

Cause and Clinical Presentation of Anaphylaxis in Singapore: From Infancy to Old Age

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Keywords

Anaphylactic shock · Anaphylaxis · Drug allergy · Food allergy · Insect venom allergy

Abstract

Background: The study objective was to compare age-related differences in the cause and clinical presentation of anaphylaxis. **Methods:** We conducted a prospective study of patients visiting the emergency department for anaphylaxis. Data were collected from 3 emergency departments from 1 April 2014 to 31 December 2015. Patient electronic records with the diagnoses of allergy, angioedema, urticaria, and anaphylaxis (ICD-9 codes 9953, 9951, 7080, 9950, 7089) were screened and cases fulfilling World Allergy Organisation criteria for anaphylaxis were included. **Results:** A total of 426 cases of anaphylaxis were identified with a median age of 23 years (range 3 months to 88 years and 9 months). The causes of anaphylaxis were food ($n = 236$, 55%), drugs ($n = 85$, 20%), idiopathic ($n = 64$, 15%), and insect bites or stings ($n = 28$, 7%). The most common food was shellfish ($n = 58$, 14%) and the most common drugs were non-steroidal anti-inflammatory drugs ($n = 26$, 6%). There were more cases of food anaphylaxis in children than in adults (72 vs. 42%, $p < 0.001$) and more cases of drug anaphylaxis in adults than in children (28

vs. 10%, $p < 0.001$). Compared to patients of other ages, infants and young children had more gastrointestinal symptoms (adjusted odds ratio [aOR] 2.1, 95% CI 1.1–3.9), while schoolchildren and adolescents had more respiratory symptoms (aOR 2.7, 95% CI 1.4–5.2). Adults had more cardiovascular symptoms (aOR 2.9, 95% CI 1.8–4.6) and hypotension (aOR 3.7, 95% CI 2.1–6.8) compared to children. However, 42% of the infants lacked blood pressure measurements. **Conclusions:** Knowledge of age-related variation in the cause and clinical presentation of anaphylaxis aids in diagnosis and acute management.

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Introduction

Anaphylaxis is a severe systemic hypersensitivity reaction. There are age-related differences in the cause, clinical presentation, and severity of anaphylaxis. In Europe and the USA food is the most common cause of child anaphylaxis, while drug and hymenoptera reactions are more common in adults [1–4]. There is increasing evidence that respiratory symptoms occur more frequently

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Table 1. Demographics of patients with anaphylaxis

	Total (<i>n</i> = 426)	Children (0–18 years; <i>n</i> = 191)	Adults (19 years and above; <i>n</i> = 235)	<i>p</i>
<i>Demographics</i>				
Male	217 (51)	112 (59)	105 (45)	0.006
Chinese	260 (61)	115 (60)	145 (62)	ns
Malay	65 (15)	26 (14)	39 (17)	ns
Indian	34 (8)	13 (7)	21 (9)	ns
Others	67 (16)	37 (19)	30 (13)	ns
<i>Medical history</i>				
Asthma	81 (19)	37 (19)	44 (19)	ns
Prior food allergy	115 (27)	74 (39)	41 (17)	<0.001
Prior drug allergy	108 (25)	17 (9)	91 (39)	<0.001
Prior sting reaction	8 (2)	1 (0.5)	7 (3)	ns
Prior anaphylaxis	59 (14)	30 (16)	29 (12)	ns

Values in parentheses are percentages. *p* < 0.05 indicates a statistically significant difference between children and adults. ns, not significant.

in children, while cardiovascular symptoms predominate in adults [5]. Adolescent and elderly patients are vulnerable to lethal anaphylaxis [3, 6].

In contrast to Western data, previous studies in Singapore showed that food was the main cause of anaphylaxis in both children [7, 8] and adults [9]. The most common triggers in children were peanut, egg, shellfish, and bird's nest [7], while the top trigger in adults was shellfish [9]. This study aims to describe and compare the demographic characteristics, clinical features, causes, and management of anaphylaxis for infants, children, and adults in Singapore. An understanding of age-related variations in the triggers and clinical spectrum of anaphylaxis helps to facilitate prompt recognition and treatment at the emergency department.

