

Accidental allergic reactions in children allergic to cow's milk proteins

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Background: Cow's milk is the main cause of food allergy in children. Patients allergic to food frequently experience accidental exposure. There are few studies analyzing this problem, most of them concerning peanut allergy. **Objective:** We sought to calculate the frequency of accidental exposure reactions in children allergic to cow's milk during a 12-month period, to analyze the clinical characteristics and circumstances surrounding the reactions, and to identify risk factors for severe reactions.

Methods: Eighty-eight children allergic to cow's milk (44 boys; median age, 32.5 months) were included in the study. A systematized questionnaire about accidental exposure was used. Reactions were classified as mild, moderate, and severe. Cow's milk- and casein-specific IgE antibody titers were determined. **Results:** Thirty-five (40%) children had 53 reactions in the previous year (53% mild, 32% moderate, and 15% severe). Most reactions took place at home (47%) under daily life circumstances (85%). Specific IgE levels to cow's milk were higher in children with severe reactions than in those with moderate (median, 37.70 vs 7.71 KUA/L; $P = .04$) or mild (3.37 KUA/L; $P = .04$) reactions. The frequency of severe reactions was 10-fold higher in asthmatic children (odds ratio, 10.2; 95% CI, 1.13-91.54).

Conclusions: Reactions to accidental exposure are frequent in children with cow's milk allergy. The proportion of severe reactions was 15%. The risk factors for such reactions included very high levels of specific IgE to cow's milk and casein and asthma. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Cow's milk allergy, accidental exposure, accidental ingestion

Food allergy is an increasingly reported health problem that particularly affects children.¹ Cow's milk is one of the foods most frequently involved in this kind of allergy, with an incidence of 2% in the first year of life.²⁻⁴ Although most patients achieve tolerance in the first few years, in a recent study 21% of patients were still allergic to this food at the age of 16 years.⁵

Abbreviations used

AAR: Accidental allergic reaction
CMP: Cow's milk protein
sIgE: Specific IgE antibody

Cow's milk is widely consumed. It contains high-value biologic proteins and a high amount of calcium, making it an ideal nutrient for children. Milk is mainly consumed in its whole form, but milk proteins are also consumed in dairy products (eg, cheese, butter, and yogurt). There are also many products containing smaller amounts of cow's milk proteins (CMPs). The presence of milk in some products is well known by consumers, whereas in many others it is unknown and might be a hidden allergen.

The 2 features of broad consumption, mainly by infants, and the presence of milk in many commercial foods, often unknown by consumers, makes accidental allergic reactions (AARs) in children allergic to CMPs a common occurrence.⁶

Allergic reactions caused by accidental intake are a major concern. Quality of life of children, parents, and caretakers is affected, not only because of the possibility of experiencing such reactions but also because of the potential life-threatening risk the reactions might entail.^{7,8}

There are few studies about AARs in children with diagnosed food allergies. Those in the literature have focused mainly on patients allergic to nuts because of the severity of nut allergy.⁹⁻¹⁶

The aims of the study are 3-fold: (1) to ascertain the frequency of AARs in children with cow's milk allergy; (2) to analyze the severity and circumstances of these reactions and the kinds of products causing these reactions; and (3) to identify possible risk factors for potentially severe reactions.

METHODS

Subject population

A cross-sectional study was performed. All children 18 months or older who were given a diagnosis of IgE-mediated allergy to CMPs in our department, were on a milk- and milk derivatives-free diet, and presented for a regular clinic visit were included.

Diagnosis was made according to previously established criteria.¹⁷ Every child was evaluated in the first year of life (median age, 7 months; range, 1-12 months) because of immediate hypersensitivity reactions after intake of infant formulas. All had positive skin prick test responses to cow's milk, its proteins (α -lactalbumin, β -lactoglobulin, or casein), or both. An oral challenge test result was positive in 20 (23%) children, and the other 68 had specific IgE antibody (sIgE) levels of greater than 2.5 KUA/L (cutoff point with 90% positive predictive value), and thus the challenge test was not necessary.¹⁷

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A questionnaire about possible AARs experienced in the last year was administered by the physician. Clinical characteristics, places, and circumstances surrounding the reaction, treatment administered, and progression were recorded. All parents of children who participated in the study signed a written informed consent form that was previously approved by our institutional ethics committee.

