

Nationwide Survey of Hospitalization Due to Pediatric Food-Induced Anaphylaxis in the United States

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Objective: Anaphylaxis is a common, serious, systemic allergic reaction. In the United States, the change of annual hospitalization rates by anaphylaxis-trigger foods and risk factors associated with severity remain unclear.

Methods: Hospital discharge records of food-induced anaphylactic reactions of individuals younger than 20 years were obtained from Kids' Inpatient Database in 2006, 2009, and 2012 and were weighted to estimate the number of hospitalizations in the United States. We identified annual hospitalization rates by patients' characteristics and anaphylaxis-trigger foods and investigated factors associated with severity and use of mechanical ventilation with multivariable logistic regression.

Results: A total of 3427 hospitalizations were obtained, and annual hospitalization rates showed a significantly increasing trend from 1.2 per 100,000 children in 2006 to 1.5 per 100,000 children in 2012 ($P < 0.001$). The leading causes of hospitalizations due to food-induced anaphylaxis were peanuts (0.35–0.48 per 100,000 children), tree nuts and seeds (0.20–0.32 per 100,000 children), and milk products (0.09–0.13 per 100,000 children), with significantly increasing trends during 2006–2012. Milk products were significantly associated with severity (odds ratio [OR], 2.0; 95% confidence interval [CI], 1.3–2.9). Ages between 13 and 20 years (OR, 2.7; 95% CI, 1.4–5.1) and comorbidity of asthma (OR, 2.1; 95% CI, 1.3–3.4) were significantly associated with the use of mechanical ventilation.

Conclusions: The annual hospitalization rates in the entire United States showed an increasing trend during 2006–2012. The rates of peanuts, tree nuts and seeds, and milk products demonstrated upward trends. Milk products, ages between 13 and 20 years, and comorbidities of asthma were related to severity and morbidity.

Key Words: anaphylaxis, Kids' Inpatient Database, severity, ventilation

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Anaphylaxis is a serious, systemic allergic reaction that occurs suddenly after contact with or ingestion of allergy-causing substances.^{1–3} Food-induced anaphylaxis is one of the most important public health problems because allergic reactions may lead to serious complications and hospitalizations and may contribute to mortality particularly among patients with asthma.^{1–4}

The leading causes of anaphylactic reactions for children are foods, and the main anaphylaxis triggers among children in Europe and North America are peanuts, tree nuts, milk, eggs, fish, and shellfish.^{1,2,4} Previous studies suggested that hospitalizations because of anaphylaxis occurred in approximately 13% to 44% of children who presented to the emergency department with allergic

reactions,^{2,4} but the accuracy of the estimations in these reports is limited because of their relatively small sample sizes.^{2,4}

Large multicenter studies at the national level for hospitalizations due to pediatric allergic reactions are scarce.^{2,4–8} Recently, a nationwide survey of pediatric hospitalizations due to allergic reactions was conducted in Finland and Sweden,⁸ which reported characteristics of the hospitalizations with respect to age, sex, month, year, and country. In the United States, most previous studies had been conducted within 1 hospital catchment area or within 1 state for short periods.^{2,4–7} Recently, a study reported the US national trend of pediatric anaphylaxis with respect to age, sex, and race/ethnicity during 2000–2009.⁹ However, nothing is known about the US national trends of hospitalizations due to food-induced anaphylaxis with respect to anaphylaxis-trigger foods (peanuts, tree nuts and seeds, milk products, eggs, etc).

The present study investigated hospitalizations for food-induced anaphylaxis with respect to patient and hospital characteristics as well as anaphylaxis-trigger foods using nationally representative database in the United States. In addition, we analyzed factors that were associated with severity and use of mechanical ventilation.

METHODS

Study Population and Participation

We analyzed discharge record data about hospitalized patients younger than 20 years with food-induced anaphylaxis based on the national representative Kids' Inpatient Database (KID) for the years 2006, 2009, and 2012. The data of the KID were compiled by the Agency for Healthcare Research and Quality.^{10,11} The KID is a large national all-payer hospital pediatric discharge database. It is designed to generate robust national estimates of annual pediatric hospitalizations and to present hospital use, outcome, and cost for children 20 years or younger.^{10,11} The KID sampling frame was constructed based on all US short-term, non-federal, general, and specialty hospitals that had more than 3 million pediatric discharges from 38 states in 2006 and 44 states in 2009 and 2012 that participated in the Healthcare Cost and Utilization Project.^{10,11} Discharge-level weight variables (DISCWT) were provided with KID and used in this study to obtain the national estimates of hospitalizations in the United States.^{10,11}

Hospitalization discharge records were extracted from KID database in 2006, 2009, and 2012, and hospitalizations with food-induced anaphylactic reactions were identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* code (995.6x: anaphylactic reaction or shock due to food) in the primary diagnosis field. Food-induced anaphylactic reactions were subdivided into types of anaphylaxis-trigger foods using *ICD-9-CM* codes (peanuts: 995.60, tree nuts and seeds: 995.64, milk products: 995.67, eggs: 995.68, fish: 995.65, crustaceans: 995.62, and others: 995.60, 995.66, and 995.69). The discharge records were weighted to estimate the number of hospitalizations in the United States.

