Jiang, Xu, Xiang World Allergy Organization Journal (2021) 14:100605
http://doi.org/10.1016/j.waojou.2021.100605

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Age-related differences in characteristics of anaphylaxis in Chinese children from infancy to adolescence

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ABSTRACT

Background: Little is known about anaphylaxis in Chinese children. This study aimed to determine the age-specific patterns of anaphylaxis in Chinese children.

Methods: We conducted a retrospective study of anaphylaxis cases attending an allergy department in a tertiary children's hospital.

Results: A total of 279 anaphylactic reactions in 177 patients were analyzed. Overall, 57.6% (102/177) of first anaphylaxis events occurred in infants (0–2 ys). Foods were the most common culprits (88.5%), followed by food + exercise/exercise (4.7%), and drugs (4.3%). The main food allergens were cow's milk (32.9%), egg (21.4%), and wheat (20.7%) in infants, compared with fruits/vegetables at 35.9% in preschool-age children (3–6 ys) and 31.6% in school-age children (7–12 ys). The most commonly implicated drug triggers were vaccines (n = 5, comprising DTaP n = 2, group A + C meningococcal polysaccharide vaccine n = 1, Sabin vaccine n = 1, and not specified n = 1). Among the 5 vaccine-induced anaphylaxis patients, 4 had severe cow's milk allergy. The clinical manifestations were mainly mucocutaneous (86.0%), followed by respiratory (68.8%), gastrointestinal (23.7%), neurological (10.4%), and cardiovascular (0.7%). Compared with patients of other ages, infants had higher rates of hives (0-2ys 77.4%, 3-6ys 50%,7-12ys 57.9%, 13-17ys 38.9%, $p = 0.016$) and vomiting (0-2ys 20.7%, 3-6ys 1.6%,7-12ys 8.8%, $p < 0.001$), while wheezing was more frequent in school-age children (0-2ys 21.4%, 3-6ys 25%, 7-12ys 38.6%, 13-17ys 5.6%, $p = 0.017$) and abdominal pain was more common in adolescents (0-2ys 2.1%,3-6ys 15.6%, 7-12ys 14.0%, 13-17ys 72.3%, $p < 0.001$). Regarding treatment, 9.3% of anaphylaxis events and 24.1% of life-threatening reactions were treated with epinephrine.

Conclusions: We observed age-related clinical patterns of anaphylaxis in this study, with hives and vomiting most commonly reported in infants and cardiovascular symptoms rarely reported in children. Wheat was the third most culprit food allergen after egg and milk in infancy. Education regarding more aggressive use of epinephrine in the emergency setting is clearly needed. Recognition of age-related symptoms in anaphylaxis can aid physicians in prompt diagnosis and acute management.

Keywords: Anaphylaxis, Food allergy, Infancy, Vaccine

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http://doi.org/10.1016/j.waojou.2021.100605

Received 28 August 2021; Received in revised from 13 October 2021; Accepted 21 October 2021
Online publication date xxx

INTRODUCTION

Anaphylaxis is a serious, usually rapid onset, systemic hypersensitivity reaction that may cause death. Patients with anaphylaxis most commonly experience symptoms involving the skin or mucus, followed by respiratory and gastrointestinal symptoms, although some severe anaphylaxis events can occur without skin features or circulatory failure.[1,2] The estimated prevalence is 0.3%–5.1%, with the variation depending on the study methodologies, definitions and criteria used, and geographical regions.[3] The rates of anaphylaxis also vary among different age groups. Anaphylaxis has been highlighted in young children aged 0–4 years.[3] Unfortunately, recurrence of anaphylaxis reactions occurs in 26.5%–54.0% of patients.[4]

The organ involvement and triggers of anaphylaxis are related to different age groups. Respiratory presentations occur more commonly in children, while cardiovascular symptoms predominate in adults.[5] Anaphylaxis can be difficult to diagnose in younger age group (eg, 0–2 years) because infants cannot express the symptoms well and often have difficulties in recognizing them.[6] Although the trigger profiles for anaphylaxis are age-dependent and vary among different geographic areas, the key elicitors worldwide are foods, insect venoms, and drugs. Foods are the most culprit trigger of anaphylaxis in children.[7] In infants, cow's milk and egg are the most frequently reported foods allergens implicated in anaphylactic reactions worldwide, while the patterns of anaphylaxis triggers in older children and adolescents in Asian countries differ from those in Western countries. Wheat and buckwheat were the third most common food allergens after egg and milk in children in Asian countries such as Japan and Korea.[8–11] Meanwhile, in the United States and Europe, peanuts and tree nuts are reported to be the main food triggers in older children.

In China, there are relatively comprehensive retrospective data from a general hospital reflecting anaphylaxis in adolescent and adult patients, but the clinical profiles of anaphylaxis in young children are incomplete. Therefore, there is a need for data on the characteristics of anaphylaxis among young children. To understand the clinical profile of anaphylaxis in Chinese children, we summarized 279 anaphylactic reactions referred to a children's hospital. In this study, we sought to determine the age specific characteristics in the clinical presentation of anaphylaxis in Chinese children, thereby helping to facilitate prompt recognition and treatment at the emergency department and raise awareness to improve prevention.

