

# A Multicenter Retrospective Case Study of Anaphylaxis Triggers by Age in Korean Children

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**Purpose:** Although anaphylaxis is recognized as an important, life-threatening condition, data are limited regarding its triggers in different age groups. We aimed to identify anaphylaxis triggers by age in Korean children. **Methods:** We performed a retrospective review of medical records for children diagnosed with anaphylaxis between 2009 and 2013 in 23 secondary or tertiary hospitals in South Korea. **Results:** A total of 991 cases (mean age = 5.89 ± 5.24) were reported, with 63.9% involving patients younger than 6 years of age and 66% involving male children. Food was the most common anaphylaxis trigger (74.7%), followed by drugs and radiocontrast media (10.7%), idiopathic factors (9.2%), and exercise (3.6%). The most common food allergen was milk (28.4%), followed by egg white (13.6%), walnut (8.0%), wheat (7.2%), buckwheat (6.5%), and peanut (6.2%). Milk and seafood were the most common anaphylaxis triggers in young and older children, respectively. Drug-triggered anaphylaxis was observed more frequently with increasing age, with antibiotics (34.9%) and nonsteroidal anti-inflammatory drugs (17.9%) being the most common causes. **Conclusions:** The most common anaphylaxis trigger in Korean children was food. Data on these triggers show that their relative frequency may vary by age.

**Key Words:** Anaphylaxis; children; epidemiology

## INTRODUCTION

Anaphylaxis is a severe, systemic allergic reaction typically caused by food, drugs, or insect venom. The lifetime prevalence

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of anaphylaxis from all triggers is estimated to be 0.05%-2%.<sup>1</sup> Although anaphylaxis is predominately a childhood condition, most studies reporting on the clinical features and causes have focused on adult or combined adult and pediatric populations.<sup>2-4</sup> Therefore, the prevalence and triggers of anaphylaxis in childhood cannot be assessed accurately because there are minimal pediatric data.

To date, drugs and insect stings are the most common anaphylaxis triggers in adults. By comparison, food is the most common cause in children.<sup>2,5-7</sup> For example, a retrospective review of 5 years of Australian emergency department charts revealed that food (85%), unknown (9%), drugs (6%), and insect stings (3%) were the principal agents responsible for anaphylaxis in children.<sup>2</sup> A separate study in the United States reported similar patterns.<sup>8</sup> While drugs and insect stings are more prevalent triggers for adolescents than for infants and young children,<sup>2</sup> insect stings are more likely to trigger large local reactions or urticaria than anaphylaxis in infants.

Few reports have investigated how the causes of anaphylaxis change throughout childhood. Therefore, we sought to better understand anaphylaxis triggers among different age groups of Korean children.

## MATERIALS AND METHODS

### Study design and participants

Data were collected retrospectively on patients under 18 years of age who were diagnosed with anaphylaxis between January 2009 and December 2013 in 23 secondary or tertiary pediatric allergy hospitals covering most major cities in South Korea. Using the International Statistical Classification of Diseases, 10th Revision (ICD-10) as a reference, T78.0 (anaphylactic reaction due to food), T78.2 (anaphylactic shock, unspecified), T80.5 (anaphylactic reaction due to serum), T63.4 (toxic effect of venom of other arthropods, labeled insect sting anaphylaxis for this study), and T88.6 (anaphylactic reaction due to adverse effect of correct drug or medicament properly administered) were selected as anaphylaxis-associated codes. Medical record reviews ensured that each anaphylaxis category met 2005 Anaphylaxis Symposium (AS) criteria.<sup>9</sup>

Demographic data, including age, sex, and personal and family histories of allergies, were collected. Laboratory results were examined (when available) to determine the anaphylaxis causes. Clinical manifestations of anaphylaxis were classified into 5 groups: cutaneous, respiratory, cardiovascular, gastrointestinal, and general. All symptoms were documented and investigated.

