

FATAL AND NEAR-FATAL ANAPHYLACTIC REACTIONS TO FOOD IN CHILDREN AND ADOLESCENTS

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Abstract Background and Methods. Reports of fatal or near-fatal anaphylactic reactions to foods in children and adolescents are rare. We identified six children and adolescents who died of anaphylactic reactions to foods and seven others who nearly died and required intubation. All the cases but one occurred in one of three metropolitan areas over a period of 14 months. Our investigations included a review of emergency medical care reports, medical records, and depositions by witnesses to the events, as well as interviews with parents (and some patients).

Results. Of the 13 children and adolescents (age range, 2 to 17 years), 12 had asthma that was well controlled. All had known food allergies, but had unknowingly ingested the foods responsible for the reactions. The reactions were to peanuts (four patients), nuts

(six patients), eggs (one patient), and milk (two patients), all of which were contained in foods such as candy, cookies, and pastry. The six patients who died had symptoms within 3 to 30 minutes of the ingestion of the allergen, but only two received epinephrine in the first hour. All the patients who survived had symptoms within 5 minutes of allergen ingestion, and all but one received epinephrine within 30 minutes. The course of anaphylaxis was rapidly progressive and uniphasic in seven patients; biphasic, with a relatively symptom-free interval in three; and protracted in three, requiring intubation for 3 to 21 days.

Conclusions. Dangerous anaphylactic reactions to food occur in children and adolescents. The failure to recognize the severity of these reactions and to administer epinephrine promptly increases the risk of a fatal outcome. (N Engl J Med 1992;327:380-4.)

THERE are few reports in the medical literature of fatal or near-fatal anaphylactic reactions caused by food. There is no code for the diagnosis of food-induced anaphylaxis in the *International Classification of Diseases*, so it has been difficult to ascertain the incidence of fatal food-induced anaphylactic reactions. Before the recent survey of Yunginger et al.,¹ the medical literature consisted mainly of isolated case reports. Yunginger and coworkers described seven cases of fatal anaphylaxis due to food allergy that occurred over a period of 16 months. These reactions occurred primarily in adults who unknowingly ingested the allergen while eating away from home. Factors believed to have contributed to the fatal outcome included the patients' denial of symptoms, reliance on the use of oral antihistamines alone for treatment, and failure to administer epinephrine immediately after the onset of symptoms. We undertook a survey of severe food-induced anaphylactic reactions in children and adolescents.

METHODS

Over a 14-month period, 6 fatal and 7 near-fatal cases of food-induced anaphylaxis in children and adolescents were identified, 12 of which occurred in three metropolitan areas. The cases were made known to the investigators by physicians, the patients' parents, or (in two cases) local groups that distributed information about allergies. A near-fatal reaction was defined as an episode of anaphylaxis requiring admission to an intensive care unit for intubation, mechanical ventilation, and vasopressor support. Severe symptoms were defined as obvious respiratory distress, retractions, wheezing, and in some cases, cyanosis or loss of consciousness. Information regarding the reactions was obtained from ambulance and hospital records, statements or discussions with the persons and physicians

involved, and personal or telephone interviews with parents and, in some cases, the patients. The frequency of fatal or near-fatal food-induced anaphylactic reactions in children and adolescents was not addressed in this survey, since no systematic attempt was made to investigate all possible anaphylactic reactions related to food ingestion during this period.

