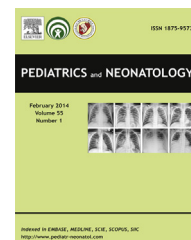


Available online at www.sciencedirect.com

ScienceDirect

journal homepage: <http://www.pediatr-neonatal.com>

ORIGINAL ARTICLE

Emergency Department Visits for Food Allergy in Taiwan: A Retrospective Study

Chan-Fai Chan ^{a,b}, Po-Hon Chen ^b, Ching-Feng Huang ^{c,d},
Tzee-Chung Wu ^{b,e,*}

^a Department of Pediatrics, National Yang-Ming University Hospital, Yilan, Taiwan

^b Division of Gastroenterology, Children's Medical Center, Taipei Veterans General Hospital, Taipei, Taiwan

^c Department of Pediatrics, Tri-service General Hospital, Taipei, Taiwan

^d National Defense University, Taiwan

^e School of Medicine, National Yang-Ming University, Taipei, Taiwan

Received Apr 15, 2013; received in revised form Nov 4, 2013; accepted Nov 26, 2013

Key Words

anaphylaxis;
emergency
department;
epinephrine;
food allergens;
food allergy

Background: Little is known about the characteristics of patients who visit the emergency department (ED) due to food allergy in Taiwan. This study aims to assess the triggers, clinical presentations, and management of patients presenting to a tertiary ED for food allergy.

Methods: This is a retrospective study of 369 visits presenting to the ED of Taipei Veterans General Hospital, Taipei, Taiwan for food allergy over a 2 year period. Patients' demographics, food allergens, presenting features, and management were addressed and analyzed. Adult and pediatric cases were also compared.

Results: The patients had an average age of 32.9 years [standard deviation (SD) $\pm$ 20.6]; the cohort was 66.9% adult and 53.7% male. Seafood (67.5%), fish (6.2%), and fruits (4.3%) were the major foods eliciting acute allergic reactions. Overall itchy mucocutaneous lesion was the most common presentation (85.6%), followed by anaphylaxis (12.2%), respiratory distress (1.4%), and anaphylactic shock (0.8%). Mucocutaneous involvement was more common in the pediatric population (92.6% vs. 82.2%, $p = 0.007$), whereas anaphylaxis was more prevalent in adults (15.4% vs. 5.7%, $p = 0.0068$). Antihistamines (98.6%) and systemic corticosteroids (63.1%) were commonly used medications. Only 2.2% of patients with anaphylaxis received epinephrine. The average duration in the ED was 1.6 hours (SD $\pm$ 1.8). No death was documented in the current study.

Conclusion: Seafood, fish, and fruits are common foods which cause acute allergic reactions in Taiwan. Although most food allergies are mild, anaphylactic shock still presents in about 1% of patients. Only a minority of patients with anaphylaxis receive epinephrine. As anaphylaxis may

* Corresponding author: Division of Gastroenterology, Children's Medical Center, Taipei Veterans General Hospital, Number 201, Shih-Pai Road, Section 2, Taipei 11217, Taiwan.

E-mail address: tcwu@vghtpe.gov.tw (T.-C. Wu).

be life-threatening, prompt education and use of an epinephrine auto-injector deserves further concern.

Copyright © 2014, Taiwan Pediatric Association. Published by Elsevier Taiwan LLC. All rights reserved.

1. Introduction

During the past decades the prevalence of food allergy has increased dramatically worldwide, making it an important public health issue.^{1–6} Although most food allergies cause minor symptoms, a small proportion of patients still suffer from potentially fatal reactions. In contrast to most published reports from Western countries, which demonstrated peanut and tree nuts to be the most common foods causing severe reactions,⁷ limited data revealed seafood to be the main cause of food-induced anaphylaxis in Asia.⁸ Patients with moderate-to-severe food allergies are often sent to a nearby emergency room. Better outcome depends on prompt recognition and timely management of these life-threatening reactions. Despite universal recommendations for the use of epinephrine in anaphylaxis, underuse of epinephrine has been widely reported.⁹ Currently, little is known about the characteristics of patients visiting the emergency department (ED) for food allergy in Taiwan. In order to improve the quality of health care, it is therefore necessary to investigate the common food allergens and current practice in the ED. The aim of this study is to assess the food triggers, clinical presentations, and management in patients presenting to a tertiary ED for food allergy in Taiwan.