Laboratory data included the total and specific serum immunoglobulin E levels directed against trigger agents and skin prick and oral provocation test results. For patients who were simultaneously exposed to a variety of possible triggers and for whom no laboratory data were available, triggers were coded as

“unknown.”

All data were recorded in case report form and entered into a customized Microsoft Access database by a single pediatric allergist. The study was approved by the Institutional Review Board of each participating hospital.

### Triggers

The anaphylaxis triggers in this study were classified as food, drugs and radiocontrast media (RCM), exercise, insect stings, or idiopathic factors. Where possible, foods were also characterized more specifically as major food allergens based on the Food Allergen Labeling and Consumer Protection Act of 2004 (*e.g.*, peanuts, tree nuts, fish, eggs, soy, and shellfish, including crustacean or molluscan).<sup>10</sup> Records that implicated an unspecified seafood product were characterized as “seafood.” The “other food” category included items that were few in number and did not have a common category (*e.g.*, red ginseng, Cacao). Multiple component food items typically served hot (*e.g.*, pizza, hamburger, and ramen) were coded as “unspecified foods.” “Idiopathic factor” is generally diagnosed when no trigger can be identified despite a detailed history of the episode and a comprehensive evaluation. When more than 1 food item was reported or a specific food was not listed, the “idiopathic factor” category was also used. Taking a combination of medications was recorded as “unspecified drugs.”

### Comparisons by age group

Because anaphylaxis triggers differ between young children and adolescents, we analyzed them by 4 age groups based on developmental milestones: infants,  $\leq 2$  years; preschoolers, 3 to 6 years; school age children, 7 to 12 years; and adolescents, 13 to 18 years.

### Statistic analysis

Statistical analyses were performed using version 19.0 of SPSS for Windows (SPSS, Chicago, IL, USA). Taking a cross-sectional approach, this report is limited to raw, stratified descriptions of variables. Missing data were reduced by queries to the study centers. Sex, date of birth, and date of reaction formed the minimum set of information used as an inclusion criterion. Other data missing from a medical record were coded as missing variables.

## RESULTS

### Demographics

During the 5 years of the study period, a total of 991 pediatric anaphylaxis events occurred in the 23 South Korean secondary and tertiary pediatric allergy hospitals in this study. A high proportion of these events (66.0%) affected male patients. The mean age of the study subjects was 5.89 years ( $\pm 5.24$ ). Of the 991 study subjects, 363 (24.6%) were infants, 270 (27.2%) were

preschoolers, 191 (19.3%) were school age, and 167 (16.9%) were adolescents.

Food allergy (66.3%), atopic dermatitis (47.4%), asthma (24.6%), and allergic rhinitis (22.2%) were common comorbid allergic conditions in these patients. A family history of any allergic diseases was identified in 55.8% of patients for whom medical records were available (n=858). One hundred and ninety-eight (23.1%) had experienced recurrent episodes of anaphylaxis to the same allergen after the first anaphylaxis episode.

The number of events diagnosed annually gradually increased every year from 2009 to 2013 in all hospitals. Eighty-five events (8.6%) were diagnosed in 2009 followed by 117 (11.8%), 166 (16.8%), 262 (26.4%), and 361 (36.4%) in each subsequent year, respectively.

Food was the commonest trigger (74.7%), followed by drugs including RCM (10.7%), exercise (3.6%), insect stings (1.8%), and idiopathic factors (9.2%) (Table 1).