Serum samples were obtained from one patient at autopsy (Patient 3), from one patient during a near-fatal reaction (Patient 12), and from three control patients with food-induced anaphylaxis who were admitted to an intensive care unit with angioedema, severe bronchospasm, hypoxia, hypotension, and loss of consciousness, but who did not require intubation. The samples were stored frozen at -20°C until they were analyzed for serum tryptase (analysis kindly performed by Dr. Larry Schwartz, Medical College of Virginia, Richmond). An increased level of serum tryptase, a neutral protease found almost exclusively in mast cells, is an excellent marker of mast-cell activation in anaphylactic reactions.² Multiple serum samples from two of the three control patients admitted to the intensive care unit and from Patient 12, who had near-fatal, protracted anaphylaxis, were also analyzed for tumor necrosis factor- α (TNF- α) by enzyme-linked immunosorbent assay (Genzyme, Cambridge, Mass.). The assay is highly specific and capable of detecting 12 pg of TNF- α per milliliter. TNF- α is secreted by a variety of cells and has been shown to be elevated in endotoxic shock.³

RESULTS

As shown in Table 1, the six fatal cases involved five girls and one boy, ranging in age from 2 to 16 years. Three patients reacted to peanuts, two to nuts, and one to eggs. The patients or their parents (in the case of Patient 4) were unaware that the allergens were present in the foods — a cupcake (Patient 1), a sandwich (Patient 2), a hamburger roll (Patient 4), and candy (Patients 3, 5, and 6) — that precipitated the reactions. Although five of the six children and adolescents had experienced definite allergic reactions to the incriminated food on previous occasions, none had had a near-fatal reaction. Three of the six (Patients 3, 4, and 5) were allergic to one or more foods in addition to the one that caused the fatal reactions. All the patients were considered highly atopic, with current or previous symptoms of asthma, allergic rhinitis, and atopic dermatitis. Asthma was considered

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Table 1. Characteristics of Patients Who Had Fatal Food-Induced Anaphylactic Reactions.

PATIENT No.	SEX	AGE (YR)	TYPE OF ATOPY	FOOD ALLERGY	PREVIOUS REACTIONS	AGE AT DIAGNOSIS	ASTHMA MEDICATIONS*
1	M	8	Asthma, allergic rhinitis, history of atopic dermatitis	Peanuts†	Yes, 5 yr earlier	18 mo	Cromolyn, β -adrenergic MDI
2	F	14	Asthma, allergic rhinitis, atopic dermatitis	Peanuts†	Yes, many years earlier	8 mo	Cromolyn, β -adrenergic MDI, beclomethasone MDI
3	F	15	Asthma, allergic rhinitis, atopic dermatitis	Cashews† Peanuts	? Yes, 2 wk earlier	18 mo	β -Adrenergic MDI, theophylline
4	F	2	Asthma, allergic rhinitis, atopic dermatitis	Eggs† Milk	Yes, 1 yr earlier Yes, 1 yr earlier	10 mo	Cromolyn, β -adrenergic MDI, theophylline
5	F	14	Asthma, allergic rhinitis, history of atopic dermatitis	Cashews† Walnuts Pecans	Yes, 6 mo earlier Yes, 6 mo earlier Yes, 6 mo earlier	5 yr	β -Adrenergic MDI
6	F	16	Asthma, allergic rhinitis, atopic dermatitis	Peanuts†	Yes, many years earlier	18 mo	β -Adrenergic MDI, cromolyn

*MDI denotes metered-dose inhaler.

†Cause of the anaphylactic reaction.

well controlled in all patients. In one patient (Patient 4), the dose of prednisone given for an acute exacerbation of asthma had been tapered to zero one week earlier. One patient (Patient 3) had received epinephrine and corticosteroids for an allergic reaction to food two weeks previously. During the week before the reaction, all patients received their standard asthma medications, and none had evidence of bronchospasm on the morning of the fatal reaction.

The seven nonfatal cases involved five girls and two boys, ranging in age from 9 to 17 years (Table 2). Four patients reacted to nuts, two to milk, and one to peanuts. In three cases the food allergen was contained in a cookie (Patients 8, 11, and 13), in three cases in a cake or pastry (Patients 7, 9, and 10), and in one case in cereal (Patient 12). Six of the seven patients had previously had definite reactions to the food in question, and one boy (Patient 10), who had been mistakenly identified as being allergic to peanuts, had had five previous near-fatal reactions. Five of the seven patients were allergic to one or more other foods. All the patients had asthma, and in all but one (Patient 13) it was considered to be well controlled with standard medications, and no evidence of bronchospasm was noted on the day of the reaction. Three patients had allergic rhinitis, and two had atopic dermatitis.