METHODS

Collection of data

This was a retrospective study of children who experienced suspicious symptoms of anaphylaxis referred to specialized allergy department in a tertiary children's hospital for further diagnosis. Medical records were retrospectively analyzed to identify the patients who were diagnosed with "food allergy" (ICD code T78.101), "anaphylactic shock" (ICD code T78.201), "anaphylaxis" (ICD code T78.402) and "severe allergic reactions" (ICD code T78.402) from January 2014 to December 2020. After a pediatric allergy specialist confirmed whether the patients' record meets the diagnosis criteria of World Allergy Organization (WAO) 2020 criteria.[1] A total of 177 anaphylaxis patients who met the criteria were enrolled in this study. Supplement Fig. 1 showed the review flow chart. A detailed history was collected by allergists and composed of demographic data, clinical presentations, possible triggers, diagnostic test used to confirm the suspected trigger, acute management, and combined allergic disease. The patients were divided into 4 age groups: infants (0–2 years); preschoolers (3–6 years); school-age children (6–12 years); and adolescents (13–17 years).

Clinical diagnostic criteria and severity grading

Assessment of the outpatients with anaphylaxis was based on WAO 2020 criteria,[1] On the basis of current diagnostic criteria, anaphylaxis was defined as an acute allergic reaction involving more than 2 organ systems or life-threatening compromise in breathing and/or the circulation alone.

The severity of anaphylaxis was stratified into mild-moderate, or severe during a chart review,

severe or life-threatening anaphylaxis symptoms or signs included 1 or more of the following: hypoxia (Cyanosis or SpO_2,≤92%), hypotension (SBP <70 mmHg in infants (1 month-1 year), <70+(2 × age) mmHg in chidren (aged >1 to 10 ys), and <90 mmHg in patients aged >10 ys;) or neurologic compromise (confusion, collapse, or incontinence).

Identification of the trigger

Identification of a food as the trigger for anaphylaxis was based on an acute allergic reaction for which the onset was related to a known or suspected food allergen exposure. Serum levels of specific IgE (sIgE) testing (Phadia AB Uppsala, Sweden), and/or skin prick testing. The detection limit was defined as 0.35 kUA/L, according to the manufacturer's recommendations.[13] Skin tests were regarded positive if the mean wheal diameter was ≥3 mm at the prick test. Insects or drugs induced anaphylactic episodes were diagnosed mainly based on history without any tests. If the medical record did not suggest a potential trigger and allergen specific tests were negative, the episode was diagnosed as idiopathic.

Characteristics	patients, no (%)
Age of the first episode	
0-2 years	102 (57.6)
3-6 years	34 (19.2)
7-12 years	31 (17.5)
13-17 years	10 (5.6)
Gender	
Male	119 (67.2)
Atopy status (allergic comorbidities)	
AR/AC	44 (24.8)
AS/recurrent wheezing	61 (34.4)
AD	44 (24.8)
Family allergic diseases history	71 (40.1)
Episodes before referral	
1	106 (59.8)
2	49 (27.7)
3	16 (9.0)
4	5 (2.8)
5	1 (0.5)

Table 1. Characteristics of the 177 children with anaphylaxis.
Abbreviations: AR/AC, allergic rhinitis/conjunctivitis; AS, asthma; AD, atopic dermatitis

STATISTICS

All statistical analyses were performed with the SPSS 20.0 program (IBM Inc., Chicago, IL). A descriptive analysis was used for characterization of the study population. Continuous and categorical variables were described as median, interquarile range (IQR), comparison between the different children groups were performed using *t*-test, Pearson's chi squared test, or Fisher's exact test to compare frequencies of categorical variables. A P values < 0.05 was considered statistically significant.

RESULTS

General characteristics of the 177 children with anaphylaxis

Overall, 67.2% (119/177) of the patients were male.These enrolled children were stratified into 4 age groups based on the age of anaphylaxis onset (Table 1). The data revealed that 57.6% (102/177) of first anaphylactic episode occurred at the age group 0–2 years. Forty percent of the children had experienced >1 previous episode. In addition, 34.4% (61/177) had a history of asthma or recurrent wheezing, 24.8% (44/177) had a history of allergic rhinitis/conjunctivitis, and 24.8% (44/177) had a history of atopic dermatitis.