2. Methods

2.1. Study design and population

This is a retrospective study over a 2 year period, from November 2009 to November 2011. Medical records of patients presenting to the ED of Taipei Veterans General Hospital, Taiwan, Taiwan with a clinical diagnosis of acute allergic reactions to food were reviewed. Charts were extracted using the International Classification of Disease, ninth revision (ICD-9) codes: 995.0 (other anaphylactic shock), 995.1 (angioneurotic edema), 995.3 (allergy, unspecified), 995.60 (allergy due to unspecified food), 995.61–995.69 (allergy due to specified food), 708.0 (allergic urticaria), and 708.9 (urticaria, unspecified). All medical records were reviewed thoroughly by two pediatricians who were experts in both gastroenterology and immunology. Special attention was paid to patients' previous food allergy history to help identify the cases of food allergy. Adverse reactions caused by food intolerance, food poisoning, food additive, drug, and insect bite were excluded from the study. Cases of possible food allergies where the food consumed was not mentioned were also excluded. For the patients who visited the ED more than once because of treatment failure or relapse symptoms, only one visit was counted to avoid overestimating the specific food allergen. Patients' demographics, eliciting foods, presenting features, treatment, and disposition, were recorded in detail. All edible aquatic

animals, except fish, were collectively referred to as seafood. Food allergens were classified as "mixed food" if more than one identifiable food was ingested. Clinical symptoms were sorted by four categories which included itchy mucocutaneous lesion (e.g., reddening, itching, urticaria, or angioedema), respiratory distress (e.g., wheezing, tachypnea, or dyspnea), anaphylaxis, and anaphylactic shock. The definition of anaphylaxis was involvement of two or more organ systems from the following: mucocutaneous, respiratory, cardiovascular, and gastrointestinal, as adopted from the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium.¹⁰ Anaphylactic shock was diagnosed when patients presented with signs of poor perfusion, such as hypotension plus delayed capillary refill, sudden collapse, syncope, or change of mental status, and requiring prompt resuscitation. The severity was further classified as mild (itchy mucocutaneous lesion), moderate (respiratory distress or anaphylaxis), and severe (anaphylactic shock). Eliciting foods, clinical features, and management of adult and pediatric cases were compared. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital.

2.2. Statistical analysis

The Chi-square test was used to compare between adults and children, and to investigate their independence from each other. A two-tailed $p < 0.05$ was considered a statistically significant difference.

3. Results

Over the 2 year study period, 369 visits to the ED (363 persons) were identified as having acute allergic reactions to food. There were 247 adults (66.9%) and 122 children aged < 19 years (33.1%). The median age of the patients was 32.9 years [standard deviation (SD) $\pm$ 20.6]. Eighty-five percent of the food allergies happened on the day when the food was ingested. Most patients suffered from the allergic reactions after lunch or dinner. Twenty-three percent of the cases had experienced a similar food allergy due to the same identified food in the past. Twenty-two percent of the participants performed Multiple Allergen Simultaneous Test (MAST) or ImmunoCAP at outpatient department follow up; however, only 5% got positive results. The cohort's information is shown in Table 1. Overall, seafood (67.5%), fish (6.2%), and fruits (4.3%) were the major food allergens encountered in our patients, accounting for nearly 80% of all eliciting foods. The three most common food allergens in the pediatric population were seafood (66.4%), fish (4.9%), and fruits (3.3%), followed by egg, nuts, milk, wheat, vegetables, and meat. The three most common food triggers in adults were seafood (68%), fish (6.9%), and fruits (4.9%),

Table 1 Demographic characteristics, medical history, clinical presentations, and management of patients.

	Overall	Adult	Children	<i>p</i>
Visits	369	247	122	
Demographics				
Age (y), mean $\pm$ SD	32.9 $\pm$ 20.6	42.8 $\pm$ 16.9	11 $\pm$ 5.4	
Male (%)	53.7	50.2	60.9	
Medical history				
Previous food allergy (%)	23.0	24.3	20.5	0.43
Drug allergy (%)	10	12.1	6.6	0.11
Clinical presentations				
Mucocutaneous lesion	316	203	113	0.007*
Reddening	1	1	0	
Itching	5	3	2	
Urticaria	305	195	110	
Urticaria + angioedema	5	4	1	
Respiratory distress	5	4	1	1
Dyspnea	5	4	1	
Anaphylaxis	45	38	7	0.0068*
Mucocutaneous + respiratory compromise	28	21	7	
Mucocutaneous + hypotension	8	8	0	
Mucocutaneous + persistent abdominal pain	9	9	0	
Anaphylactic shock	3	2	1	1
Management				
Antihistamine (oral/injection/both)	133 (43/21/69)	48 (5/1/42)	85 (38/20/27)	0.0001*
Antihistamine + hydrocortisone injection	231	196	35	0.0001*
Epinephrine injection	3	2	1	1
Oral prednisolone	2	1	1	0.55