As shown in Table 3, five of the six fatal reactions occurred in public places: four took place at school and one at a local fair. In five of the cases, the patients initially reported oral and abdominal symptoms, especially a sensation of itching or tingling in the mouth, tightness in the throat, and abdominal cramping and vomiting; the sixth patient, a two-year-old child, was reported to be irritable. The symptoms began 3 to 30 minutes after the ingestion of the food and became severe between 20 minutes and 2.5 hours later. Only two patients received epinephrine within one hour of ingesting the allergen, and only one of them received it at the same time as the severe symptoms began. Three of the six children and adolescents appeared to be improving before the occurrence of terminal cardiorespiratory arrest. Severe respiratory distress developed in Patient 5, and she lost consciousness; after an initial response to supplemental oxygen, severe respiratory distress and loss of consciousness recurred, and she did not recover. All the patients received epinephrine and appropriate medical care once they reached a hospital emergency room, but by then all were unresponsive and had had extended hypoxia and hypotension.

All seven near-fatal reactions occurred in private

Table 2. Characteristics of Patients Who Had Near-Fatal Food-Induced Anaphylactic Reactions.

PATIENT No.	SEX	AGE (YR)	TYPE OF ATOPY	FOOD ALLERGY	PREVIOUS REACTIONS	AGE AT DIAGNOSIS	ASTHMA MEDICATIONS*
7	F	15	Asthma	Pecans Walnuts Filberts†	Yes, at 4 yr of age Yes, at 5 yr of age ?	4 yr 5 yr	β -Adrenergic MDI, beclomethasone MDI
8	F	17	Asthma, allergic rhinitis, atopic dermatitis	Walnuts† Peanuts	Yes, at 3 yr of age No	3 yr 1 yr‡	Cromolyn, β -adrenergic MDI, beclomethasone MDI
9	F	9	Asthma	Milk†	Yes, at 2 yr of age	1 yr	Theophylline, β -adrenergic MDI
10	M	9	Asthma, allergic rhinitis, atopic dermatitis	Watermelon Fish Filberts†	Yes (>6 reactions at various ages to all 3 foods)	4 yr	Theophylline, β -adrenergic MDI
11	F	12	Asthma, allergic rhinitis	Peanuts Brazil nuts†	Yes, at 9 yr of age Yes, 2 wk earlier	7 yr	Theophylline, β -adrenergic MDI
12	F	12	Asthma	Milk†	Yes, 4 mo earlier	6 mo	Cromolyn, beclomethasone MDI
13	M	13	Asthma, history of atopic dermatitis	Peanuts† Fish	Yes, 3 mo earlier —	7 yr	Theophylline, β -adrenergic MDI

*MDI denotes metered-dose inhaler.

†Cause of the anaphylactic reaction.

‡Diagnosed by skin-prick test.

homes rather than in school, although only two occurred in the patients' own homes (Table 4). The symptoms began one to five minutes after the ingestion of the allergen and consisted of a sensation of itching and tingling in the mouth, tightness in the throat, nausea and vomiting (in three patients), and urticaria (in five patients). Generalized urticaria developed in Patient 8 before severe symptoms began, and mild angioedema developed in Patient 13. Severe symptoms developed within 12 to 130 minutes of the ingestion of the allergen in the children and adolescents, although Patient 8 initially had profuse vomiting and then felt well for 90 minutes before urticaria and severe wheezing developed. No patient received epinephrine when the initial symptoms appeared. However, four patients received epinephrine 5 to 55 minutes before the onset of severe symptoms, and three received it within 5 minutes after the onset of severe symptoms. Three patients (Patients 7, 9, and 11) improved temporarily after an injection of epinephrine. One patient (Patient 12) appeared to be doing well and was extubated after three hours, only to be reintubated two hours later, when severe bronchospasm and hypotension recurred. All patients were conscious or had been unconscious for less than five minutes when they reached the emergency room, where they received epinephrine and appropriate vasopressor medications and were intubated. Four patients underwent mechanical ventilation for 2 to 14 hours, and three for 3 days to 3 weeks.

