
Clinical features of acute anaphylaxis in patients admitted to a university hospital: an 11-year retrospective review (1985–1996)

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Background: Although anaphylaxis is considered a life-threatening event, there is a lack of information on the clinical characteristics at presentation, both in adults and in children.

Objective: To describe in a nonselected population the clinical characteristics and the treatments of acute anaphylaxis triggered by different agents.

Methods: This is a retrospective review of the clinical features of 113 episodes of acute anaphylaxis resulting in admission to a university hospital. Initially, the 107 patients visited the emergency room and were then admitted to the hospital.

Results: Most anaphylactic events (63%) occurred at home. The most frequent symptoms involved the respiratory system (78%) and the skin (90%). Drugs, especially nonsteroidal anti-inflammatory drugs and antibiotics, were the most frequent cause of anaphylaxis in adults (49%). Patients with drug-induced anaphylaxis were older and more often had cardiovascular symptoms (hypotension and tachycardia) ($P = 0.0064$). Hymenoptera venom was the second most frequent cause of anaphylaxis (29%). Most of the patients with hymenoptera venom anaphylaxis were male (80%) and more frequently they had no history of atopy ($P = 0.012$). In food-induced anaphylaxis, the cardiovascular system was less likely to be involved ($P < 0.05$) (39%). Seafood seems to be frequently involved in food-induced anaphylaxis in our area. Specific immunotherapy-induced anaphylaxis occurred more often in younger patients ($P = 0.032$). Epinephrine seems to be underused in Italy (only 15% of patients received it), especially for respiratory symptoms.

Conclusions: Anaphylaxis triggered by different agents may have different clinical presentations and may occur in different types of patients. In Italy, the inadequate use of epinephrine for anaphylaxis treatment needs to be publicized to both physicians and the general population.

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INTRODUCTION

Anaphylaxis is an acute, severe reaction that results from the release of preformed and newly synthesized bioactive mediators from mast cells and basophils.¹ Foods, venoms, and drugs are the most common exogenous antigens which can provoke an IgE-mediated

reaction, whereas exercise, radiocontrast media, and some nonsteroidal anti-inflammatory drugs (NSAIDs) may induce clinical symptoms with a yet not completely understood mechanism. When no etiologic agent is found despite repeated evaluations, the term idiopathic anaphylaxis is used.²

Although anaphylaxis is considered a life-threatening event, there is a lack of information on the clinical characteristics at presentation, in both adults and children, of anaphylaxis triggered by different agents. In this study, we describe the clinical features of 113 episodes of acute, severe anaphylaxis

which occurred in 107 patients admitted to an emergency room (ER) of a university hospital. The purpose of the present investigation was to describe, in a nonselected population, the clinical characteristics at presentation of anaphylaxis and the types of treatment administered and to evaluate any differences in anaphylaxis triggered by different agents.

METHODS

Selection of Patients

A retrospective chart review of all patients admitted from 1985 to 1996 to a university hospital (Az. Ospedaliera di Careggi, Florence, Italy) after an ER visit in the same hospital with a diagnosis of acute anaphylaxis was performed. A computer search of all the patients admitted to the hospital was done by the medical information resource staff using the diagnosis code for anaphylaxis (995.0) or anaphylaxis induced by animal venom (989.5). The codes used were the official diagnosis codes published by the Italian Central Institute of Statistics.³ From a total of 198 medical records, we personally examined and extracted data with a standard questionnaire. Only the data of patients, who were admitted coming directly from the ER of the hospital and who experienced at least two of the main anaphylactic reaction indicators (hypotension, inspiratory dyspnea, such as stridor plus sense of suffocation, and urticaria/angioedema) at the time of admission or in the hour before admission, were entered into the database (Excel 5.0 software, Microsoft, Redmond, WA). Inpatients were not considered. Finally, a total of 107 charts were reviewed for the following