Triggers

The anaphylactic triggers for the 279 anaphylactic events were shown in Table 2 and Fig. 1. The triggers were able to be determined in 97.5% (272/279) of reactions. Foods were the most common causative agents (88.5%,247/279), followed by food + exercise/exercise (4.7%, 13/279) and drugs (4.3%,13/279). There was no case of insect venom-induced anaphylaxis. The

	Age, year, median (range)	Total, n = 279, n (%)	Age groups				
			0–2years (n = 140)	3–6 years (n = 64)	7–12years (n = 57)	13–17years (n = 18)	P value
Suspect triggers							
foods	4.2 (2 ms-15 years)	247 (88.5)	134 (95.7)	55 (85.9)	47 (82.5)	11 (61.1)	< 0.001
milk	3.3 (2 ms-8 years)	53 (19.0)	46 (32.9)	3 (4.7)	4 (7)	0 (0)	< 0.001
egg	1.4 (4 ms-13 years)	31 (11.1)	30 (21.4)	0 (0)	0 (0)	1 (5.6)	< 0.001
wheat	1.0 (5 ms-4 years)	30 (10.8)	29 (20.7)	1 (1.5)	0 (0)	0 (0)	< 0.001
buckwheat	5.6 (2–11 years)	12 (4.3)	2 (1.4)	7 (10.9)	3 (5.3)	0 (0)	0.014
corn	10 years	1 (0.4)	0 (0)	0 (0)	1 (1.8)	0 (0)	0.269
peanut	6.9 (7 ms-10 years)	4 (1.4)	1 (0.7)	0 (0)	3 (5.3)	0 (0)	0.02
nuts	5.0 (23 ms-13 years)	14 (5.0)	4 (2.9)	6 (9.4)	3 (5.3)	1 (5.6)	0.141
soybean	7.5 (2–11 years)	6 (2.2)	1 (0.7)	2 (3.1)	3 (5.3)	0 (0)	0.156
fruit and vegetable	6.5 (2–15 years)	50 (17.9)	8 (5.7)	23 (35.9)	18 (31.6)	1 (5.6)	< 0.001
seafoods	4.5 (8 ms-13 years)	13 (4.7)	7 (5)	3 (4.7)	2 (3.5)	1 (5.6)	0.973
spices	5.7 (3–8 years)	6 (2.2)	1 (0.7)	2 (3.1)	3 (5.3)	0 (0)	0.156
mix foods	5.2 (11 ms-13 years)	13 (4.7)	5 (3.6)	5 (7.8)	2 (3.5)	1 (5.6)	0.595
foods unclear	10.4 (4–15years)	14 (5.0)	0 (0)	3 (4.7)	5 (8.8)	6 (33.3)	< 0.001
foods + exercise/ exercise	12.3 (9–14 years)	13 (4.7)	0 (0)	1 (1.6)	7 (12.3)	5 (27.8)	< 0.001
drug	3.5 (3 ms-6 years)	12 (4.3)	6 (4.3)	6 (9.3)	0 (0)	0 (0)	0.062
idiopathic	8.6 (4–14 years)	7 (2.5)	0 (0)	2 (3.1)	3 (5.3)	2 (11.1)	**0.015**

Table 2. Triggers of the 279 anaphylactic reactions. *Fruits and vegetables include: peach (n = 9), pitaya (n = 6), mango (n = 6), lychee (n = 5), pear (n = 3), Physalis peruviana L (n = 2), longan (n = 2), apple (n = 2), melon (n = 1), rambutan (n = 2), orange (n = 1), blueberry (n = 1), cauliflower (n = 1), kiwifruit (n = 1), grape (n = 1), sea buckthorn (n = 1), and watermelon (n = 1), cherry (n = 1).Nuts include: walnut (n = 8), cashew nut (n = 3), pistachio nut (n = 2), almond (1), hazelnut (n = 2), not specified (n = 1).Mix foods represented that the offending foods may contain multiple potential allergens several food allergens, such as cake, cookies,pizza; food unclear represented the food triggers were not determined during chart review, such as the reactions occur just after a meal that may ingest several foods*