AARs were defined as symptoms suggesting immediate hypersensitivity (cutaneous-mucosal: urticaria/angioedema, rash, and conjunctivitis; gastrointestinal: vomiting, abdominal pain, and diarrhea; respiratory: dyspnea, wheezing, cough, cyanosis, stridor, loss of voice, and rhinitis; and systemic: loss of consciousness, weakness, and dizziness), with acute onset that subsided in less than 24 hours.

Urticaria lasting more than 24 hours, reactions caused by intentional intake of milk or derivatives, reactions caused by skin contact with milk (except those exceeding the contact region or requiring treatment for their control), and AARs definitely related to other foods in children with several food allergies were not included as AARs in this study.

AAR severity was classified based on symptoms as mild, moderate, and severe, according to investigator-defined criteria. Mild reactions were those with cutaneous symptoms (angioedema excluded), rhinitis, or conjunctivitis. Moderate reactions included angioedema or gastrointestinal symptoms, which might or might not be associated with those considered mild. Severe reactions were those involving the lower respiratory tract (loss of voice, dyspnea, wheezing, stridor, and/or cyanosis) or systemic symptoms (loss of consciousness, weakness, or dizziness).

Serum specific IgE determination

Serum sIgE to cow's milk and casein (ImmunoCAP Specific IgE; Phadia AB, Uppsala, Sweden) was determined periodically, as clinically indicated, in the follow-up visits of these children.

Statistical analysis

The χ^2 test was used to calculate the association between qualitative variables, with the Fisher exact test used when the case number was less than 5 in any of the categories. The Mann-Whitney test was used to compare nonparametric numeric variables (age and serum total and specific IgE levels). The statistical calculations were carried out with the statistical program SPSS 12.0 (SPSS, Inc, Chicago, Ill).

RESULTS

Eighty-eight children (44 boys) were included over a 16-month period. At the time of the study, the median age was 32.5 months (range, 18-147 months). Forty (46%) children had atopic dermatitis, and 29 (33%) had asthma. Fifty children (57%) had other food allergies (egg, 47; seeds, 11; legumes, 8; and fish, 5).

Thirty-five (40%) children reported AARs during the year before the visit. Twenty-one children experienced only 1 AAR, 12 experienced 2 AARs, and 2 experienced 3 and 5 AARs, respectively. This accounted for a total of 53 reactions.

Twenty-two of the 53 children who did not report reactions within the previous year had them previously associated with a food, according to clinical records. This means that 57 (65%) children allergic to CMPs had AARs at some time in their lives related to a food.

Place and circumstances

Reactions took place at home in 25 (47%) cases, at a neighbor's home in 10 (19%) cases, at day care in 10 (19%) cases, at school in 3 (6%) cases, and at other places in 3 (6%) cases.

On 6 (11%) occasions, children were at a birthday party or some other kind of family celebration. Forty-five (85%) reactions took place under daily-life circumstances.

Kinds of products causing the reaction and exposure

Forty-four (83%) AARs were attributable to foods. Two reactions were caused by cosmetics. On 7 occasions, no suspected product was identified. Thirty-eight (83%) of the 46 identified products were packaged, 7 (15%) were sold without wrapping, and in 1 case packaging was not known. Exposure was due to ingestion in 39 (74%) AARs and skin or mucosal contact in 7 (13%) AARs.

Kind of food

Cow's milk in its original form or dairy products caused 15 AARs (cow's milk, 8; yogurt, 5; hydrolyzed infant formula, 1; and cheese, 1). In 29 reactions the causative foods were as follows: cold cuts, 8; biscuits or bread, 6; appetizers, 8; sweets, 2; chocolates, 2; ice cream, 2; and commercial vegetable purée, 1. In 13 of these products, milk or its proteins were specified on the labeling. In 1 case the cosmetic causing a reaction was found to contain milk.