In a previous report of anaphylaxis in 25 patients, three distinct clinical patterns were observed: uniphasic, biphasic, and protracted anaphylaxis.⁴ Three of the children and adolescents in our study who died appeared to have had a uniphasic, rapid progression

Table 4. Timing of Near-Fatal Food-Induced Anaphylactic Reactions.

PATIENT No.	SETTING	INITIAL ONSET OF SYMPTOMS	TIME OF EPINEPHRINE DOSE	ONSET OF SEVERE SYMPTOMS	TYPE OF SYMPTOMS	TIME OF INTUBATION	DURATION OF INTUBATION
		<i>min after ingestion</i>				<i>min after ingestion</i>	
7	Friend's house	5	25	80	Skin, respiratory	90	6 hr
8	Friend's house	2	130	130	Gastrointestinal, respiratory, skin	155	2 hr
9	Vacation home	5	30	60	Skin, gastrointestinal, respiratory	70	3 days
10	Relative's house	1	15	30	Skin, respiratory	40	2 wk
11	Home	3	10	15	Skin, respiratory	45	14 hr
12	Home	2	15	12	Skin, gastrointestinal, respiratory	40	3 wk
13	Relative's house	5	30	25	Respiratory, skin	65	10 hr

of symptoms. The other three had biphasic responses, with early oral and abdominal symptoms followed by a relatively symptom-free period of one to two hours and then by respiratory symptoms and hypotension. Among the seven children with nonfatal reactions, four had a uniphasic response, in which severe symptoms developed within 30 minutes of allergen ingestion. Three patients had protracted anaphylaxis requiring ventilatory support and treatment with vasopressor medications for more than 24 hours, and in one case for 21 days (Patient 12). Patient 12 had such markedly reduced left ventricular output that attempts were made to implant an intraarterial cardiac-assist device. Cardiac function returned to normal four to five weeks after the ingestion of the allergen.

As shown in Table 5, serum tryptase concentrations were analyzed in one postmortem sample (from Patient 3), one sample from a patient with a near-fatal reaction (Patient 12), and samples from three control patients with food-induced anaphylaxis who were admitted to an intensive care unit with severe bronchospasm, hypoxia, and hypotension. In only one specimen did the levels exceed 2.5 ng per milliliter. In cases of anaphylaxis, the serum tryptase level is generally expected to exceed 10 ng per milliliter, and in cases of anaphylaxis due to bee stings and drugs, levels in excess of 100 ng per milliliter are common.⁵ Since the clinical course of Patient 12, who had protracted anaphylaxis and prolonged hypotension, appeared similar to that of endotoxic shock, TNF- α concentrations were measured. The TNF- α levels in this patient and in two control patients were within the normal range throughout the course of anaphylaxis.

DISCUSSION

The prevalence of allergic reactions to food in the general population is unknown. In two prospective studies of allergy to cow's milk, 2.2 to 2.5 percent of children younger than three years of age were found to be clinically reactive.^{6,7} In a third prospective trial, 8 percent of children under three years of age had an

Table 3. Timing of Fatal Food-Induced Anaphylactic Reactions.

PATIENT No.	SETTING	INITIAL ONSET OF SYMPTOMS	TIME OF EPINEPHRINE DOSE	ONSET OF SEVERE SYMPTOMS	TYPE OF SYMPTOMS	TIME OF DEATH
		<i>min after ingestion</i>				<i>min after ingestion</i>
1	School	10	125	125	Gastrointestinal, respiratory	180
2	School*	20	80	65	Gastrointestinal, respiratory	95
3	School	20	180	150	Gastrointestinal, respiratory	300
4	Fair	30	60	35	Skin, respiratory	105
5	School	30	90	35 and 100†	Gastrointestinal, respiratory	240
6	Home	3	25	20	Gastrointestinal, respiratory	120

*The symptoms began at home.