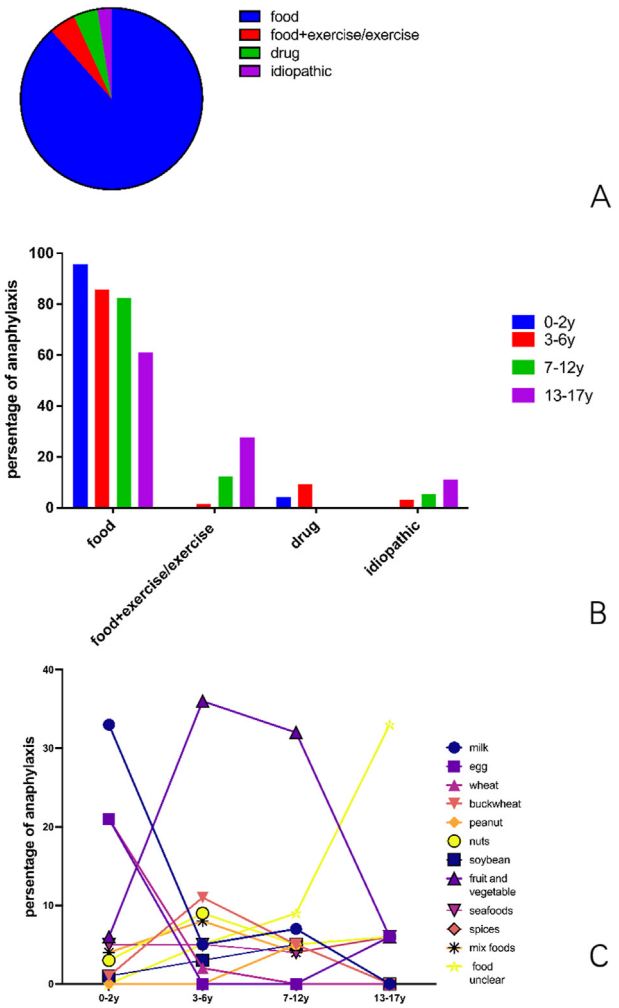

Fig. 1 The anaphylactic triggers for the 279 anaphylactic events. A. The anaphylactic triggers for the 279 anaphylactic events (food 88.5%, food + exercise/exercise 4.7%, drug 4.3%, idiopathic 2.5%); B. When analyzing the differences between triggers with regards to age groups, food-induced anaphylaxis were more common in the age group 0–2 years, while food + exercise/exercise-induced and idiopathic anaphylaxis were significantly higher in the age group 13–17 years; C. When comparing the differences between food causes with regards to age groups, milk, egg, and wheat were significantly more common in infants; Fruits/vegetables were significantly more frequent in children aged 3–6 years and children aged 7–12 years.

triggers were unable to be determined in 2.5% (7/279) of all reactions, which were classified as idiopathic. When analyzing the differences between triggers with regards to age groups, food-induced anaphylaxis was more common in the age group 0–2 years ((95.7%, 134/140) vs.(85.9%, 55/64) [p = 0.017], (82.5%,47/57) [p = 0.004], (61.1%,11/18) [p < 0.001]), while food + exercise/exercise-induced and idiopathic anaphylaxis were significantly higher in the age group 13–17 years.

Food triggers

The most frequently implicated foods were cow's milk (18.9%,53/279), fruits/vegetables (17.9%,50/279), egg (11.1%, 31/279), and wheat (10.8%,30/279). The most common fruit trigger was peach (n = 9), followed by pitaya (n = 6) and mango (n = 6), and the most common nut trigger was walnut (n = 8), followed by cashew nut (n = 3) and pistachio nut (n = 2). The culprit food allergens varied according to different age groups. Among infants, the most frequent food triggers were milk (32.9%,46/140), egg (21.4%,30/140), and wheat (20.7%,29/140) (Table 1). Among children aged 3–6 years, fruits and vegetables (35.9%,23/64), buckwheat (10.9%,7/64), and nuts (9.4%,6/64) were the most common offending food triggers (Fig. 1). Similar patterns were noted in school aged children aged 7–12 years (Fig. 1). When comparing the differences between food causes with regards to age groups, milk, egg, and wheat were significantly more common in infants (milk (32.9%, 46/140) vs. (4.7%, 3/64)[p < 0.001], (7%,4/57) [p < 0.001], (0%,0/18) [p < 0.001]; egg (21.4%,30/140)vs.(0%,0/64) [p < 0.001], (0%,0/57) [p < 0.001], (5.6%,1/18) [p < 0.001]; wheat (20.7%,29/140) vs. (1.5%,1/64)[p < 0.001], (0%,0/57) [p < 0.001], (0%,0/18) [p < 0.001]), while fruits/vegetables were significantly more frequent in children aged 3–6 years ((35.9%,23/64) vs.(5.7%,8/140)[p < 0.001], (5.6%,1/18) [p < 0.001]) and children aged 7–12 years (31.6%, 18/57) vs. (5.7%,8/140) [p < 0.001], 31.6% (18/57) vs. 5.6% (1/18) [p = 0.031]).

Drug triggers

The most frequently implicated drug triggers were vaccines (n = 5, comprising DTaP n = 2, group A + C meningococcal polysaccharide vaccine n = 1, Sabin vaccine n = 1, and not specified n = 1), followed by antibiotics (n = 4), probiotics (n = 1), and propofol (n = 1). Among the 5 vaccine-induced anaphylaxis patients, 4 had severe cow's milk allergy (Table 3). One patient with cow's milk allergy experienced severe anaphylaxis induced by lacidophilin tablets.