In summary, 29 of the 46 identified products causing AARs were easily identifiable as milk containing, labels were not consulted in 10 cases, and milk was not specified to be contained in the products in 7 cases.

Symptoms of AARs

Symptoms at AARs are summarized in Table I. With regard to severity, 28 (53%) reactions were regarded as mild, 17 (32%) were regarded as moderate, and 8 (15%) were regarded as severe. Distribution was as follows: 17 (49%) children experienced mild reactions, 12 (34%) experienced moderate reactions, and 6 (17%) experienced severe reactions. Time from intake to onset of symptoms was less than 15 minutes in 40 (75%) reactions, 15 to 30 minutes in 2 (4%) reactions, 30 to 60 minutes in 1 (2%) reaction, and 60 to 120 minutes in 1 (2%) reaction. In 9 cases this information was not recorded.

Treatment

Thirty (57%) AARs required pharmacologic treatment: antihistamines in 27 (51%), systemic corticosteroids in 6 (11%), epinephrine in 4 (8%), and bronchodilator agents in 6 (11%). Seven reactions required treatment with more than 1 drug. Twenty-two (42%) AARs subsided spontaneously without treatment. In 1 case treatment was not recorded.

Place of treatment

Nineteen (63%) AARs were treated at the place of the reaction (13 at home and 6 at a day-care center). Eleven required emergency department assistance (7 at a general pediatrician's office and 4 at the emergency department of a hospital). Two of these latter children required hospital admission (one of them to the intensive care unit).

Progression

Most of reactions resolved either spontaneously or with treatment within a few hours. Thirty-three (62%) reactions resolved in less than 1 hour, and 17 (32%) resolved in 1 to 6 hours. In only 1 (2%) case did symptoms last between 7 and 24 hours. In 2 cases this information was not known.

TABLE I. Symptoms reported during AARs

	No.	Percent
Cutaneous-mucosal	49	92
Urticaria	37	
Perioral	23	
Other areas	14	
Angioedema	17	
Rash	4	
Conjunctivitis	4	
Respiratory	11	21
Shortness of breath	8	
Cough	7	
Wheezing	5	
Rhinitis	4	
Gastrointestinal	9	17
Vomiting	8	
Abdominal pain	3	
Diarrhea	1	
Systemic symptoms	3	6
Dizziness	2	
Weakness	1	
Only 1 organ	41	77
Two or more organs	12	23

Clinical characteristics of children with severe reactions

The clinical characteristics of children with severe reactions are summarized in Table II. Six children experienced 8 AARs. It is worth noting that children 4 and 5 had 2 potentially severe AARs in the last year. Five of 8 reactions took place at home, and 1 took place at a day-care center. All of them required emergency treatment; 2 children were admitted to the hospital, and 1 was admitted to the intensive care unit.

Specific IgE levels against milk and casein were greater than 24 KUA/L in 5 cases. Five of the 6 children had asthma.

Analysis of the association between AAR severity and risk factors

Table III summarizes the distribution of the AARs and the analyzed risk factors. Severity of AARs showed a clear association with levels of sIgE to cow's milk and casein. Median sIgE levels to cow's milk were greater in the group of children with severe AARs than in those with moderate reactions (37.70 vs 7.71 KUA/L, $P = .044$). This difference was even greater between the groups with severe and mild reactions (3.37 KUA/L, $P = .009$) or those who did not experience any reaction in the last year (3.89 KUA/L, $P = .004$). Analysis of data on sIgE levels to casein showed a similar association.

Another factor associated with potential severe reactions was asthma. The frequency of severe AARs compared with moderate, mild, or absent reactions was 10-fold higher in asthmatic children (odds ratio, 10.19; 95% CI, 1.13-91.54; $P = .022$).