†The severe symptoms subsided after treatment with supplemental oxygen and then recurred.

Table 5. Serum Tryptase and TNF- α Concentrations in Patients Who Had Food-Induced Anaphylaxis.*

SOURCE OF SERUM SAMPLE	HOURS AFTER INGESTION	TRYPTASE†	TNF- α ‡
		ng/ml	pg/ml
Patient 3	—§	2.1	—
Patient 12	0.75	1.2	48
	5	<1	—
	8	<1	41
	24	<1	41
	48	<1	43
	72	1.5	43
Control 1	1	<1	47
	5	<1	44
	24	<1	41
Control 2	0.5	<1	41
	1	<1	41
	5	<1	41
Control 3	2	<1	—
	2.5	<1	—
	4	3.4	—
	24	<1	—

*Samples were obtained from Patients 3 and 12 and from three control patients with food-induced anaphylaxis who were admitted to an intensive care unit with severe bronchospasm, hypoxia, and hypotension. Normal values were determined in 15 patients with atopy (median age, 13 years; range, 10 to 18).

†The normal range is less than 2.5 to 5 ng per milliliter.

‡The normal range is 21.7 to 64.3 pg per milliliter (median, 41.3; mean, 42.6).

§The sample was obtained after death.

adverse reaction to at least one food.⁸ Similar data are not available for older persons. The perceived prevalence of food hypersensitivity reported by adults in a household survey was 25 percent,⁹ but the actual prevalence is probably in the range of 1 to 2 percent.

The six fatal and seven near-fatal cases of food-induced anaphylaxis share several features. All the patients had asthma and were taking bronchodilator medications. Two patients with fatal reactions had been taking oral corticosteroids within one month of the reaction. There appeared to be no significant difference in the severity of the asthma between the two groups. The asthma in all but one of the patients with nonfatal reactions appeared to be well controlled by medication, whereas two patients with fatal reactions and one with a nonfatal reaction had serious wheezing in the two weeks before the anaphylactic reaction. All the patients had a history of serious anaphylactic reactions to food, and all but two had had such reactions to the food responsible for the fatal or near-fatal reaction. Patient 10, who had had numerous severe anaphylactic reactions, had not been evaluated by an allergist but believed he was allergic to peanuts; he later proved nonreactive to peanuts on a double-blind, placebo-controlled food challenge and open feeding. Another patient (Patient 3) was not fully aware of her sensitivity to cashews — that is, she knew only that some types of nuts “did not agree with her.” None of the patients were aware that the implicated allergen was in the food they ate, indicating that attempts at strict avoidance are often unsuccessful. In a follow-up study of children with an allergy to peanuts, Bock

and Atkins¹⁰ found that 50 percent of the children had accidentally ingested some form of peanuts in the year before the survey, and 75 percent had done so within the preceding five years. Most parents did not appreciate the potential severity of allergic reactions to food. Although self-injectable epinephrine had been prescribed for three of the six children with fatal reactions, none had it available at the time of the reaction. Only one patient with a nonfatal reaction (Patient 8) gave herself an injection of epinephrine, and injectable epinephrine had been prescribed for only three of the patients with nonfatal reactions.