* $p < 0.05$.

followed by milk, meat, vegetables, egg, and nuts. Seventeen percent of adults and 14.8% of children ingested two or more suspected food allergens prior to when the allergic reactions happened.

Overall, itchy mucocutaneous lesion was the most common presentation (85.6%), followed by anaphylaxis (12.2%), respiratory distress (1.4%), and anaphylactic shock (0.8%). Mucocutaneous involvement was more common in the pediatric population (92.6% vs. 82.2%, $p = 0.007$). Of the 45 patients suffering from anaphylaxis, 38 out of 247 (15.4%) were adults and seven of out 122 (5.7%) were children. Anaphylaxis was more prevalent in adults compared with children (15.4% vs. 5.7%, $p = 0.0068$; Figure 1). The frequency of other clinical symptoms was not significantly different between the two groups.

Moderate-to-severe reactions including respiratory distress, anaphylaxis, and anaphylactic shock comprised 14.3% of all food allergies. Sixty-two percent of patients with anaphylaxis presented with mucocutaneous lesion plus respiratory compromise. Foods causing these serious reactions in children included unspecified seafood and fish. Seafood (shrimp, crab), fish, and fruits (pineapple, kiwi, and persimmon) were documented to be responsible for these reactions in adults (Table 2). Although peanuts and nuts are important food allergens which cause anaphylaxis in Western countries, they only caused minor reactions in our study and all cases of anaphylactic shock were elicited by seafood.

Regarding treatment, most patients received antihistamines (98.6%), followed by systemic corticosteroids

(63.1%), bronchodilator inhalation (2.2%), and epinephrine injections (0.8%). No patient was given epinephrine inhalation. Single usage of antihistamines was prescribed to 85 pediatric patients and 48 adults, respectively, (69.7% vs. 19.4%, $p < 0.0001$). Up to 196 adults received antihistamines plus hydrocortisone injections, whereas only 35 children received such management (79.4% vs. 28.7%, $p < 0.0001$). All patients with anaphylactic shock received epinephrine injections, whereas only one (2.2%) out of the 45 patients with anaphylaxis received epinephrine injection. Among the 363 patients, five were admitted after initial management (1 persistent urticaria, 1 respiratory distress, 2 anaphylaxis, and 1 anaphylactic shock).

The overall average duration in the ED was 1.6 hours ($SD \pm 1.8$). Patients who suffered from anaphylaxis were observed in the ED for an average of 2.9 hours prior to discharge ($SD \pm 2.8$). No death was documented in our patients. Of the 363 persons, five revisited the ED for recurrent attack by the same food.

4. Discussion

To our knowledge this is the first study which was conducted in the ED to evaluate acute allergic reactions to food in Taiwan. Our study not only describes the clinical features of the patients, but also lists the possible food triggers in detail, especially for patients with moderate-to-severe allergic reactions. Many reports state that food is