A strong association was found between asthma and sIgE levels. Asthmatic children have higher titers of sIgE to cow's milk than nonasthmatic subjects (median, 21.85 vs 2.87 KUA/L; $P < .001$). A similar association was found for sIgE levels to casein (median, 13.45 vs 2.26 KUA/L; $P = .001$). The low number of children with severe AARs prevents an analysis of whether

asthma is an independent factor for having severe reactions or is just a modifier of the effect of sIgE levels. No statistically significant differences were found with other analyzed variables (ie, severity of the first reaction, atopic dermatitis, sex, age, or total serum IgE level).

DISCUSSION

Although AARs are frequent among children with food allergy, there are few studies on this topic. In this group of patients allergic to CMPs, the frequency of AARs over a period of 12 months was 40%. This figure is very high considering that only reactions in the last year were evaluated. The frequency might have been overestimated because of reactions caused by other foods or other eliciting factors that might have been reported. Excluding reactions lasting more than 24 hours and considering evidence of exposure to CMPs before the reaction makes this hypothesis less probable. On the other hand, there could have been recall bias, mainly in mild reactions, and thus the frequency of AARs could be even higher. The possible inclusion of AARs that occurred before the last 12 months is unlikely because this information is systematically collected at every annual visit. When the date of the reaction could not be accurately recorded, we checked that the reaction had not been registered in previous visits.

Accidental intake of foods depends on many factors. One factor could be the availability of commonly consumed foods, such as cow's milk. Exposure to fish, legumes, or seafood in children allergic to these foods is less likely because of lower availability. Yu et al⁹ calculated an annual incidence rate of 14.3% of accidental ingestion in a group of 252 Canadian children allergic to peanuts. Other studies carried out in North American children also allergic to peanuts found annual rates from 33% to 50%, and the rate at 5 years varied from 55% to 75%.^{10,14,15} In England data on the annual rate of AARs in children allergic to peanuts, nuts, or both decreased from 55% to 7% after implementation of an allergy management plan.¹⁶ The low rate of AARs in Canadian children might be due to strict legislation in the labeling of food products and higher awareness in schools.^{9,18}

Spanish regulations regarding food labeling follow European guidelines. When this study was carried out (2004-2005), every ingredient had to be indicated, but those "compound ingredients" present in less than 25% of manufactured products were excluded (this regulation does not apply for additives). Currently, legislation demands that manufacturers indicate the most allergenic foods, such as cow's milk or egg, regardless of the amount present in the final product. This measure will undoubtedly contribute to the decreased risk of accidental exposure to foods in allergic children.

Mild AARs comprised 53% of the total, followed by moderate (32%) and severe (15%) AARs. In studies in children allergic to peanuts, the proportion of mild AARs was lower (22% to 43%), but other kinds of reactions were more frequent and might be due to the nature of the allergen.^{9,19}

The most frequent route of exposure was oral. Six reactions were due to skin contact, and 1 reaction was caused by contact with the oral mucosa. The first reactions were mild or moderate (urticaria, 4; angioedema and rash, 2, with conjunctivitis associated with one of them) and resolved spontaneously in 3 cases, with oral antihistamine in 2 cases, and with antihistamine and steroids in 1 case. The reaction caused by mucosal exposure was severe (details are shown in Table II). Reactions caused by skin