Five of the six fatal reactions occurred in public settings, while the children and adolescents were in school or at a fair, whereas all the near-fatal reactions took place in private homes. At least one of the patients' parents was present during three of the six fatal reactions and during four of the seven nonfatal reactions, suggesting that the presence of parents, who might be more capable of detecting the child's symptoms early, could not account for differences between the two groups. Instead, it appears that it is easier to respond more rapidly to a medical emergency in a home than in a public place — a circumstance that may allow the earlier institution of appropriate medical intervention. The fact that two thirds of the fatal reactions and none of the near-fatal reactions occurred at school must raise some question about the ability of school health care systems to deal with such medical emergencies. Although symptoms developed almost immediately in all patients, four of the six patients with fatal reactions, as compared with only one of the seven patients with nonfatal reactions, had deceptively mild symptoms for one hour or more before severe respiratory compromise developed. It was interesting that all the children and adolescents with nonfatal reactions but only one child with a fatal reaction had cutaneous symptoms. No patient who died received epinephrine before severe respiratory symptoms developed, whereas all the patients with nonfatal reactions received epinephrine before or within five minutes of the development of severe symptoms. However, four of the children who received epinephrine before severe symptoms developed became progressively sicker and eventually required intubation.

In view of the varied reaction kinetics in these cases and the failure to find significantly elevated serum tryptase levels in several children with systemic anaphylaxis, mechanisms in addition to classic mast-cell-mediated reactions must be considered. The usual early symptoms of food-induced anaphylaxis include oral pruritus, a sensation that the lips and tongue are swelling and the throat is tightening, urticaria and angioedema, nausea, cramping and vomiting, shortness of breath, stridor, and wheezing.¹¹ As was the case in the children we studied, these symptoms occur shortly after the ingestion of a food allergen and are believed to result from IgE-mediated activation of mast cells. However, many children appeared to have

either progressive symptoms despite injections of epinephrine or a second wave of symptoms that were poorly responsive to epinephrine. The failure to respond to epinephrine and conventional therapy was noted by Smith et al.,¹² who had difficulty reversing anaphylaxis in two of three patients intentionally stung by bees under carefully controlled conditions.

A number of cytokines may be released from cells activated during an allergic reaction. Two cytokines, TNF- α and interleukin-6, have been implicated in the pathogenesis of hypotension in endotoxic shock,^{3,13} and TNF- α may be released by monocytes, lung macrophages, and dermal mast cells during allergic reactions.^{14,15} However, the level of TNF- α was not elevated in our patient with prolonged hypotension, decreased cardiac contractility, an increased alveolar-arterial oxygen gradient, and encephalopathy, or in two control patients admitted to the intensive care unit with anaphylaxis. No change in TNF- α levels was found that might account for the hypotensive state.

Studies have shown that IgE-dependent, antigen-induced anaphylactic death occurs at a similar rate in mast-cell-deficient mice and normal, sensitized congenic mice.^{16,17} It appears that the release of cytokines or mediators by cells bearing Fc ϵ II receptors (cells bearing low-affinity IgE receptors) can induce a marked decline in pulmonary conductance and dynamic compliance, hypotension, and death. The absence of a substantial increase in mast-cell tryptase in many children with food-induced anaphylaxis suggests a number of possibilities. Mast cells may release minimal amounts of tryptase and normal amounts of other mediators after receiving certain activation signals; basophils, which do not release histamine in the early stages of a food-induced allergic reaction,¹⁸ may have an important role in the later stages of the anaphylactic response; or cells other than mast cells (e.g., macrophages, monocytes, and endothelial cells) may be activated through Fc ϵ II receptors or cytokines and mediators released early in the reaction.

It is our belief and that of other investigators studying food allergy that the frequency of fatal and near-fatal food-induced anaphylactic reactions has risen over the past several years. With the increasing use of protein additives in commercially prepared foods,¹⁹ it is likely that the prevalence of severe food-induced anaphylactic reactions will continue to rise. In view of this possibility, we would like to recommend the following. Epinephrine should be prescribed and kept available for all children and adolescents with IgE-mediated food allergies, and caretakers should be trained in the appropriate administration of this

medication. All children and adolescents with a food allergy who have an allergic reaction should be observed for three to four hours after the reaction in a center capable of dealing with anaphylaxis. Finally, children and adolescents with a food allergy should be evaluated and educated about food allergy by a knowledgeable physician, and the parents of such children should be taught ways of ensuring a rapid response by schools and other public institutions in the event of the accidental ingestion of a food allergen.