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Measurements of Variables

Patient characteristics included age categories (0–2, 3–6, 7–12, and 13–20 years), sex (male or female), race/ethnicity (black, Hispanic, white, Asian and Pacific Islanders, or others), primary payer information (private, Medicare/Medicaid, self-pay, or no insurance/information), and income quartiles for counties of residence for patient's ZIP Code (eg, very low is <\$39,000; low is \$39,000–\$47,999; high is \$48,000–\$62,999; and very high is >\$63,000 in 2012; detailed data are summarized in Supplement 1, <http://links.lww.com/PEC/A280>). Comorbidity of asthma was identified in secondary diagnosis fields using *ICD-9-CM* codes (493.xx).

Hospital characteristics consisted of hospital region (Northeast, Midwest, South, West), hospital type (urban teaching, urban nonteaching, or rural), and bed size (small, medium, or large). The definitions of bed size were different across the location of the hospital. For instance, in the Northeast region, hospital bed size was classified small if rural hospital had 1 to 49 beds, urban nonteaching hospital had 1 to 124 beds, or urban teaching hospital had fewer than 250 beds. The bed size was considered medium if rural hospital had 50 to 99 beds, urban nonteaching hospital had 125 to 199 beds, and urban teaching hospital had 250 to 424 beds. A large-size hospital could be defined by 100 beds or more for rural hospital, 200 beds or more for urban nonteaching hospital, and 425 beds or more for urban teaching hospital (see Supplement 2, <http://links.lww.com/PEC/A281>).

Outcomes

The outcomes of interest were annual hospitalization rates due to food-induced anaphylactic reactions by sex, race/ethnicity, and types of anaphylaxis-trigger foods with trend analyses between 2006 and 2012. Annual hospitalization rates were calculated: the number of hospitalizations due to food-induced anaphylaxis as the numerator and the population of each subgroup as the denominator derived from the US census in 2006, 2009, and 2012.^{12–15}

Severity of illness (minor, medium, major, or extreme) was captured from the hospitalization's All Patient Refined Drug-Related Groups (APR-DRG) code.¹⁶ The system of DRG was developed and used for Medicare as a prospective payment system to classify hospital cases into 1 of approximately 500 groups to have similar hospital resource use; APR-DRG is a refinement of the system, and it accounts for severity of illness and risk of mortality. We defined medium, major, or extreme of severity by APR-DRG as severe and mild of severity as nonsevere and investigated factors associated with severity. Use of noninvasive or invasive mechanical ventilation was identified using *ICD-9* procedure

codes (9390, 9670, 9671, 9672, 9604, and 9605) and Clinical Classifications Software code (216). We also analyzed factors related to use of mechanical ventilation.

Statistical Analysis

The number of hospitalizations by patient and hospital characteristics and types of trigger foods were calculated using DISCWT. We calculated 95% confidence intervals (CIs) for the annual incidence rates of hospitalizations, assuming a normal approximation to a Poisson distribution. We used χ^2 test for trend analyses for annual hospitalization rates between 2006 and 2012. We conducted univariable and multivariable logistic regressions with dichotomous outcomes to explain factors associated with severity and use of mechanical ventilation. Results were adjusted for covariates and were reported with 95% CIs. Two-sided $P < 0.05$ was considered statistically significant for all tests. Data were analyzed using STATA software version 14.1 (StataCorp LP, College Station, Tex).

RESULTS

We identified a total of 988 hospitalizations with food-induced anaphylaxis in 2006, 1113 hospitalizations in 2009, and 1326 in 2012 among children 20 years or younger in the United States using DISCWT. The patient characteristics of annual hospitalization rates by sex and race/ethnicity are summarized in Table 1 and Supplement 3, <http://links.lww.com/PEC/A282>. The total annual hospitalization rates significantly increased from 2006 to 2012 (from 1.15 to 1.53 per 100,000 children, $P < 0.001$). The hospitalization rates in boys were consistently higher than those in girls from 2006 to 2012 (0.66–1.76 per 100,000 children in boys, 0.48–1.28 per 100,000 children in girls during 2006–2012). The rates in both boys and girls showed significantly increasing trends ($P < 0.001$). The rates among Asian and Pacific Islanders and black children were greater than those among white and Hispanic children over the study period. The rates among all race/ethnicity categories showed significant upward trends (white, $P < 0.001$; black, $P < 0.001$; Hispanic, $P = 0.003$; Asian and Pacific Islander, $P < 0.001$).