TABLE II. Clinical characteristics of children with severe AARs

Patient no.	Age at diagnosis (mo)	Asthma	Other food allergies	Specific IgE antibodies (KUA/L)				Accidental allergic reactions							
				At diagnosis		At study		Age at AAR (y)	Product	Amount	Route of exposure	Time to onset (min)	Symptoms	Treatment	Place
				CM	Casein	CM	Casein								
1	5	Yes	Egg	2.15	2.77	>100	>100	25	CMP extense hydrolyzed	50 mL	Oral	<15	Vomiting, cough, dyspnea	β ₂ -Agonist	GP
2	7	No	No	49.9	77.9	8.88	6.66	39		Boiled ham	200 g	oral	15-30	Urticaria, AE, vomiting, diarrhea, abdominal pain, dyspnea, weak	Antihistamines
3	9	Yes	Egg, banana	17.0	21.6	50.6	42.8	91	Cow's milk	<1 mL	Oral	<15	AE, rhinitis, cough, dyspnea, abdominal pain	Ep, steroids, antihistamines, β ₂ -agonists	ICU 24 h
4	8	Yes	No	39.2	ND	26.6	24.3	34	Vegetables puree	~150 g	Oral	<15	AE, vomiting, cough, dyspnea, wheezing	Ep, steroids, antihistamines, β-agonists	24 h hospital admission
								35	Cosmetic	Unknown	Mucosal contact	<15	AE, rash, vomiting, cough, dyspnea, wheezing	Ep, steroids, antihistamines, β ₂ -agnoists, O ₂	ED
5	2	Yes	Egg	53.8	22.6	25.9	28.8	29	Cow's milk	<1 mL	Oral	<15	Cough, dyspnea, wheezing	Antihistamines, β ₂ -agonists	GP
								29	Cow's milk	<1 mL	Oral	<15	Cough, dyspnea, wheezing	Antihistamines, β ₂ -agonists, inhaled steroid	GP
6	8	Yes	No	15.9	15.8	48.8	48.9	34	Sausage	1-2 U	Oral	<15	urticaria, rhinitis, conjunctivitis, dyspnea, wheezing	None	GP

CM, Cow's milk; GP, general pediatrician; AE, angioedema; ED, emergency department; Ep, epinephrine; ICU, intensive care unit; ND, not done.

TABLE III. Analysis of association between AAR severity and risk factors

	No AAR	AAR severity			P value*
		Mild	Moderate	Severe	
Male sex, no. (%)	26 (49)	8 (47)	8 (67)	2 (33)	.676†
Age at study (mo)					
Median (P25-P75)	30 (26-41)	32 (26-41)	38 (30-43)	29 (32-62)	.115‡
Asthma, no. (%)	18 (34)	5 (29)	4 (33)	5 (83)	.022†
Atopic dermatitis, no. (%)	22 (42)	13 (76)	9 (75)	3 (50)	1.00†
Severity, first reaction, no. (%)					.342§
Mild	19 (36)	7 (41)	3 (25)	1 (17)	
Moderate	30 (57)	6 (35)	7 (58)	5 (83)	
Severe	4 (40)	4 (40)	2 (20)	0 (0)	
Total IgE (kU/L)					
Median	121	58	107	237	.131‡
P25-P75	43-304	20-187	47-287	94-407	
Range	7-2815	5-856	6-1603	76-574	
Cow's milk sIgE (kUA/L)					
Median	3.89	3.37	7.71¶	37.70#	.004‡
P25-P75	1.54-12.68	1.23-19.40	1.97-34.93	21.65-63.20	
Range	<0.35->100	<0.35->100	0.624->100	8.88->100	
Casein sIgE (kUA/L)					
Median	2.18**	2.76**	6.08††	35.80‡‡	.004‡
P25-P75	0.89-9.19	1.01-9.01	2.10-24.63	19.89-61.93	
Range	<0.35->100	<0.35->100	<0.35->100	6.66->100	

P, Percentile.

Mann-Whitney U test: #/¶P = .044; #/||P < .01; ‡‡/††P = .044; ‡‡/**P < .01.

*P value: comparison between severe AARs versus mild or moderate AARs or no reaction.

†Fisher test.

‡Mann-Whitney U test.

§ χ^2 Test.

contact are frequently reported in children highly sensitized to milk and peanuts.^{20,21} In some cases indirect contact with an object contaminated with minimal amounts of the involved food or just a kiss are enough to trigger a reaction. It is important that parents and caretakers are aware of this possibility to diminish the risk of AARs.^{22,23}

The high frequency of accidental exposure and the severity of some reactions underline the importance of avoiding AARs for parents of children allergic to CMPs. Identifying risk factors for severe reactions was one of the aims of this study. Of all analyzed factors, those associated with severe reactions were higher levels of sIgE to cow's milk and casein, as well as asthma. Serum titers of sIgE give us an idea of the intensity of the sensitization. It has been previously demonstrated that children with higher titers of sIgE against cow's milk, egg, and other foods are more likely to have symptoms after their ingestion.^{17,24-27} It has also been shown that lower levels of these antibodies predict a better outcome in the natural history of children allergic to cow's milk and egg.^{5,28,29} However, Summers et al³⁰ did not find an association between serum specific IgE concentrations and severity of the allergic reaction among patients allergic to peanuts and tree nuts. In addition, it is possible to have an anaphylactic reaction with a low sIgE level, and there is no sIgE level that can predict how severe a reaction can be.