case	age(y)/ sex	history of allergy	symptoms of food allergy	drug triggers	Route of intramuscular	clinical reaction to drug	T-IgE(KU/L)	sIgE of food allergens (KUA/L)	sIgE of aeroallergens (KUA/L)
1	1/F	CMA	CMA:anaphylaxis	DTaP	intramuscular	Cyanosis, palpebral edema	237	cow's milk > 100, egg-0.71	T-IgE 237, cat dander-1.30, dog dander-11.5
2	2/M	CMA, wheat allergy, asthma	CMA:anaphylxsi; WA (wheat allergy):anaphylaxis	DTaP 、Group A + C Mening-ococcal Polysacc-haride Vaccine	intramuscular	DTaP: urticaria、wheezing, shortness of breath; Group A + C Meningococcal Polysaccharide Vaccine:cyanosis, breathing difficulty, urticaria	1756	cow's milk > 100,egg-14.3,wheat-36.9, peanut-2.89,soybean-9.68	T-IgE 1756, Der p-0.56, Der f-0.48KUA/L,Alternaria-0.36,cockroach-1.93, cat dander -4.84, dog dander-15.9, Artemisia vulgaris-1.49, Ambrosia elatior-2.59
3	2/F	CMA,AR	CMA:urticaria;	lacidophilin tablets	oral	breathing difficulty, urticaria	332	cow's milk-46.7, egg-12.7,wheat-0.79	T-IgE 332, cat dander-1.73, dog dander-6.40
4	3/M	CMA, egg allergy, soybean allergy, AD AS	CMA:anaphylaxis; soybean allergy: anaphylaxis; egg allergy:omitting	probiotics、propofol	Oral (probiotics) Intravenous (propofol)	probiotics: urticaria、wheezing; propofol: urticaria, wheezing	3223	egg-87.3,cow's milk- > 100,wheat-50.4,peanut-31.8,soybean-23.3,crab-1.14,shrimp-1.14;	T-IgE 3223, Der P-2.24, Der f-0.68, Aspergillus fumigatus-6.01, Alternaria-8, cat dander-17.7, dog dander-81.8, Ambrosia elatior-2.72, Artemisia vulgaris-11.1;
5	5/M	CMA, egg allergy	CMA:urticaria; egg allergy: urticaria	Sabin vaccine	intramuscular	loss of consciousness		unrecorded	unrecorded

Table 3. Characteristics of medication-induced anaphylaxis in five severe cow's milk allergy patients. *CMA: cow's milk allergy; DTaP: diphtheria, tetanus, and pertussis vaccine*

	Total n = 279,n (%)	0-2years (n = 140) infants	3-6 years (n = 64) preschool children	7-12years (n = 57) School-aged children	13-17years (n = 18) Adolescent	P value
Symptoms, n (%)						
Mucocutaneous	240 (86.0)	124 (88.6)	51 (79.7)	48 (84.2)	17 (94.4)	0.273
Hives	168 (60.2)	96 (77.4)	32 (50.0)	33 (57.9)	7 (38.9)	**0.016**
Itching	25 (9.0)	8 (6.5)	6 (0.9)	7 (12.3)	4 (22.2)	0.082
Redness/Rash	6 (2.1)	4 (3.2)	1 (1.6)	0 (0)	1 (5.6)	0.327
Angioedema	77 (27.6)	42 (33.9)	14 (21.9)	16 (28.1)	5 (27.8)	0.654
Oropharyngeal	33 (11.8)	16 (11.4)	12 (18.8)	3 (5.3)	2 (11.1)	0.143
Throat closing or swelling	22 (7.9)	10 (7.1)	8 (12.5)	2 (3.5)	2 (11.1)	0.249
Difficulty swallowing	1 (0.4)	1 (0.7)	0 (0)	0 (0)	0 (0)	1
Throat tingling or itching	7 (2.5)	3 (2.1)	3 (4.7)	1 (1.8)	0 (0)	0.484
Hoarseness	5 (1.8)	4 (2.9)	1 (1.6)	0 (0)	0 (0)	0.724
Respiratory	192 (68.8)	92 (65.7)	42 (65.6)	45 (78.9)	13 (72.2)	0.295
wheezing	69 (24.7)	30 (21.4)	16 (25)	**22** (**38.6**)	1 (5.6)	**0.017**
shortness of breath	44 (15.8)	13 (9.3)	12 (18.6)	**12** (**21.1**)	**7** (**38.9**)	**0.012**
Breathing difficulty	103 (36.9)	54 (38.5)	18 (28.1)	20 (35.1)	11 (61.1)	0.076
cough	51 (18.3)	28 (20.0)	12 (18.8)	11 (19.3)	0 (0)	0.179
Gastrointestinal	66 (23.7)	34 (24.3)	12 (18.8)	14 (24.6)	6 (33.3)	0.58
nausea	1 (0.4)	0 (0)	0 (0)	1 (1.8)	0 (0)	0.269
pain	34 (12.2)	3 (2.1)	10 (15.6)	8 (14.0)	**13** (**72.3**)	< 0.001
vomiting	39 (14.0)	**29** (**20.7**)	1 (1.6)	5 (8.8)	4 (22.2)	< 0.001
diarrhea	9 (3.2)	4 (2.9)	2 (3.1)	3 (5.3)	0 (0)	0.783
Cardiovascular	2 (0.7)	2 (1.4)	0 (0)	0 (0)	0 (0)	0.31
hypotension	2 (0.7)	2 (1.4)	0 (0)	0 (0)	0 (0)	0.31
Neurologic	29 (10.4)	17 (12.1)	4 (6.3)	6 (10.5)	2 (11.1)	0.851
persistent crying, restlessness	9 (3.2)	9 (6.4)	0 (0)	0 (0)	0 (0)	**0.028**
loss of consciousness/ Confusion	20 (7.2)	8 (5.7)	4 (6.3)	6 (10.5)	2 (11.1)	0.214
incontinence	1 (0.4)	1 (0.7)	0 (0)	0 (0)	0 (0)	1
severe anaphylaxis	31 (11.1)	16 (11.4)	8 (12.5)	5 (8.7)	3 (16.6)	0.845