Methods

This was a prospective observational study of patients with anaphylaxis attending 3 emergency departments in Singapore: National University Hospital, KK Women's and Children's Hospital, and Tan Tock Seng Hospital. Surveillance of emergency department data was conducted over 21 months, from April 1, 2014, to December 31, 2015. An electronic database search using International Statistical Classification of Diseases and Related Health Problems (ICD-9) codes for anaphylaxis (9950), angioedema (9951), allergy (9953), and urticaria (7080, 7089) was performed. A trained research nurse and 2 clinicians reviewed patient notes and collected information onto standardised data forms. The diagnosis of anaphylaxis was based on World Allergy Organisation

(WAO) anaphylaxis guidelines [10] and was confirmed by review of the presenting symptoms, signs, and parameters. An independent third clinician reviewed cases where the diagnosis was unclear. Cases that did not fulfil WAO diagnostic criteria were excluded. Hypotension was defined as less than 70 mm Hg + double the age in children below 10 years, and less than 90 mm Hg in children above 10 years and adults.

Age Stratification

Patients were stratified into 6 age groups: infants (0–2 years); young children (2–5 years); schoolchildren (6–11 years); adolescents (12–18 years); adults (19–65 years); and elderly (66 years and above).

Statistical Analysis

Analysis was performed using SPSS version 20. Continuous data were described using the mean and standard deviation (SD) for data with a normal distribution, and median and interquartile range (IQR) for data not normally distributed. Differences between groups for categorical variables were determined using the χ^2 analysis. The Mann-Whitney U test and Student *t* test were used for comparisons between nonparametric and parametric continuous variables, respectively. A *p* value < 0.05 was considered statistically significant.

Results

Population Characteristics

The initial electronic database search revealed 7,373 allergy-related attendances. After review, 426 cases (6%) of anaphylaxis were identified comprising 191 (45%) children and 235 (55%) adults. The median age was 23 years

Table 2. Comparison of triggers of anaphylaxis in children and adults

	Children (0–18 years) (<i>n</i> = 191)	Adults (19 years and above) (<i>n</i> = 235)	<i>p</i>
Food	137 (72)	99 (42)	<0.001
Shellfish	24 (13)	34 (15)	
Shrimp	8	17	
Crab	3	4	
Abalone	1	2	
Limpet	1	1	
Octopus	–	1	
Squid	1	–	
Sea cucumber	–	1	
Snail	–	1	
Shellfish (not specified)	10	7	
Nuts	29 (15)	6 (3)	
Peanut	14	4	
Cashew	3	1	
Chestnut	–	1	
Hazelnut	1	–	
Pistachio	1	–	
Walnut	4	–	
Nut (not specified)	6	–	
Milk	10 (5)	–	
Egg	5 (3)	1 (0.4)	
Wheat	3 (2)	2 (1)	
Fish	8 (4)	1 (0.4)	
Other food	58 (30)	55 (24)	
Alcohol	–	1	
Bird's nest	1	2	
Chinese herb	1	1	
Honey product	3	–	
Pancake or flour	3	3	
Kiwi	3	–	
Galacto-oligosaccharide	–	1	
Others ^a	47	47	
Drugs	19 (10)	66 (28)	<0.001
NSAID	10 (5)	16 (7)	
Antibiotics	1 (0.5)	14 (6)	
β-Lactam	–	10	
Paracetamol	2 (0.5)	2 (1)	
Other drugs	6 (3)	34 (14)	
Vaccine	–	1	
Contrast and dye	–	5	
Traditional medication	1	3	
Chemotherapy	–	4	
Other drugs ^b	5	21	
Insect bites or stings	2 (1)	26 (11)	<0.001
Hymenoptera	–	16	
Insect (not specified)	2	10	
Others	7 (4)	6 (3)	ns
Exercise	4	4	
Food-dependent exercise induced	1	–	
Hamster bite	2	2	
Idiopathic	26 (14)	38 (16)	ns

Values in parentheses are percentages. *p* < 0.05 indicates a statistically significant difference between children and adults. ns, not significant; NSAID, non-steroidal anti-inflammatory drug.

^a Unknown food (52), combination of different foods (33), meat (4), fruit and vegetable (4), grain (1).

^b Unknown drug (9), combination of different drugs (14), omeprazole (2), monoclonal antibody (1).

Table 3. Comparison of triggers of anaphylaxis in different age groups

	Food anaphylaxis			Drug anaphylaxis			Sting anaphylaxis		
	%	OR	95% CI	%	OR	95% CI	%	OR	95% CI
Infant (<2 years, <i>n</i> = 19)	90	11.5	2.6–51	0	–	–	0	–	–
Young child (2–5 years, <i>n</i> = 33)	73	3.6	1.6–8.1	6	0.2	0.04–0.7	6	0.5	0.1–2.2
Schoolchild (6–11 years, <i>n</i> = 57)	72	3.5	1.8–6.6	9	0.2	0.1–0.6	0	–	–
Adolescent (12–18 years, <i>n</i> = 82)	67	2.8	1.6–4.7	15	0.4	0.2–0.8	0	–	–
Adult (19–65 years, <i>n</i> = 214)	43	1.0	na	29	1.0	na	12	1.0	na
Elderly (>65 years, <i>n</i> = 20)	35	0.7	0.3–1.9	20	0.6	0.2–1.9	5	0.4	0.1–3.1

OR, odds ratio in comparison to the reference group of adults (19–65 years); na, not applicable.