In the present study sIgE levels against cow's milk and casein were greater than 24 KUA/L in 5 of the 6 children with severe reactions. This level is much higher than the median of the rest of the groups. Vander Leek et al¹⁰ previously reported that children presenting with only cutaneous symptoms had significantly lower levels of sIgE against peanuts than those with respiratory or gastrointestinal symptoms (median, 1.25 vs 11.65 KUA/L; $P = .004$).

Asthma is known to be a risk factor for anaphylaxis.^{30,31} Recently, Järvinen et al³² reported that children with food-induced anaphylaxis receiving multiple doses of epinephrine had asthma more often than children receiving a single dose. In our study group asthmatic children were found to experience severe reactions with a 10-fold higher frequency than children without asthma. This might indicate that the asthmatic response in the context of a severe anaphylactic reaction is more frequent in children who were previously given diagnoses of asthma. Results of this study of risk factors associated with severity should be cautiously interpreted because of the low number of severe reactions.

This study has helped us understand the high frequency of children with CMP allergy who have AARs. These reactions were severe in 17% of children, and in some cases hospital admission was necessary. Furthermore, in this group of patients, higher titers of sIgE against cow's milk and casein and concurrent asthma were found to be risk factors for severe reactions.

A joint effort will be needed to decrease the number and severity of AARs. This effort should involve health care professionals, allergists, and pediatricians who are aware of the problem; parents and caretakers to prevent accidental intakes; authorities to improve regulations regarding food labeling and to enforce them, as well as to encourage public awareness; and finally food manufacturers to provide precise information about the contents of their products.

Clinical implications: Awareness of AARs experienced by children with cow's milk allergy is essential to avoiding reactions, especially the most severe.