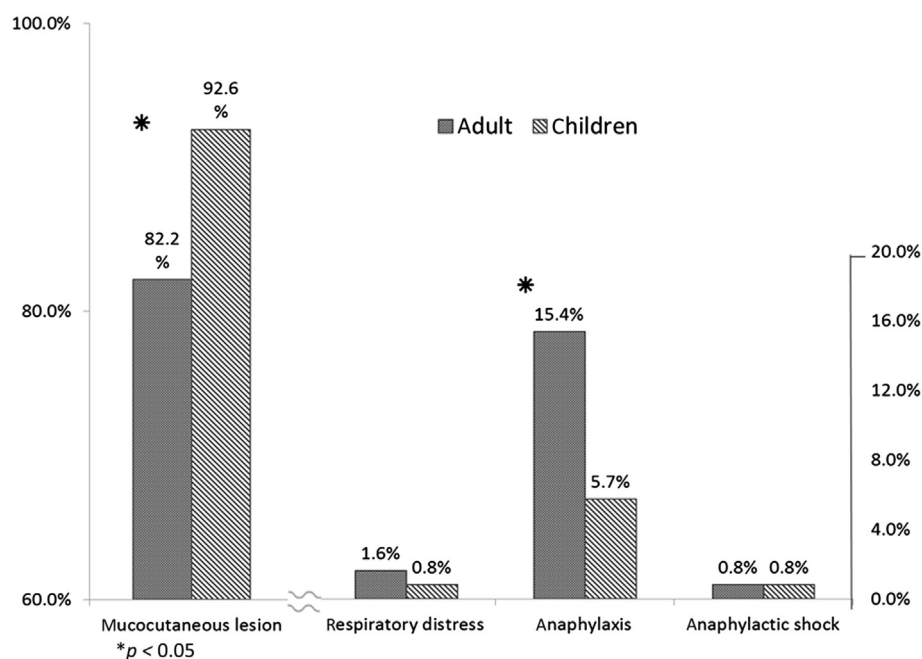


Figure 1 Distribution of clinical presentations in adults and children.

the leading cause of anaphylaxis and common food allergens differ between areas. In 2007, Oren et al¹¹ performed a review of medical records to evaluate patients who presented to the ED with food-induced anaphylaxis in US. Their study showed that among the 12 cases treated with epinephrine, nine were caused by peanut and tree nuts. A retrospective study conducted in New York, USA showed that peanut was the most common food allergen to cause anaphylaxis in hospitalized patients < 20 years old.¹² Uguz et al¹³ performed a questionnaire survey to assess allergic reactions to food in the UK in 2005. According to their results, nearly half of the severe food allergies were elicited by peanut and tree nuts. Data from Australia, Sweden, and Germany revealed similar results.^{14–16}

However, unlike those from most Western countries, our study showed that seafood and fish were mainly responsible for severe food allergies in Taiwan. Despite nuts being important food allergens to cause anaphylaxis in Western

countries, they caused minor reactions in our patients. These results were consistent with those of other Asian reports. One report from Hong Kong showed that nearly half of the cases of anaphylaxis presenting to the ED were elicited by food, 70% of which was seafood.¹⁷ Two studies from Thailand also found that seafood was the main cause of anaphylaxis.^{18,19} Wu et al⁸ published a nationwide questionnaire survey of food allergy in Taiwan in 2012. According to their results, seafood, especially shrimp and crab, was responsible for > 60% of all moderate-to-severe reactions.

Some suppose that different cultural backgrounds, dietary habits, and cooking methods account for the regional differences.^{20,21} As observed in two recent studies, maternal consumption of peanut during pregnancy seems to be associated with peanut sensitization.^{22,23} Although peanut allergy is not common as compared with Western countries, most Taiwanese women avoid peanuts during

Table 2 Types of food allergens and their correlation with clinical severity.

Foods	Adult			Children		
	Overall, n (%)	Mild	Moderate/severe	Overall, n (%)	Mild	Moderate/severe
Seafood	168 (68)	142	26	81 (66.4)	74	7
Fish	17 (6.9)	12	5	6 (4.9)	4	2
Fruit	12 (4.9)	9	3	4 (3.3)	4	0
Milk	2 (0.8)	2	0	2 (1.6)	2	0
Meat	2 (0.8)	2	0	1 (0.8)	1	0
Vegetable	2 (0.8)	2	0	2 (1.6)	2	0
Egg	1 (0.4)	1	0	3 (2.5)	3	0
Nut	1 (0.4)	1	0	3 (2.5)	3	0
Wheat	0 (0.4)	0	0	2 (1.6)	2	0
Mixed food	42 (17)	32	10	18 (14.8)	18	0
Total	247 (100)	203	44	122 (100)	113	9

pregnancy, wishing to protect their babies from peanut allergy. Peanuts are also typically dry-roasted in Western countries, whereas in Asia they are usually fried or boiled, which reduces the allergenic property of peanut proteins.^{24,25} Traditionally, most Taiwanese women drank lots of “peanut hoof soup” during lactation, as it is generally believed that this enhances breast milk production. We speculate that the avoidance of peanuts during pregnancy and early exposure to peanuts with reduced allergenicity through breast milk in young infants induce oral tolerance, but this remains to be determined.