Table 2 shows patient and hospital characteristics. Approximately 90% of patients hospitalized with food-induced anaphylaxis were covered by private insurance or Medicare/Medicaid. The proportions of children covered by private insurance decreased, whereas those covered by Medicare/Medicaid increased from 2006 to 2012. The Northeast region had the highest proportions of hospitalizations. The highest numbers of hospital

TABLE 1. Annual Hospitalization Rates (per 100,000 Children) With Respect to Sex and Race/Ethnicity With Trend Analyses

	2006		2009		2012		<i>P</i>
	Rate	95% CI	Rate	95% CI	Rate	95% CI	
Total	1.15	1.08–1.23	1.29	1.21–1.36	1.53	1.50–1.54	<0.001
Sex							
Male	0.66	0.59–0.74	1.09	1.00–1.20	1.76	1.64–1.89	<0.001
Female	0.48	0.41–0.55	0.70	0.62–0.86	1.28	1.17–1.39	<0.001
Race/ethnicity							
White	0.83	0.75–0.92	1.01	0.92–1.10	1.17	1.08–1.28	<0.001
Black	1.35	1.15–1.57	2.36	2.09–2.65	2.26	2.00–2.55	<0.001
Hispanic	0.75	0.63–0.89	1.05	0.91–1.21	1.05	0.92–1.20	0.003
Asian*	1.79	1.37–2.27	2.47	0.26–3.45	3.13	2.62–3.73	<0.001

*Asian and Pacific Islander.

TABLE 2. Characteristics of Patients and Hospitals by Geographic Location, Hospital Type and Size, and Distributions of Comorbidity of Asthma, Severity, and Use of Mechanical Ventilation

	2006		2009		2012	
	n	%	n	%	n	%
Total	988		1113		1326	
Primary payer information						
Medicare/Medicaid	253	25.6	319	28.6	487	36.7
Private	632	64.0	691	62.0	767	57.8
Others	101	10.2	104	9.3	72	5.4
Median household income quartiles for patient's ZIP Code						
Very low	234	24.7	245	23.0	305	23.0
Low	177	18.7	192	18.1	208	15.7
High	188	19.8	266	24.9	302	22.7
Very high	348	36.7	362	33.9	511	38.5
Hospital region						
Northeast	447	45.3	450	40.4	491	37.0
Midwest	160	16.2	178	16.0	206	15.5
South	182	18.4	211	18.9	264	20.0
West	199	20.1	274	24.6	366	27.6
Hospital type						
Urban teaching	726	74.4	808	75.7	1028	77.5
Urban nonteaching	197	20.2	223	21.0	260	19.6
Rural	53	5.4	35	3.3	38	2.9
Hospital size						
Small	133	13.6	151	2.5	146	11.0
Medium	346	35.4	313	29.3	329	24.8
Large	498	51.0	603	56.5	851	64.1
Comorbidity of asthma	279	28.2	361	32.5	452	34.1
Severe (APR-DRG code)	254	25.7	277	24.8	360	27.1
Mechanical ventilation	30	3.0	33	3.0	72	5.4

admissions due to anaphylaxis were urban teaching hospital with a large bed size.

Table 3 presents the annual hospitalization rates of food-induced anaphylaxis with respect to types of anaphylaxis-trigger foods. The leading causes of food-induced anaphylaxis were peanuts (0.35–0.48 per 100,000 children), tree nuts and seeds (0.20–0.32 per 100,000 children), and milk products (0.07–0.13 per 100,000 children) with significantly increasing trends (peanuts,

$P < 0.001$; tree nuts/seeds, $P < 0.001$; milk products, $P = 0.007$). The hospitalization rates associated with egg allergy showed a significantly decreasing trend from 0.07 per 100,000 in 2006 to 0.05 per 100,000 in 2012 ($P = 0.03$). The hospitalization rates associated with fish and crustaceans allergies were stable over the study period.