(range 3 months to 88 years and 9 months). There was a slight predominance of males among the children and of females among the adults ($p = 0.006$; Table 1).

Causes of Anaphylaxis

Based on emergency department data, an eliciting cause was identified in 362 cases (85%). Food was the most common trigger ($n = 236$, 55%), followed by drugs ($n = 85$, 20%), and insect bites or stings ($n = 28$, 7%). In 64 cases (15%), a cause was not identified and anaphylaxis was classified as idiopathic.

Seventy-eight cases (18%) of anaphylaxis were linked to previously known triggers, of which 72% were due to food, with the most common being shellfish ($n = 19$, 24%), peanut ($n = 12$, 15%), and tree nut ($n = 10$, 13%).

Food anaphylaxis was more common in children than in adults (72 vs. 42%, $p < 0.001$). Drug anaphylaxis was more common in adults than in children (28 vs. 10%, $p < 0.001$; Table 2). Insect bite and sting anaphylaxis was most common in adults (Table 3). A prior history of food allergy was more common in children than in adults (39 vs. 17%, $p < 0.001$), while a prior history of drug allergy was more common in adults than children (39 vs. 9%, $p < 0.001$; Table 1).

Spectrum of Clinical Presentation across Different Ages

There were 243 cases (57%) with involvement of 2 systems, 147 (35%) with 3 systems, and 36 (8%) with 4 systems. The most common system involved was the skin ($n = 419$, 98%), followed by the respiratory ($n = 345$, 81%), cardiovascular ($n = 165$, 39%), and gastrointestinal ($n = 142$, 33%) systems. A quarter of the patients ($n = 98$, 23%) experienced hypotension. One patient experienced a biphasic reaction.

Compared to patients of other ages, infants and young children had more gastrointestinal symptoms (odds ratio [OR] 2.4, adjusted OR [aOR] 2.1, 95% CI 1.1–3.9), while schoolchildren and adolescents had more respiratory symptoms (OR 3.0, aOR 2.7, 95% CI 1.4–5.2) after adjustment for gender, past medical history, and cause of anaphylaxis (Fig. 1a). Adults had more cardiovascular symptoms (OR 3.1, aOR 2.9, 95% CI 1.8–4.6) and hypotension (OR 4.6, aOR 3.7, 95% CI 2.1–6.8) compared to children (Fig. 1b).

Treatment of Anaphylaxis across Different Ages

Adrenaline was used for acute management ($n = 352$, 83%) via intramuscular ($n = 325$, 92%), intravenous ($n = 4$, 1%), and subcutaneous ($n = 23$, 7%) routes. Additional treatment in the emergency department included: inhaled bronchodilators ($n = 119$, 28%), antihistamines ($n = 391$, 92%), steroids ($n = 365$, 86%), and intravenous fluids ($n = 173$, 41%). Antihistamines and steroids were used consistently regardless of age, whereas the use of adrenaline, fluids, and bronchodilators varied significantly with age (Fig. 2).

Four adults required intubation and mechanical ventilation, all for drug anaphylaxis – 2 for antibiotics and 2 for nonsteroidal anti-inflammatory drugs (NSAIDs). There were no fatalities.

Discussion

This multicentre study, carried out in an ethnically diverse population, showed differences in the pattern of anaphylaxis between infants, children, and adults. The ethnic distribution in our study was comparable to national data [11].