Nearly 90% of our patients presented with mucocutaneous manifestation, which was the most common symptom in the present study. Isolated gastrointestinal involvement was not found in the study, which might be due to a lack of awareness from the ED physicians. We believe parts of the pediatric population present food allergy as gastrointestinal bleeding, namely milk protein-induced proctitis, which is not seen in adults. Despite most food allergies causing only minor reactions, 12% of our patients still suffered from anaphylaxis, mainly mucocutaneous involvement plus dyspnea. The incidence was lower than other reports.^{26,27} We believed that the true incidence was underestimated due to the underdiagnosis of anaphylaxis. Also, possible food allergies without record of food allergens were excluded. Our study showed that anaphylaxis was more prevalent in adults than in children, which may be due to repeated exposure to the causative food allergens in adults.

Current guidelines suggest prompt use of epinephrine in anaphylaxis and that delayed use leads to poor prognosis.^{28–30} Despite the universal recommendations, use of epinephrine in anaphylaxis is not common. For example, an 11 year retrospective review performed in Italy showed that only 15% of patients with anaphylaxis received epinephrine.³¹ Clark et al²⁶ conducted a multicenter study of food allergy with 678 ED patients. Half of the participants were identified as having severe allergic reactions, but only 24% received epinephrine. An online questionnaire performed by Jacobs et al²⁷ in the US showed that only 34% of suspected cases of food-induced anaphylaxis were given epinephrine. Another report by Russell et al³² revealed a higher percentage of epinephrine use in which half of the anaphylaxis patients received intramuscular epinephrine, either in a pre-hospital setting or during ED visits. This trend of epinephrine underuse was also illustrated in our study. Of the 45 patients who fulfilled the criteria of anaphylaxis, only 2.2% received epinephrine. This underuse may be due to physicians’ concern about the adverse effects of epinephrine. Also, there might be a lack of consensus among physicians and existing guidelines on how to appropriately manage patients at risk for anaphylaxis.³³ Most of our anaphylaxis patients received antihistamines and corticosteroids. However, usage of these drugs, either alone or in combination, cannot be a substitute for epinephrine’s life-saving role.³⁴

A convenient device used to treat anaphylaxis is the preload epinephrine auto-injector, namely the Epipen[®] (Mylan Inc.).³⁵ Currently, there are two fixed doses available, 0.15 mg and 0.30 mg. The 0.15 mg device is recommended for children whose weight is 15–25 kg, and the 0.30 mg for those > 25 kg, as well as adults.^{36,37} The optimal way to deliver epinephrine to children whose weight is < 15 kg has not yet been established. Prescribing

the exact dosage by drawing from an ampule, or empirically use the 0.15 mg device, are the two options for parents. Intramuscular injection into the lateral thigh (vastus lateralis muscle) is the preferred route in first-aid treatment. For up to 20% of patients with anaphylaxis, two doses of epinephrine are needed.^{38–40} Educating both patients at risk of anaphylaxis and their parents on how and when to use the epinephrine auto-injector is important.

Our patients stayed in the ED for an average of 1.6 hours prior to discharge. Those who suffered from anaphylaxis were observed for an average of 2.9 hours prior to being sent home. Because of the risk of biphasic reactions in anaphylaxis patients, prolonged observation of up to 12–24 hours should be considered.^{17,41}

Twenty-two percent of the participants performed MAST/CAP tests at OPD follow up; however, only 5% got positive results. The low positive rate may be due to lost follow up of the patients and longtime interval between the food allergy and laboratory test. Another possible reason is that some of the food allergens may not be included in the MAST/CAP tests used. According to the 2013 update of the world allergy organization anaphylaxis guidelines, the Ara h components in peanuts (especially Ara h 2), prebiotics galactooligosaccharides, orally ingested mites, gelatin, and Anisakis simplex were identified as new anaphylaxis triggers.⁴² More studies are needed to further determine the necessity of including these new food allergens in current allergen tests to help identify patients at risk of food allergy.

One possible limitation of our study is that this is a retrospective chart review which depends on accurate and complete documentation of the medical records. To overcome this, all charts were reviewed thoroughly by two pediatricians with expertise in both gastroenterology and immunology. Another limitation is the use of ICD-9 codes as the method to trace patients, as symptoms and signs may not be correctly coded. In order to include all food allergies, we reviewed not only the code for 995.60 (allergy due to unspecified food), 995.61–995.69 (allergy due to specified food), but also 995.0 (other anaphylactic shock), 995.1 (angioneurotic edema), 995.3 (allergy, unspecified), 708.0 (allergic urticaria), and 708.9 (urticaria, unspecified).