Table 4. Symptoms of the 279 anaphylaxis events

Treatment	Total n = 225,n (%)	mild/ moderate,n = 196	severe reactions n = 29	P value
Treatment at home	85 (37.8)	80 (40.8)	5 (17.2)	**0.007**
Self-relief	31 (13.8)	28 (14.3)	3 (10.3)	0.377
Oral antihistamines	50 (22.2)	48 (24.5)	2 (6.9)	**0.018**
Nebulized β-agonist	6 (2.7)	6 (3.1)	0	0.419
Oral Montelukast	2 (0.9)	2 (1.0)	0	0.751
Treatment in ED	131 (58.2)	110 (56.1)	21 (72.4)	0.052
Epinephrine	21 (9.3)	14 (7.1)	7 (24.1)	**0.011**
Systemic corticosteroid	69 (30.7)	58 (29.6)	11 (37.9)	0.164
Antihistamines	39 (17.3)	32 (16.3)	6 (20.7)	0.243
Nebulized β-agonist	16 (7.1)	15 (7.7)	1 (3.4)	0.617
Oxygen Supplement	3 (1.3)	2 (1.0)	1 (3.4)	0.35
unclear	13 (5.8)	10 (5.1)	3 (10.3)	0.242
Hospitalization	5 (2.2)	3 (1.5)	2 (6.9)	0.133
Intensive Care	4 (1.8)	3 (1.5)	1 (3.4)	0.438

Table 5. Treatments administered in 225 anaphylaxis events

Food dependent exercise induced anaphylaxis (FDEIA) and exercise-induced anaphylaxis (EIA)

Seven patients (4.0%,7/177) experienced 13 anaphylaxis events during exercise, of whom 3 (42.9%, 3/7) had a history of asthma. The mean age was 12.3 years old (range, 9–14 years). Ten episodes (76.9%,10/13) occurred during exercise after meal; however the causative food was not determined.

Symptoms of anaphylaxis

Table 4 summarized the symptoms of anaphylaxis in which skin symptoms were most frequent (86.0%, 240/279), followed by respiratory system (68.8%,192/279), gastrointestinal tract (23.7%,66/279), oropharyngeal (11.8%,33/279), neurological (10.4%,29/279), and cardiovascular (0.7%,2/279). When analyzing different clinical patterns among age groups, infants had higher rates of hives ($p = 0.016$) and vomiting ($p < 0.001$), while wheezing was more common in school-age children ($p = 0.017$) and abdominal pain was more frequent in adolescents ($p < 0.001$). Thirty-one reactions (11.1%,31/279) presented as severe anaphylaxis, but there was no difference among the groups. In the infant group, 17 reactions (12.1%,17/140) presented with nonspecific neurologic symptoms, such as persistent crying/restlessness (6.4%,9/140).

Treatment of anaphylaxis

Table 5 and supplement Fig. 2 showed the treatments of the 225 anaphylactic episodes. Acute management were not accessible for 54 anaphylactic events. Among the 225 anaphylaxis with detailed management records, 13.8% (31/225) self-resolved, and 37.8% (85/225) were home-treated. Antihistamines were the most common medications, especially in mild to moderate reactions ($p = 0.018$). Fifty-two percent of the anaphylactic events were treated in the emergency department. Emergency treatment records were not available for 5.8% (13/225) of these reactions. Among the reactions with emergency treatment records, 30.7% (69/225)were received with glucocorticoids and only 9.3% (21/225) were treated with epinephrine, while 24.1% (7/29) of severe reactions were treated with epinephrine. Four patients needed intensive care.

Recurrent anaphylaxis

Seventy-one (40.1%,71/177) patients experienced recurrent anaphylaxis, recurrent reactions triggered by the same agent (foods n = 37, medication n = 1, exercise n = 1) in 54.9% (39/71) patients. Among the patients with food triggered recurrent anaphylaxis, milk was the most frequent cause (n = 8), followed by wheat (n = 6) and egg (n = 4).

DISCUSSION

In this study, we investigated the spectrum of clinical characteristics in children who experienced anaphylaxis to the allergy department of a large tertiary children's hospital, and found differences in the patterns of anaphylaxis among infants, preschool-age children, school-age children, and adolescents.