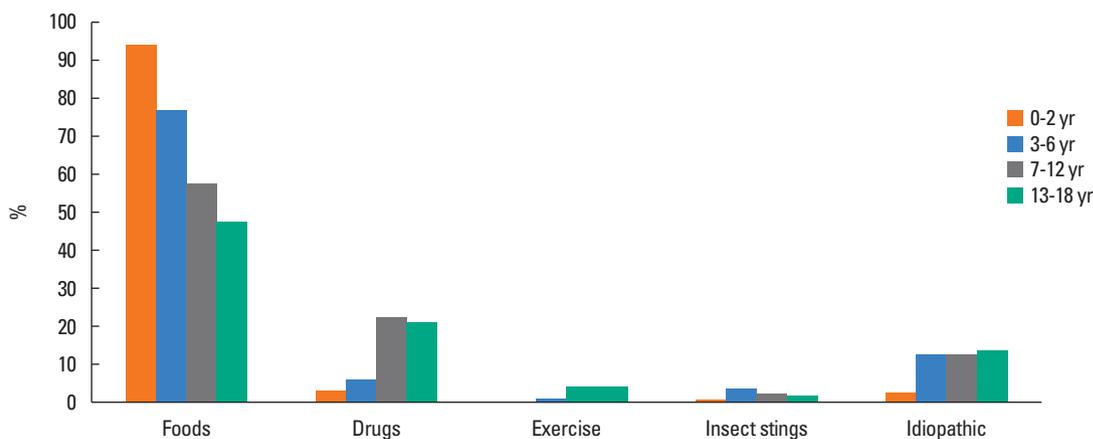
Food triggers occurred in significantly earlier age groups compared to drug triggers (mean age=4.66±4.72 years vs 9.65±4.74,  $P<0.05$ , Fig. 1). Although drug triggers were more prevalent with increasing age, food triggers were the most common cause of anaphylaxis in late childhood and adolescence.

#### Food triggers of anaphylaxis by age

In 740 food-induced anaphylaxis cases, milk (210 cases, 28.4%), egg white (101 cases, 13.6%), walnuts (59 cases, 8.0%), and wheat (53 cases, 7.2%) were the most frequent single food causes (Table 2). Tree nuts (13.2%) were the third most common food trigger group, which includes walnuts as the most common tree nut trigger, followed by pine nuts, cashews, and almonds. Food items reported <3 times in the study are not listed in detail, including other tree nuts (pecans, hazelnuts, sunflower seeds, macadamias, pistachios, and chestnuts), fruit (kiwi, peaches, apples, cherries, melon, jack fruit, and pineapples), cereals (sweet corn, oats, red beans, barley, and pota-

**Table 1.** Clinical characteristics of the study subjects

Characteristics	No. (%) (N=991)
Gender (male)	654 (66.0)
Age (year)	
0-2	363 (36.6)
3-6	270 (27.2)
7-12	191 (19.3)
13-18	167 (16.9)
Family history of allergic diseases	384/688 (55.8)
Past history of allergic diseases	
Asthma	220/896 (24.6)
Allergic rhinitis	276/911 (22.2)
Atopic dermatitis	447/914 (47.4)
Chronic urticarial	31/894 (3.5)
Food allergy	595/897 (66.3)
Drug allergy	48/875 (5.5)
Previous anaphylaxis history of same allergen	198/858 (23.1)
Symptoms	
Skin	952 (96.1)
Respiratory	842 (85.0)
Gastrointestinal	264 (26.6)
Neurologic	154 (15.5)
Cardiovascular	142 (14.3)
Occurrence year	
2009	85 (8.6)
2010	117 (11.8)
2011	166 (16.8)
2012	262 (26.4)
2013	361 (36.4)
Triggers	
Food	740/991 (74.7)
Drugs and radiocontrast media (RCM)	106/991 (10.7)
Idiopathic	91/991 (9.2)
Exercise	36/991 (3.6)
Insect stings	18/991 (1.8)



**Fig. 1.** Anaphylaxis triggers by age.

**Table 2.** Food triggers of anaphylaxis

Food	No. (%) (N=740)
Milk	210 (28.4)
Egg white	101 (13.6)
Peanut	46 (6.2)
Soy	10 (1.4)
Tree nuts	98 (13.2)
Walnut	59 (8)
Pine nuts	17 (2.3)
Cashew	6 (0.8)
Almond	4 (0.5)
Other tree nuts*	12 (1.6)
Wheat	53 (7.2)
Buckwheat	48 (6.5)
Crustacean	26 (3.5)
Shrimp	13 (1.8)
Crab	11 (1.5)
Shellfish	2 (0.3)
Fish	22 (3.0)
Other seafood (small octopus, squid)	6 (0.8)
Meat	23 (3.1)
Fruit	20 (2.7)
Kiwi	6 (0.8)
Peach	5 (0.7)
Other fruit <sup>†</sup>	9 (1.2)
Pupa	6 (0.8)
Cereals	7 (0.9)
Chinese yam	4 (0.5)
Others <sup>‡</sup>	9 (0.7)
Unspecified foods	51 (6.9)