In conclusion, seafood, fish, and fruits are major food allergens causing acute allergic reactions in Taiwan. Although most food allergies are mild, anaphylactic shock still presents in about 1% of patients. Educating both patients at risk of these serious allergic reactions and their parents about how and when to use an epinephrine auto-injector is important.

Conflicts of interest

All authors declare no conflicts of interest.

Acknowledgments

This research was supported by grant V102C-110 from Taipei Veterans General Hospital, Taiwan. The authors would like to thank Li-Shu Wang, Children’s Medical Center, Taipei Veterans General Hospital, for field investigation and data statistical analysis.

References

1. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 2007;120:638–46.
2. Keil T. Epidemiology of food allergy: what's new? A critical appraisal of recent population-based studies. *Curr Opin Allergy Clin Immunol* 2007;7:259–63.
3. Branum AM, Lukacs SL. Food allergy among children in the United States. *Pediatrics* 2009;124:1549–55.
4. Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011;128:e9–17.
5. Soller L, Ben-Shoshan M, Harrington DW, Fragapane J, Joseph L, St Pierre Y, et al. Overall prevalence of self-reported food allergy in Canada. *J Allergy Clin Immunol* 2012;130:986–8.
6. Allen KJ, Koplin JJ. The epidemiology of IgE-mediated food allergy and anaphylaxis. *Immunol Allergy Clin North Am* 2012;32:35–50.
7. Järvinen KM. Food-induced anaphylaxis. *Curr Opin Allergy Clin Immunol* 2011;11:255–61.
8. Wu TC, Tsai TC, Huang CF, Chang FY, Lin CC, Huang IF, et al. Prevalence of food allergy in Taiwan: a questionnaire-based survey. *Intern Med J* 2012;42:1310–5.
9. Simons FE. Pharmacologic treatment of anaphylaxis: can the evidence base be strengthened? *Curr Opin Allergy Clin Immunol* 2010;10:384–93.
10. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson Jr NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391–7.
11. Oren E, Banerji A, Clark S, Camargo Jr CA. Food-induced anaphylaxis and repeated epinephrine treatments. *Ann Allergy Asthma Immunol* 2007;99:429–32.
12. Lin RY, Anderson AS, Shah SN, Nurruzzaman F. Increasing anaphylaxis hospitalizations in the first 2 decades of life: New York state, 1990–2006. *Ann Allergy Asthma Immunol* 2008;101:387–93.
13. Uguz A, Lack G, Pumphrey R, Ewan P, Warner J, Dick J, et al. Allergic reactions in the community: a questionnaire survey of members of the anaphylaxis campaign. *Clin Exp Allergy* 2005;35:746–50.
14. de Silva IL, Mehr SS, Tey D, Tang ML. Paediatric anaphylaxis: a 5 year retrospective review. *Allergy* 2008;63:1071–6.
15. Vetander M, Helander D, Flodström C, Ostblom E, Alfvén T, Ly DH, et al. Anaphylaxis and reactions to foods in children – a population-based case study of emergency department visits. *Clin Exp Allergy* 2012;42:568–77.
16. Beyer K, Eckermann O, Hompes S, Grabenhenrich L, Worm M. Anaphylaxis in an emergency setting - elicitors, therapy and incidence of severe allergic reactions. *Allergy* 2012;67:1451–6.
17. Smit DV, Cameron PA, Rainer TH. Anaphylaxis presentations to an emergency department in Hong Kong: incidence and predictors of biphasic reactions. *J Emerg Med* 2005;28:381–8.
18. Piromrat K, Chinratanasit S, Trathong S. Anaphylaxis in an emergency department: a 2-year study in a tertiary-care hospital. *Asian Pac J Allergy Immunol* 2008;26:121–8.
19. Techapornroong M, Akrawinhawong K, Cheungpasitporn W, Ruxrungtham K. Anaphylaxis: a ten years inpatient retrospective study. *Asian Pac J Allergy Immunol* 2010;28:262–9.
20. Woods RK, Abramson M, Bailey M, Walters EH. International prevalences of reported food allergies and intolerances. Comparisons arising from the European Community Respiratory Health Survey (ECRHS) 1991–1994. *Eur J Clin Nutr* 2001;55:298–304.