We investigated factors associated with severe conditions using multivariable logistic regressions (Table 4). In crude analysis, milk products (odds ratio [OR], 1.60; 95% CI, 1.1–2.3), crustaceans (OR, 1.8; 95% CI, 1.1–2.8), and others (OR, 1.7; 95% CI, 1.3–2.1) were significantly associated with severe conditions. After adjusting for age, asthma, and patient and hospital characteristics, the association between milk products and the severity remained significant (adjusted OR, 2.0; 95% CI, 1.3–3.0).

We conducted multivariable logistic regression to ascertain the relationship between age categories, comorbidity of asthma, milk products, and use of noninvasive or invasive mechanical ventilation. In crude analysis, age category of 13 to 20 years (OR, 2.5; 95% CI, 1.4–4.5) and comorbidity of asthma (OR, 2.2; 95% CI, 1.4–3.4) showed statistically significant results (Table 5). After adjusting for sex, race/ethnicity, median household income, and years in admission, age category of 13 to 20 years (OR, 2.3; 95% CI, 1.3–4.2) and comorbidity of asthma (OR, 2.2; 95% CI, 1.4–3.4) remained significant.

DISCUSSION

Annual hospitalization rates due to anaphylaxis significantly increased from 2006 to 2012. Hospitalized patients who were male, Hispanic, or Asian or lived in very high-income areas had higher annual hospitalization rates. Peanuts, tree nuts and seeds, and milk products were the leading causes of anaphylactic reactions resulting in hospitalizations with increasing trends. Milk products were significantly associated with severity. Furthermore, the highest age category (13–20 years) and the comorbidity of asthma were significantly associated with the use of mechanical ventilation.

Incidence and hospitalization rates for anaphylaxis were reported in many countries; however, large multicenter studies at the national level were scarce.^{3,5,7,17–20} Recently, a nationwide survey in Sweden and Finland during 1999–2011 revealed that the annual hospitalization rates ranged from 7.8 per 100,000 to 15.8 per 100,000 children in Finland and from 13.7 per 100,000 children to 31.8 per 100,000 children in Sweden.⁸ In addition, the trends in hospitalizations for food-induced anaphylaxis in US children during 2000–2009 were reported (0.60 per 1000 hospitalizations in 2000 to 1.26 per 1,000 hospitalizations in 2009).⁹

TABLE 3. Proportion of Food Products That Induced Anaphylactic Reaction, Comorbidity of Asthma, and Use of Noninvasive and Invasive Mechanical Ventilation

Food Products	2006		2009		2012		P
	Rate	95% CI	Rate	95% CI	Rate	95% CI	
Peanuts	0.35	0.31–0.39	0.38	0.34–0.42	0.48	0.44–0.53	<0.001
Tree nuts/seeds	0.20	0.17–0.23	0.24	0.21–0.28	0.32	0.28–0.36	<0.001
Milk products	0.09	0.07–0.11	0.09	0.07–0.12	0.13	0.11–0.16	0.007
Eggs	0.07	0.05–0.09	0.04	0.03–0.06	0.05	0.04–0.07	0.03
Fish	0.08	0.07–0.11	0.08	0.06–0.10	0.09	0.07–0.11	0.39
Crustaceans	0.04	0.03–0.05	0.05	0.03–0.06	0.04	0.03–0.06	0.55
Others*	0.29	0.26–0.33	0.36	0.32–0.40	0.36	0.33–0.41	0.01

*Allergic reaction due to unspecified, food additives, and other unspecified.

TABLE 4. Logistic Regression for the Association Between Food Products and Severity

Food Products	Crude			Adjusted (Age, Asthma)			Adjusted (Full*)		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Peanuts	—	—	—	—	—	—	—	—	—
Tree nuts/seeds	0.89	0.67–1.19	0.45	0.93	0.69–1.25	0.62	0.94	0.68–1.29	0.70
Milk products	1.60	1.13–2.28	0.009	1.91	1.32–2.76	0.001	1.98	1.33–2.94	0.001
Egg	1.05	0.63–1.73	0.86	1.32	0.78–2.24	0.30	1.21	0.69–2.11	0.50
Fish	1.04	0.65–1.65	0.88	0.98	0.60–1.58	0.93	0.82	0.49–1.37	0.46
Crustaceans	1.75	1.10–2.77	0.02	1.41	0.86–2.33	0.18	1.25	0.74–2.12	0.40
Fruits	1.31	0.79–2.18	0.29	1.25	0.74–2.09	0.40	1.10	0.64–1.88	0.73
Others†	1.66	1.30–2.11	<0.001	1.61	1.26–2.07	<0.001	1.65	1.27–2.14	<0.001

*Adjusted for age, sex, race/ethnicity, median household income, primary payer information, hospital size, location and type, comorbidity of asthma, and years.

†Allergic reaction due to unspecified, food additives, and other unspecified.