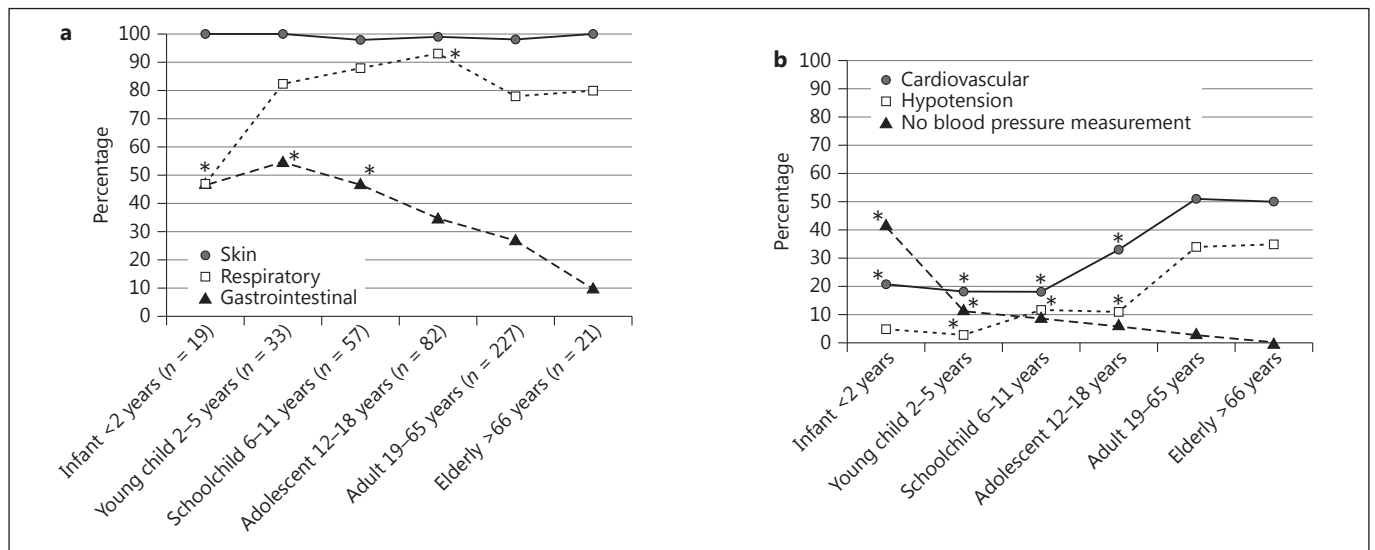


Fig. 1. Clinical involvement across different age groups. **a** Skin, respiratory, and gastrointestinal symptoms. **b** Cardiovascular symptoms and hypotension. Blood pressure measurements were lacking in 42% of infants. * $p < 0.05$, indicating statistical significance in the system involved compared to the reference group of adults (aged 19–65 years).

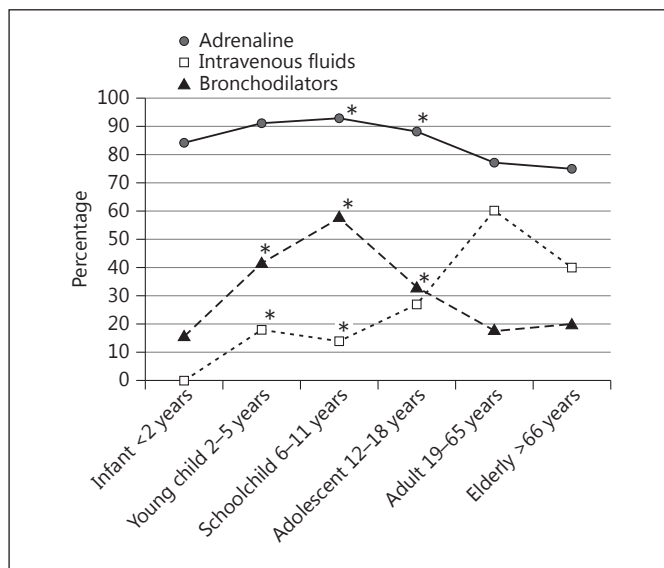


Fig. 2. Treatment trends across different age groups. * $p < 0.05$, indicating statistical significance in the treatment administered compared to the reference group of adults (aged 19–65 years).

The symptoms and signs of anaphylaxis varied considerably with age. Infants and preschool children demonstrated more gastrointestinal symptoms, similar to a prior study conducted at one of our study sites [8] and a study

by Rudders et al. [12] on 605 children who presented to a Boston emergency department with food anaphylaxis. These authors noted that although preschool children had more signs of stridor and wheeze, there were no significant differences in overall respiratory involvement and age. In contrast, our study showed that adolescents (aged 12–18 years) had the most respiratory symptoms. We postulated that this was due to the adolescent's ability to communicate breathing discomfort and co-operate with a physical examination compared to the young child. Compared to the study by Rudders et al. [12], our elicitors of adolescent anaphylaxis included a high proportion of shellfish anaphylaxis (13 vs. 5%) and NSAID drug anaphylaxis, reflecting the high incidence of locally published antipyretic drug allergy [13–15].

In our study, children had lower rates of cardiovascular involvement and hypotension compared to adults. However, 42% of infants lacked blood pressure recording (Fig. 1b). Internationally, infant anaphylaxis remains under-recognised and blood pressure readings are often omitted [16].