21. Shek LP, Lee BW. Food allergy in Asia. *Curr Opin Allergy Clin Immunol* 2006;6:197–201.
22. DesRoches A, Infante-Rivard C, Paradis L, Paradis J, Haddad E. Peanut allergy: is maternal transmission of antigens during pregnancy and breastfeeding a risk factor? *J Invest Allergol Clin Immunol* 2010;20:289–94.
23. Sicherer SH, Wood RA, Stablein D, Lindblad R, Burks AW, Liu AH, et al. Maternal consumption of peanut during pregnancy is associated with peanut sensitization in atopic infants. *J Allergy Clin Immunol* 2010;126:1191–7.
24. Beyer K, Morrow E, Li XM, Bardina L, Bannon GA, Burks AW, et al. Effects of cooking methods on peanut allergenicity. *J Allergy Clin Immunol* 2001;107:1077–81.
25. Maleki SJ, Viquez O, Jacks T, Dodo H, Champagne ET, Chung SY, et al. The major peanut allergen, Ara h 2, functions as a trypsin inhibitor, and roasting enhances this function. *J Allergy Clin Immunol* 2003;112:190–5.
26. Clark S, Bock SA, Gaeta TJ, Brenner BE, Cydulka RK, Camargo CA, et al. Multicenter study of emergency department visits for food allergies. *J Allergy Clin Immunol* 2004;113:347–52.
27. Jacobs TS, Greenhawt MJ, Hauswirth D, Mitchell L, Green TD. A survey study of index food-related allergic reactions and anaphylaxis management. *Pediatr Allergy Immunol* 2012;23:582–9.
28. Simons FE, Arduoso LR, Bilò MB, El-Gamal YM, Ledford DK, Ring J, et al. World Allergy Organization anaphylaxis guidelines: summary. *J Allergy Clin Immunol* 2011;127:587–93. e1–22.
29. Bock SA, Muñoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;107:191–3.
30. Bock SA, Muñoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001–2006. *J Allergy Clin Immunol* 2007;119:1016–8.
31. Cianferoni A, Novembre E, Mugnaini L, Lombardi E, Bernardini R, Pucci N, et al. Clinical features of acute anaphylaxis in patients admitted to a university hospital: an 11-year retrospective review (1985–1996). *Ann Allergy Asthma Immunol* 2001;87:27–32.
32. Russell S, Monroe K, Losek JD. Anaphylaxis management in the pediatric emergency department: opportunities for improvement. *Pediatr Emerg Care* 2010;26:71–6.
33. Kastner M, Harada L, Wasserman S. Gaps in anaphylaxis management at the level of physicians, patients, and the community: a systematic review of the literature. *Allergy* 2010;65:435–44.
34. Keet C. Recognition and management of food-induced anaphylaxis. *Pediatr Clin North Am* 2011;58:377–88.
35. Simons FE, World Allergy Organization. Epinephrine auto-injectors: first-aid treatment still out of reach for many at risk of anaphylaxis in the community. *Ann Allergy Asthma Immunol* 2009;102:403–9.
36. Sicherer SH, Simons FE, Section on Allergy and Immunology, American Academy of Pediatrics. Self-injectable epinephrine for first-aid management of anaphylaxis. *Pediatrics* 2007;119:638–46.
37. Simons FE. First-aid treatment of anaphylaxis to food: focus on epinephrine. *J Allergy Clin Immunol* 2004;113:837–44.
38. Rudders SA, Banerji A, Corel B, Clark S, Camargo Jr CA. Multicenter study of repeat epinephrine treatments for food-related anaphylaxis. *Pediatrics* 2010;125:e711–8.
39. Manivannan V, Campbell RL, Bellolio MF, Stead LG, Li JT, Decker WW. Factors associated with repeated use of epinephrine for the treatment of anaphylaxis. *Ann Allergy Asthma Immunol* 2009;103:395–400.

40. Järvinen KM, Sicherer SH, Sampson HA, Nowak-Wegrzyn A. Use of multiple doses of epinephrine in food-induced anaphylaxis in children. *J Allergy Clin Immunol* 2008;**122**:133–8.
41. Tole JW, Lieberman P. Biphasic anaphylaxis: review of incidence, clinical predictors, and observation recommendations. *Immunol Allergy Clin North Am* 2007;**27**:309–26.
42. Simons FE, Arduoso LR, Dimov V, Ebisawa M, El-Gamal YM, Lockey RF, et al. World allergy organization anaphylaxis guidelines: 2013 update of the evidence base. *Int Arch Allergy Immunol* 2013;**162**:193–204.