\*Other tree nuts: pecans, hazelnuts, sunflower seeds, macadamia nuts, pistachios, and chestnuts; <sup>†</sup>Other fruits: apples, cherries, melons, jack fruit, and pineapples; <sup>‡</sup>Others: perilla, sesame, pumpkins, cacao, red ginseng, garlic, and goat milk.

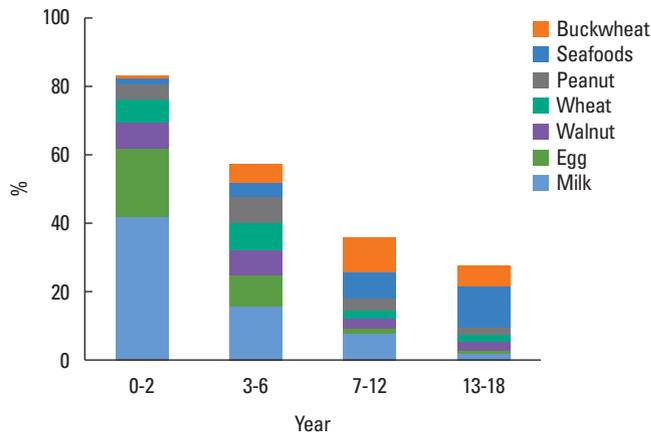
toes), and others (perilla, sesame, pumpkins, cacao, red ginseng, garlic, and goat milk). Pupa (0.8%) and Chinese yams (0.5%) were ranked among the least common triggers.

Food triggers differed by age group, with milk and seafood as the top triggers in age groups less than 6 years and greater than 7 years, respectively (Fig. 2). In patients less than 6 years of age, the most common triggers are milk, egg whites, walnuts, and wheat. In age groups with ages greater than 7 years, the common anaphylaxis triggers are buckwheat and seafood.

Table 3 shows the changes in specific food triggers over time. Frequencies of milk and tree nut-induced anaphylaxis showed a tendency to increase over time.

**Drug triggers of anaphylaxis by age**

The drug triggers were antibiotics (37 cases, 34.9%), nonsteroidal anti-inflammatory drugs (NSAIDs, 19 cases, 17.9%), vaccines (10 cases, 9.4%), and drugs and RCM (7 cases, 6.6%) (Ta-



**Fig. 2.** Food triggers of anaphylaxis by age.

**Table 3.** Changes in specific food triggers over time

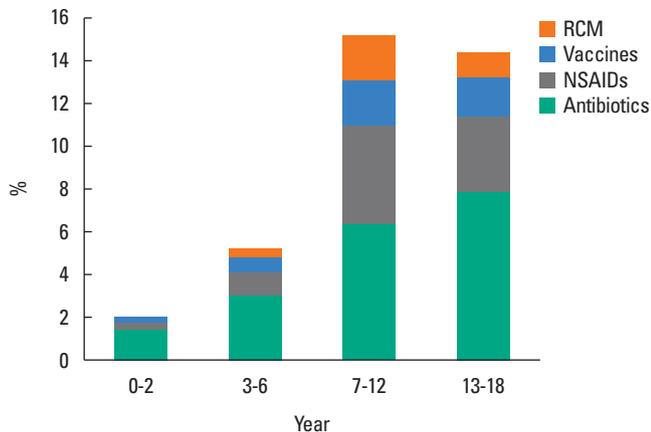
Allergens	No. (%)				
	2009 (n=85)	2010 (n=117)	2011 (n=166)	2012 (n=262)	2013 (n=361)
Milk	13 (15.3)	23 (19.7)	31 (18.7)	65 (24.8)	78 (21.6)
Egg white	7 (8.2)	8 (6.8)	15 (9.0)	32 (12.2)	39 (10.8)
Tree nuts	7 (8.2)	6 (5.1)	11 (6.6)	25 (9.5)	49 (13.6)
Wheat	6 (7.1)	7 (6.0)	11 (6.6)	9 (3.4)	20 (5.5)
Peanut	5 (6.9)	1 (0.9)	7 (4.2)	17 (6.5)	16 (4.4)
Buckwheat	5 (5.9)	12 (10.3)	7 (4.2)	9 (3.4)	15 (4.2)