REFERENCES

1. Sampson HA. Update on food allergy. *J Allergy Clin Immunol* 2004;113:805-19.
2. Host A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. *Allergy* 1990;45:587-96.
3. Saarinen KM, Juntunen-Backman K, Jarvenpää AL, Kuitunen P, Løpe L, Renlund M, et al. Supplementary feeding in maternity hospitals and the risk of cow's milk allergy: a prospective study of 6209 infants. *J Allergy Clin Immunol* 1999;104:457-61.
4. García-Ara MC, Boyano-Martínez MT, Díaz-Pena JM, Martín-Muñoz F, Pascual-Marcos C, García-Sánchez G, et al. Incidencia de alergia a proteínas de leche de vaca en el primer año de vida y su repercusión en el consumo de hidrolizados. *An Pediatr (Barc)* 2003;58:100-5.
5. Skripak JM, Matsui EC, Mudd K, Wood RA. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2007;120:1172-7.
6. Levy Y, Segal N, Garty B, Danon YL. Lessons from the clinical course of IgE-mediated cow milk allergy in Israel. *Pediatr Allergy Immunol* 2007;18:589-93.
7. Östblom E, Egmar AC, Gardulf A, Lilja G, Wickman M. The impact of food hypersensitivity reported in 9-year-old children by their parents on health-related quality of life. *Allergy* 2008;63:211-8.
8. Primeau MN, Kagan R, Joseph L, Lim H, Dufresne C, Duffy C, et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. *Clin Exp Allergy* 2000;30:1135-43.
9. Yu JW, Kagan R, Verreault N, Nicolas N, Joseph L, St Pierre Y, et al. Accidental ingestions in children with peanut allergy. *J Allergy Clin Immunol* 2006;118:466-72.
10. Vander Leek TK, Liu AH, Stefanski K, Blacker B, Bock A. The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. *J Pediatr* 2000;137:749-55.
11. Furlong TJ, DeSimone J, Sicherer SH. Peanut and tree nut allergic reactions in restaurants and other food establishments. *J Allergy Clin Immunol* 2001;108:867-70.
12. Sicherer SH, Furlong TJ, DeSimone J, Sampson HA. The US Peanut and Tree Nut Allergy Registry: characteristics of reactions in schools and day care. *J Pediatr* 2001;138:560-5.
13. Sicherer SH, Furlong TJ, DeSimone J, Sampson HA. Self-reported allergic reactions to peanut on commercial airliners. *J Allergy Clin Immunol* 1999;104:186-9.
14. Bock SA, Atkins FM. The natural history of peanut allergy. *J Allergy Clin Immunol* 1989;83:900-4.
15. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanuts and tree nuts in children. *Pediatrics* 1998;102:e6.
16. Ewan PW, Clark AT. Efficacy of a management plan based on severity assessment in longitudinal and case-controlled studies of 747 children with nut allergy: proposal for good practice. *Clin Exp Allergy* 2005;35:751-6.
17. García-Ara C, Boyano-Martínez MT, Díaz-Pena JM, Martín-Muñoz F, Reche-Frutos M, Martín-Esteban M. Specific IgE levels in the diagnosis of immediate hypersensitivity to cow's milk protein in the infant. *J Allergy Clin Immunol* 2001;107:185-90.
18. Vadas P, Perelman B. Presence of undeclared peanut protein in chocolate bars imported from Europe. *J Food Prot* 2003;66:1932-4.
19. Mehl A, Wahn U, Niggemann B. Anaphylactic reactions in children—a questionnaire-based survey in Germany. *Allergy* 2005;60:1440-5.
20. Tan BM, Sher MR, Good RA, Bahna SL. Severe food allergies by skin contact. *Ann Allergy Asthma Immunol* 2001;86:583-6.
21. Bahna SL. Adverse food reactions by skin contact. *Allergy* 2004;59(Suppl 78):66-70.
22. Tkachyk SJ. Basketball urticaria/angioedema. *Can J Allergy Clin Immunol* 2000;5:6-7.
23. Hallett R, Haapanen L, Teuber SS. Food allergies and kissing. *N Engl J Med* 2002;346:1833.
24. García-Ara MC, Boyano-Martínez MT, Díaz-Pena JM, Martín-Muñoz MF, Martín-Esteban M. Cow's milk-specific immunoglobulin E levels as predictors of clinical reactivity in the follow-up of the cow's milk allergy infants. *Clin Exp Allergy* 2004;34:866-70.
25. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;107:891-6.
26. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;100:444-51.
27. Boyano-Martínez MT, García-Ara MC, Díaz-Pena JM, Muñoz FM, García-Sánchez G, Esteban MM. Validity of specific IgE antibodies in children with egg allergy. *Clin Exp Allergy* 2001;31:1464-9.
28. Savage JH, Matsui EC, Skripak JM, Wood RA. The natural history of egg allergy. *J Allergy Clin Immunol* 2007;120:1413-7.
29. Boyano-Martínez MT, García-Ara MC, Díaz-Pena JM, Martín-Esteban M. Prediction of tolerance on the basis of quantification of egg white-specific IgE antibodies in children with egg allergy. *J Allergy Clin Immunol* 2002;110:304-9.
30. Summers CW, Pumphrey RS, Woods CN, McDowell G, Pemberton PW, Arkwright PD. Factors predicting anaphylaxis to peanuts and tree nuts in patients referred to a specialist center. *J Allergy Clin Immunol* 2008;121:632-8.
31. Simons FER, Frew AJ, Ansotegui IJ, Bochner BS, Golden DBK, Filkelman FD, et al. Risk assessment in anaphylaxis: current and future approaches. *J Allergy Clin Immunol* 2007;120(suppl):S2-24.
32. Järvinen KM, Sicherer SH, Sampson HA, Nowak-Węgrzyn A. Use of multiple doses of epinephrine in food-induced anaphylaxis in children. *J Allergy Clin Immunol* 2008;122:133-8.