on the age of the child. Severe anaphylaxis and biphasic reactions appear to be rare in our population, possibly because of relatively rapid treatment with adrenaline and corticosteroid. Further studies focusing on the predictors for severe anaphylaxis and biphasic reactions would guide firstline physicians on risk stratification and resource allocation.

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