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REFERENCES

1. Yunginger JW, Sweeney KG, Sturmer WQ, et al. Fatal food-induced anaphylaxis. *JAMA* 1988;260:1450-2.
2. Schwartz LB, Yunginger JW, Miller J, Bokhari R, Dull D. Time course of appearance and disappearance of human mast cell tryptase in the circulation after anaphylaxis. *J Clin Invest* 1989;83:1551-5.
3. Natanson C, Eichenholz PW, Danner RL, et al. Endotoxin and tumor necrosis factor challenges in dogs simulate the cardiovascular profile of human septic shock. *J Exp Med* 1989;169:823-32.
4. Stark BJ, Sullivan TJ. Biphasic and protracted anaphylaxis. *J Allergy Clin Immunol* 1986;78:76-83.
5. Yunginger JW, Nelson DR, Squillace DL, et al. Laboratory investigation of deaths due to anaphylaxis. *J Forensic Sci* 1991;36:857-65.
6. Host A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life: clinical course in relation to clinical and immunological type of hypersensitivity reaction. *Allergy* 1990;45:587-96.
7. Hide DW, Guyer BM. Cows milk intolerance in Isle of Wight infants. *Br J Clin Pract* 1983;37:285-7.
8. Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics* 1987;79:683-8.
9. Sloan AE, Powers ME. A perspective on popular perceptions of adverse reactions to foods. *J Allergy Clin Immunol* 1986;78:127-33.
10. Bock SA, Atkins FM. The natural history of peanut allergy. *J Allergy Clin Immunol* 1989;83:900-4.
11. Bochner BS, Lichtenstein LM. Anaphylaxis. *N Engl J Med* 1991;324:1785-90.
12. Smith PL, Kagey-Sobotka A, Bleecker ER, et al. Physiologic manifestations of human anaphylaxis. *J Clin Invest* 1980;66:1072-80.
13. Starnes HF Jr, Pearce MK, Tewari A, Yim JH, Zou J-C, Abrams JS. Anti-IL-6 monoclonal antibodies protect against lethal *Escherichia coli* infection and lethal tumor necrosis factor- α challenge in mice. *J Immunol* 1990;145:4185-91.
14. Vecchiarelli A, Siracusa A, Cenci M, Puliti M, Abbritti G. Effect of corticosteroid treatment on interleukin-1 and tumour necrosis factor secretion by monocytes from subjects with asthma. *Clin Exp Allergy* 1992;22:365-70.
15. Walsh LJ, Trinchieri G, Waldorf HA, Whitaker D, Murphy GF. Human dermal mast cells contain and release tumor necrosis factor α , which induces endothelial leukocyte adhesion molecule 1. *Proc Natl Acad Sci U S A* 1991;88:4220-4.
16. Ha TY, Reed ND. Systemic anaphylaxis in mast-cell-deficient mice of W/W^a and S1/S1^d genotypes. *Exp Cell Biol* 1987;55:63-8.
17. Takeishi T, Martin TR, Katona IM, Finkelman FD, Galli SJ. Differences in the expression of the cardiopulmonary alterations associated with anti-immunoglobulin E-induced or active anaphylaxis in mast cell-deficient and normal mice: mast cells are not required for the cardiopulmonary changes associated with certain fatal anaphylactic responses. *J Clin Invest* 1991;88:598-608.
18. Sampson HA. The role of food allergy and mediator release in atopic dermatitis. *J Allergy Clin Immunol* 1988;81:635-45.
19. Gern JE, Yang E, Evrard HM, Sampson HA. Allergic reactions to milk-contaminated "nondairy" products. *N Engl J Med* 1991;324:976-9.