**Table 4.** Drug triggers of anaphylaxis

Drug	No. (%) (N=106)
Antibiotics	37 (34.9)
Cephalosporins	24 (22.6)
Penicillin	8 (7.5)
Other antibiotics*	5 (4.7)
Nonsteroidal anti-inflammatory drugs	19 (17.9)
Vaccine	10 (9.4)
Influenza vaccine	7 (6.6)
Others vaccine <sup>†</sup>	3 (2.8)
Immunotherapy	3 (2.8)
Other drugs <sup>‡</sup>	14 (13.2)
Unspecified drugs	16 (15.1)
Radiocontrast media	7 (6.6)

\*Other antibiotics: macrolide and fucidate; <sup>†</sup>Other vaccines: DTP and human papillomavirus; <sup>‡</sup>Other drugs: idursulfase, rocuronium, acetaminophen, methylprednisolone, aspirin, lidocaine, remicade, and oxcarbazepine.

ble 4). Muscle relaxants, idursulfase, anticonvulsants, and lidocaine were each indicated <3 times in the study. Cephalosporins (24 cases, 22.6%) and the influenza vaccine (7 cases, 6.6%) were the most frequent causes of antibiotics and vaccine-in-



**Fig. 3.** Drug triggers of anaphylaxis by age. RCM, radiocontrast media; NSAIDs, nonsteroidal anti-inflammatory drugs.

duced anaphylaxis, respectively. Antibiotics were the most common drug triggers in all age groups. NSAIDs and RCMs were the more prevalent triggers in patients older than 7 years (Fig. 3).

## DISCUSSION

To our knowledge, this is the first nationwide study to investigate common triggers of anaphylaxis by age in children in Korea and throughout the rest of Asia. The pattern of allergens reported as triggers for anaphylaxis was rather different between age groups. Although food was the most common cause of anaphylaxis in childhood, the frequency of drugs as triggers increased with age. Among the food triggers, milk, egg white, walnut, and wheat were the most common causes of anaphylaxis in young children. In older children, seafood and buckwheat were the most likely triggers.

In the present study, the main causes of anaphylaxis were food (74.7%), drugs and RCM (10.7%), idiopathic factors (9.2%), exercise (3.6%), and insect stings (1.8%). These results are quite different from those of a recent study of anaphylaxis epidemiology in Korean adults, wherein most cases were induced by drugs (46.6%), food (24.2%), insect stings (16.5%), and exercise (5.9%).<sup>6</sup> As in this study, common anaphylaxis triggers for adults differed by age groups and geographical area. In Korean adults younger than 30 years old, food was the most common trigger, whereas drugs were the prime cause in patients older than 31 years. Seafood was the most common cause of food-induced anaphylaxis in Korean adults, and we found similar results in adolescents. Therefore, we suggest that seafood-induced anaphylaxis starts in adolescents and persists in young adulthood. This may partly reflect the fact that young children probably eat less seafood than adults in Korea.