Anaphylaxis was increased in children especially in infancy. The incidence of anaphylaxis in young children aged 0–4 years old was nearly 3 times higher than that in older age groups.[3] Accordingly, in the present study, the peak of anaphylaxis occurred in children aged 0–2 years, with more than one-half (58%) of the patients with anaphylaxis referred to our department having their first anaphylactic episode under 2 years old. A variable range of rates were reported in previous studies. Huang et al[12] demonstrated that 3% of their patients with anaphylaxis were infants, a study conducted by Silva et al[13] which suggested this frequency as 18%, and a Singapore study showed a rate of 22.1%.[14] The diagnosis of anaphylaxis in infancy was difficult because of the ambiguity symptoms and unique-related characteristics, and this may contribute to the different percentage among the studies. Although a considerable variations was observed in the different studies, it is noteworthy that infants are high risk population of anaphylaxis. Further investigations should be done for prompt recognition of anaphylaxis in infants.

Foods were found to be the most frequent trigger of anaphylaxis in all age groups, especially younger age groups. In general, milk was the predominant food trigger, followed by fruits and vegetables, hen's egg and wheat. The offending food showed age-specific patterns. Similar to previous published studies, we confirmed that cow's milk and egg were key food triggers. These 2 foods were involved in 54.3% of the anaphylaxis events in infants. Unlike Western data where nuts were the third most frequent triggers in infants besides cow's milk and egg,[15,16] wheat was the third most common food cause in infants in the current study, consistent with previous studies in Japan suggesting that wheat was the third most common food trigger in Japanese children after egg and milk.[8,17,18] In Korea, wheat was the fourth key food allergen after egg, cow's milk, and walnut for infant anaphylaxis. A retrospective study on all food induced anaphylaxis patients recorded by the European Allergy Vigilance Network indicated that the main food triggers in infants were cow's milk (59%), hen's egg (20%), wheat (7%), and peanut (3%).[19] The onset age for wheat allergy in the majority was within 1 year old.[20] A study on a cohort of Thai children suggested that the onset of wheat allergy occurred very early in life, with 94% of wheat allergy patients developing their first reaction within the first year of life, and it was worth noting that the reactions occurred at their first introduction to wheat as a complementary food (90%).[21] Fruits/vegetables were the most common food allergens in preschool-age children and school-age children, consistent with previously published data in China stating that fruits and vegetables were the most common food triggers in children aged 4–9 years. A nationwide multi-center survey in the United States suggested that shellfish were common triggers in children aged >6 years.[22] Peanut and tree-nuts were common triggers in older preschool-age children based on data from the European Allergy Vigilance Network.[19] As such, the offending foods for food-triggered anaphylaxis and food allergies showed variable distributions because of differences in food cultures among countries. Differences in food triggers were correlation to not only genetic factor, local diets, and environments, but also differences in patient populations and study methods.

The proportion of drug-induced anaphylaxis in our study population was relatively low at only 4.3%, consistent with the frequency in a previous study in the Chinese population.[23] Studies based on emergency room and hospitalized patients

revealed that the frequency of drug-induced anaphylaxis ranged from 26.9% to 53%.[24–26] The low percentage of drug causes may be contribute to the fact that the patients included in this study were recruited from the outpatients in an allergy department rather than from hospitalized patients. In terms of drug triggers, and in contrast to previously published studies, it is noteworthy that vaccines were the most common drug triggers in the present study, especially among infants, followed by antibiotics. Recently, a study based on pharmacovigilance data demonstrated that antibiotics, injection of Traditional Chinese Medicine (TCM), and biologics were the top three drug triggers in Chinese children,[27] while studies in the Western countries like United States and countries in Europe found that antibiotics, particularly β-lactams and NSAIDs, were the main drug triggers. The higher rate of vaccine-induced anaphylaxis in the present study may be partially related to the fact that more than one-half of the study subjects were infants. Among the 5 vaccine-induced anaphylaxis patients, 4 had severe cow's milk allergy and the most frequent causative vaccine was DTaP. Case reports have described acute allergy reactions caused by DTaP vaccine in patients with cow's milk allergy,[28] potentially triggered by residual trace caseins in the culture medium. The oral Sabin vaccine may contain trace alpha-lactalbumin and its administration may cause allergic reactions in children with cow's milk allergy.[29] However, the vast majority of cow's milk allergic children receive these vaccines uneventfully. When milk allergen appears as an unintentional contaminant, the amount is variable and might elicit reactions only from some lots of medication or only in some exquisitely allergic patient.[30] Thus, no special precautions are required when administering vaccines to milk-allergic patients.[30,31] If a milk allergic patient suffer an allergic reaction to one of these vaccines, the possibility of milk protein contaminating the vaccine should be considered.[32]

There were no anaphylaxis events triggered by insect bites in the present study, consistent with published data in the Chinese population.[23] The data from China are notably lower than those in reports from Western countries. A study on Germany children and teenagers revealed that bee venom (24%) was the second most trigger of anaphylaxis.[33] A possible reason for the difference may be that patients with insect-induced anaphylaxis in China are preferentially referred to an emergency room for treatment, rather than an allergy department.