In our study, the clinical outcome was favourable among all age groups. Only 7 patients (1.6%) required high dependency and intensive care admission. These patients consisted of 4 adults who required mechanical ventilation, of whom 2 had cardiovascular involvement, and 3 children who were admitted for observation of their

cardiorespiratory status, of whom none required ventilator support. Biphasic reactions were rare, with a prevalence of 0.2% in our study, which is comparable to a prevalence of 0.6% in a prior study of child anaphylaxis in Singapore [8]. In contrast, Smit et al. [17] reported biphasic reactions in 5.3% of anaphylaxis cases at a Hong Kong tertiary emergency department. The inclusion criteria of that study were different. Using clinical codes and diagnosis by triage nurse and emergency physician, adrenaline administration was lower at 67% and patients were more unstable, with an intensive care admission rate of 27%. Smit et al. [17] also reported that biphasic patients took 3 times longer from the start of anaphylaxis to presentation at the emergency department compared to uniphasic patients. Our outcomes could be related to the close geographic proximity of patients to emergency care and the high rates of adrenaline treatment (83%).

Our study demonstrated that food anaphylaxis in adults was the most common type, as opposed to drug anaphylaxis seen in reports from Western [18–20] and some Asian [21, 22] countries. Food was the most common cause of anaphylaxis in prior studies of adults in Singapore [9], China [23], and Saudi Arabia [24], and in the general population in Thailand [25] and Hong Kong [17]. Shellfish was the most common food allergen in our study, echoing findings from Asian countries such as Thailand [25], Taiwan [26], and Hong Kong [17]. In Singapore, the predominance of food anaphylaxis in adulthood might be related to the nature of shellfish allergy and its persistence into adult life. Additionally, we postulated that house dust mite (HDM) sensitisation due to the pan-allergen tropomyosin was the underlying reason behind the described cases of shellfish [27], pancake [28], and hamster bite [29] anaphylaxis.

Environmental exposure to inhaled tropomyosin from HDM is postulated to be the primary sensitiser for shellfish allergy [27]. In Singapore, the prevalence of HDM sensitisation is high and increases with age. HDM sensitisation increased from 11% at 18 months to 23% at 36 months in a prospective birth cohort study of healthy children [30], to 91% in a population of clinically atopic children with mean age of 7.3 years [31]. In a study of HDM sensitisation among mainland Chinese migrants, prevalence was low in migrants who had recently arrived in Singapore, and increased to 50% in migrants who had spent more than 8 years in Singapore [32]. As HDM sensitisation requires time, it was unsurprising that in our study the median age of shellfish anaphylaxis was in adulthood (median age 24.5 years, IQR 14.4–41.6).

In tropical and sub-tropical climates with a high humidity, dust mites may reside in wheat flour left at room temperature [33, 34]. Oral mite anaphylaxis results from the consumption of mite-contaminated flour in cooked foods such as pancakes [28]. Hamster bite anaphylaxis has been described in case reports from Japan [35] and Singapore [29]. The putative allergen found in hamster saliva has possible cross-reactivity with the HDM species *Dermatophagoides pteronyssinus* (Der P) [29].

An adult woman experienced food anaphylaxis after the consumption of milk formula. Further investigation proved that the trigger was galacto-oligosaccharide, a prebiotic added to cow's milk formula [36]. Since 2009, we have identified 25 confirmed cases among schoolchildren and adults, 16 of whom have been described in previous publications [36–38]. These subjects reacted to galacto-oligosaccharide-supplemented formula milk with the predominant symptoms of dyspnoea, wheeze, angioedema, and urticaria.

Among the food anaphylaxis patients, 24% reacted to a known allergen, particularly shellfish, peanuts, and other nuts. The factors contributing to accidental shellfish exposure included its widespread usage in Asian cuisine [39] and the practice of eating out [40], with the possibility of allergens being hidden in the food consumed and a lack of understanding of food labels.

Limitations

Our study was limited to emergency department data. A final diagnosis of the eliciting allergen after review by an allergist would have been ideal but was not within the scope of the study.

Conclusion

There were age-related differences in the causes and clinical presentations of anaphylaxis. Specific causes of anaphylaxis, such as oral mite and galacto-oligosaccharide exposure, were unique in our Singaporean population. The recognition of age-related system involvement in anaphylaxis aids the allergist and emergency physician in diagnosis and acute management.

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Statement of Ethics

The Institutional Review Boards at National University Hospital, KK Women's and Children's Hospital, and Tan Tock Seng Hospital approved the study.

Disclosure Statement

The authors declare that they have no conflicts of interests.

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