Our results also showed the similar increasing trend. However, the hospitalization rates in the United States were much lower than those in Finland and Sweden. There are several speculations to explain these differences. First, admission criteria for children who visited the emergency department with anaphylaxis may have been different across these countries. Second, the differences of the rates between Finland, Sweden, and the United States may reflect the difference in payment systems and costs of patient care because Sweden and Finland have National Health Insurance systems, and access to health care service in Sweden and Finland would have been better than that in the United States. In addition, the methodologies of data extraction in our study were different from those in the previous studies, which may have affected the results.

Our study found that male children had higher hospitalization rates than female children. This result is consistent with those reported by the majority of previous studies.^{18–21} A few studies have examined the effect of difference in race/ethnicity and socioeconomic status on the incidence and hospitalization rates due to anaphylaxis. One study from the United Kingdom showed that race/ethnicity had no effects on the incidence of admission due to anaphylaxis.^{21,22} In contrast, we and Rudders et al⁹ showed higher hospitalization rates among Asian, Pacific Islanders, and black children than those among white and Hispanic children in the United States. In addition, hospitalized children were more likely to live in higher median household income areas, which

may have reflected the better access to hospitals among children living in higher household income areas. Thus race/ethnicity and socioeconomic status may play important roles in hospitalizations due to food-induced anaphylaxis.

Few studies reported the national trends of hospitalizations focusing on types of anaphylaxis-trigger foods. We revealed the increasing trends of hospitalizations due to anaphylaxis induced by peanuts, tree nuts and seeds, and milk products. Although these foods are well known as the leading causes for food allergies in the United States, more attention would be required to prevent anaphylactic reactions among children especially allergic to peanuts, tree nuts and seeds, and milk products.

The association between peanuts consumption and the severity of anaphylaxis is still controversial. Only 1 study reported that peanuts caused more severe anaphylactic reactions than other foods, such as eggs and milk.^{19,23,24} However, our results showed that milk products were significantly associated with severity, whereas the other food types, including peanuts, were not associated with severity, after adjusting for potential confounders. Although no food product was associated with the use of mechanical ventilation, the number of use of mechanical ventilation was relatively small, and the power of the study was insufficient to reveal any association between the food types and the use of mechanical ventilation. Further studies are warranted to validate such association.

Teenage years and asthma were thought to be the most important risk factors for morbidity and mortality due to food-induced anaphylaxis.^{25–28} We found that the age category of 13 to 20 years and comorbidities of asthma were significantly associated with the use of mechanical ventilation. Hence, patients with food allergy who are teenagers and who have asthma need special attention for potential risk to develop severe conditions.

There are several limitations to our study. The number of hospitalizations and patients with comorbidity of asthma might have been underestimated because of possible miscoding or misclassification of anaphylaxis. Other food products that were not listed above could not be classified. The detailed clinical presentation, dose-response relationship between the amount of food consumed and severity of anaphylaxis, and laboratory data were unknown. Therefore, we could not adjust for the asthma-controller therapies and patient compliance. Patients may have been hospitalized several times, and we could not determine the recurrence rates. A unique feature of this study was the use of the KID, a national pediatric inpatient database, to examine hospitalizations due to food-induced anaphylactic reactions among children in the United States. Based on the KID, we were able to

TABLE 5. Logistic Regression to Investigate Factors Associated With Noninvasive or Invasive Mechanical Ventilation

Factors	Crude Analysis			Adjusted* Analysis		
	OR	95% CI	P	OR	95% CI	P
Age						
0–2 y	—	—	—	—	—	—
3–6 y	0.66	0.29–1.50	0.32	0.63	0.28–1.45	0.28
7–12 y	1.18	0.58–2.40	0.66	1.15	0.57–2.33	0.70
13–20 y	2.49	1.39–4.46	0.002	2.34	1.32–4.17	0.004
Asthma	2.17	1.40–3.37	0.001	2.15	1.38–3.35	0.001
Milk products	0.66	0.23–1.90	0.444	0.65	0.22–1.89	0.43

*Adjusted for sex, race/ethnicity, median household income, and years of admission.

calculate robust national estimates of features and burden of the hospitalizations due to food-induced anaphylactic reactions.

In summary, this study reported an increasing trend of annual hospitalization rates due to food-induced anaphylactic reactions and the effect of differences in sex, race/ethnicity, and socioeconomic status in the United States. Peanuts, tree nuts and seeds, and milk products demonstrated upward trends of the hospitalization rates. Clinicians should pay special attention for potential severity and morbidity in patients with allergy to milk products, who are teenagers, and who have asthma.

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