The 2 most common symptoms in the present study were mucocutaneous and respiratory tract, followed by gastrointestinal and neurological symptoms. In this study, children had lower frequency of cardiovascular system involvement and hypotension compared with published data for adults. Cardiovascular involvement possibly underdiagnosed because blood pressure is not generally measured.[6,34] However, given that our study was based on medical records, a record bias is also possible, because severe cases with cardiovascular involvement may be more frequently reported than mild to moderated cases. Previous studies also found age-related profiles in the clinical manifestation of anaphylaxis in Children.[15,35] Therefore, considering the age differences observed for anaphylaxis, clarification of the symptoms could facilitate early recognition and further prompt management of this potentially life-threatening reactions. Among the 4 age groups, we observed distinct differences for several symptoms. Hives, vomiting, and nonspecific neurological symptoms (eg, persistent crying, restlessness) had higher rate in infants than in older children, consistent with a previous report describing that hives, and neurological symptoms were more likely to be reported in infants.[19] The present study also supported the findings of another study in which not only hives but also vomiting were most commonly observed in children aged <2 years.[15] In our study, school-age children had more signs of wheezing, while adolescents experienced more symptoms of shortness of breath and abdominal pain. In contrast, a previous study noted that preschool-age children had more symptoms of stridor and wheezing.[15] We postulate that this difference arose because of the ability of adolescents to communicate their breathing discomfort compared with young children. Cardiovascular system involvement is rarely reported in young children, but may be under-diagnosed. We found that 1.4% of infants had cardiovascular

involvement, which was similar to the frequency of 2% for cardiovascular involvement in a cohort of 47 infants aged < 1 year with anaphylaxis.[36] However, the rate was much lower than those reported in other studies. For example, the rate was 8% in another cohort of 363 children aged 0–2 years who were diagnosed with anaphylaxis.[37]

Similar to the present study, under-use of epinephrine has been reported in previous studies.[38,39] As the first-line treatment for anaphylaxis, epinephrine is recommended by guidelines.[1] The low rate of epinephrine utilization and its lack of use as the first-line therapy in our study could be contribute to initial failure to recognize anaphylactic reactions or worrying adverse reactions associated with use of epinephrine. Clinicians should use epinephrine as a first-line management as soon as they make a diagnosis of anaphylaxis, because delayed epinephrine administration is associated with poor outcomes and a risk of hospitalization.[40,41]

Our study suggested that overuse of glucocorticoids was also the major problem besides underuse epinephrine in the emergency treatment of anaphylaxis. Previous published data in Chinese patients also demonstrated that there existed some critical gaps between actual treatment of anaphylaxis in China and international guidelines. In a review and analysis of 819 reported anaphylaxis cases in Chinese population, glucocorticoids (44.3%) was the most commonly used drugs,[39] and the percentage of glucocorticoids was 72% in another cohort of 907 Chinese patients.[23] The present study and previous published studies highlight that education and training on the initial treatment of anaphylaxis is strongly suggested for healthcare providers in China.

The present study has several weaknesses. Our review was performed in a single center. In addition, the data were collected retrospectively, and thus the diagnosis of anaphylaxis was made on the basis of reported information, rather than laboratory testing and challenge tests. Furthermore, our demographic data highlight the diverse population served by the hospital.

In summary, we observed age-related clinical profiles of anaphylaxis in the current study. Hives and vomiting were more commonly reported in infants, while certain respiratory symptoms were more frequently observed in preschool-age children. In addition, we found that cardiovascular symptoms were rarely reported in infants. The patterns of anaphylaxis triggers in older children and adolescents in Asian countries differ from those seen in European and other Western countries. Wheat was the third most common food allergen after egg and milk in infants. Hidden food allergens in medications can lead to unpredictable allergic reactions. Education regarding more aggressive use of epinephrine in the emergency setting is clearly needed. Recognition of age-related system involvement in anaphylaxis can aid allergists and emergency physicians in diagnosis and acute management.

Abbreviations

CMA: cow's milk allergy; DTaP: diphtheria, tetanus, and pertussis vaccine; NSAIDs: Non-steroidal Anti-inflammatory Drugs; AR/AC: allergic rhinitis/conjunctivitis; AS: asthma; AD: atopic dermatitis.

Authors contributions

Nannan Jiang analyzed and interpreted the data, and drafted the article.

Wei Xu made substantial contributions to acquisition of the cases.

Li Xiang made substantial contributions to conception and design, made major contributions to acquisition of the cases, and gave final approval of the version to be published.

Funding

This study was supported by Beijing Hospitals Authority Youth Programme, code:QML20201203.

Ethics approval

This study was approved by the ethics committee of Peking Union Medical College Hospital.

Availability of data and methods

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' consent for publication

All authors have approved the manuscript and agree with its submission to World Allergy Organization Journal.

Declaration of competing interest

All of authors report no competing interests or financial disclosure.

Acknowledgment
We are appreciate all the patients and investigators who participated in this study.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2021.100605.

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