In Western countries, milk and egg whites are described a frequent triggers of anaphylaxis in young children,<sup>7</sup> while in

school-age children, peanuts and tree nuts frequently trigger anaphylaxis.<sup>9</sup> In this study, milk and egg white were the most common triggers of food-induced anaphylaxis only in young children, while seafood and buckwheat were found to be triggers more often in adolescents. This may be explained by a natural desensitization that occurs in many infants and children with clinical reactivity to milk and egg whites.<sup>11,12</sup> For example, in a Danish study, 87% of subjects had recovered by 3 years of age and could tolerate.<sup>13</sup> Food-induced anaphylaxis is a severe reaction of food allergy. Therefore, change with prevalence of milk- and egg white- induced anaphylaxis in children might be associated with natural history of milk and egg white allergies.

Although milk and egg white allergies are common worldwide in early childhood, the emergence of other, common food allergens varies in different countries, reflecting diet habits, genetic background, and exposure to food allergens early in life. In this study, tree nuts (13.2%) were one of the most common foods causing anaphylaxis. Among 5,149 participants in a U.S. registry that mainly included children with parent-reported peanut and/or tree nut allergies, the most commonly reported tree nut allergies were walnut (34%), followed by cashew (20%), almond (15%), pecan (9%), pistachio (7%), and the other tree nuts (<5% each).<sup>14</sup> In a U.K. study, Brazil nuts was the most common tree nut allergen, followed by almonds, hazelnuts, and walnuts.<sup>15</sup> Although these other data did not report on anaphylaxis triggers, tree nut allergies are one of the leading causes of fatal allergic reactions, and their prevalence appears to be increasing.<sup>16</sup> The most likely tree nut to trigger allergic reactions may vary in different regions.

In this study, the most common tree nut triggers were walnuts, followed pine nuts, cashews, and almonds. Walnuts (8.0%) are a more prevalent cause of food-induced anaphylaxis than peanuts (6.2%) in this study. Although walnuts are one of the most frequent causes of food allergies and may induce fatal or near-fatal allergic reactions,<sup>14</sup> it is rarely reported as a trigger in Asia. For example, in Singapore (another Asian country), peanuts are the most common anaphylaxis trigger in preschool children.<sup>5</sup> In addition, our study demonstrated a higher prevalence of allergies to pupa, Chinese yam, and perilla compared to rates in Western countries.<sup>7,17</sup> These findings suggest that more Korean children have been exposed to pupa, Chinese yam, and perilla than children in other countries.

We found that frequencies of milk- and tree nut-induced anaphylaxis increase over time, possibly following changes in children's diets starting in early childhood. However, additional studies are needed to better understand connections between food triggers and diet patterns over time. For example, even among Asian children, common anaphylaxis food triggers vary by country. Some of these differences may be due to the availability of different types of food sources and variations in local dietary practice.

Drug triggers of anaphylaxis were caused by antibiotics,

NSAIDs, vaccines and drugs, and RCM. In Korean adults, NSAIDs are the most common drug allergens, followed by antibiotics and RCM.<sup>6</sup> In the present study, drug triggers were more common in school children compared to infants and preschoolers. When antibiotics and NSAIDs are prescribed in school children, the potential for causing anaphylaxis should be taken into account.

There were several limitations to this study. First, the retrospective nature of the medical record review may have resulted in some inaccurate diagnostic coding. Secondly, selection bias may be a factor because only patients who visited secondary or tertiary pediatric allergy hospitals were chosen to participate. These patients may have sought further diagnosis or treatment based on personal choice, such as accessibility. Thirdly, our sample may not reflect the general population of young patients with anaphylaxis because participating organizations were selected because they are centers with pediatric allergy specialists. Nevertheless, because of the large number of participating centers and subjects in this study, these results may have a sentinel role.

To our knowledge, this is the largest study to investigate the change in anaphylaxis triggers by age group in childhood. Understanding these trigger patterns may help understand the pathophysiology of food allergies.

In conclusion, the most common anaphylaxis trigger in Korean children was food, which differed for Korean adults. In addition, the prevalence of drug triggers in children increased by age. These results should help improve the knowledge base and clinical outcomes for individuals at risk for anaphylaxis, particularly for children, as well as community awareness of anaphylaxis as a potentially fatal medical disorder.

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