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information: sex, age, past history of allergic reaction, known trigger (based on the medical history), site of anaphylactic events, time of latency, symptoms, maximal and minimal blood pressures (BPs), heart rate, eosinophilia, total IgE level by a an ELISA (Kallestad Diagnostics, Monticello, MN), c3 and c4 levels, therapy (pre-hospital and in-hospital), and reaction course. We evaluated the etiologic agent as the most probable one based on the history, collected by a medical doctor, only if the exposure to it occurred within 2 hours before symptom onset. In the context of this study, anaphylaxis was a clinical diagnosis. We diagnosed monophasic anaphylaxis when the cardiac and respiratory symptoms resolved within 2 hours after the onset of the proper treatment; biphasic anaphylaxis when there was a recurrence of symptoms 2 to 72 hours after the complete resolution of the initial manifestation without any further exposure to the trigger agent; and protracted anaphylaxis when the cardiac or respiratory symptoms or both persisted 10 hours after the onset of maximal treatment.² We considered the following to be cardiac symptoms: dizziness, collapse, cardiac arrest, and palpitation. We considered the following to be respiratory symptoms: inspiratory (ie, stridor and sense of suffocation) and expiratory dyspnea, expiratory wheezing, and asthma attack. We considered vomiting and diarrhea to be gastrointestinal manifestations, and skin symptoms included urticaria and angioedema.

STATISTICAL ANALYSIS

The data were analyzed with the statistical programs STATA 4.0 for Windows (Collage Station, TX) and EPI INFO version 5.0 (Centers for Disease Control and Prevention, Atlanta, GA). The patients were categorized (positive or negative) based on the principal anaphylaxis triggering agent (venom, food, exercise, drugs, other) and type of symptoms (cardiac, respiratory, dermatologic, gastrointestinal). The relationships between the different types of anaphylaxis and other characteristics of both the patients and the anaphylaxis episodes were analyzed by calculating the odds ratio and confidence intervals using a univariate logistic regression or two-sided Fisher exact test, when indicated. A *P* value < 0.05 was considered significant.

RESULTS

Patient Demographics and Symptoms
Of 153,086 admissions (1985 to 1996) to the University Hospital through the ER, 107 patients were analyzed, for a total of 113 episodes (Table 1). In the past, 65% of the 107 patients had experienced urticaria/angioedema, 16% experienced allergic rhinitis, 13% experienced anaphylaxis, and 13% experienced asthma. Most patients (94%) had monophasic anaphylaxis, whereas two (2%) had biphasic anaphylaxis and one (1%) had a protracted course. In three patients (3%) the courses of the manifestations were unknown. In the two patients with biphasic anaphy-

laxis, the most probable trigger agent was a drug, whereas the protracted anaphylaxis was attributable to hymenoptera venom. The median hospital stay was 24 hours (range 0 to 18 days).
The mean latent period [$\pm$ standard deviation (SD)] of the 102 episodes of anaphylaxis, in which it was possible to identify the inciting agent, was 24 ± 32 minutes. Fifty-four percent of cases occurred in the home (58 of 107); 8% outdoors (9 of 107); 5% in restaurants (5 of 107); 4% in a doctor's office (4 of 107); 4% (4 of 107) on public transport. For 16% (17 of 107) of the patients, the location was not recorded. Etiologic agents and frequency of occurrence in 113 episodes of anaphylaxis are reported in Table 2.
Skin and respiratory symptoms occurred more frequently than gastrointestinal and cardiovascular symptoms (90% and 78% vs 14% and 30%, respectively). In 73 patient histories (68%), there were records of the maximal BP (MaxBP) (mean $\pm$ SD = 110 ± 41 mmHg; range = <40 to 220) and minimal BP (MinBP) (mean $\pm$ SD = 66 ± 30 mmHg; range = <20 to 120); 64 histories (60%) of the heart rate (HR) (mean $\pm$ SD = 93 ± 16 beats/minute; range = 45 to 130); 67 histories (63%) recorded the total IgE value (paper radioimmunosorbent test) (mean $\pm$ SD = 66 ± 30 UI/L; range = <20 to 120); 33 histories (31%) recorded the eosinophil count (mean $\pm$ SD = 128 ± 122 eosinophil/mm³; range = 10 to 480); 32 histories (30%) recorded the fraction 3 of the complement (c3; mean $\pm$ SD = 98 ± 24 mg/dL) as well as the fraction 4 of the complement (c4; mean $\pm$ SD = 25 ± 9.5 mg/dL). The patients, in whom BP was not recorded, showed histories of 21 occurrences of dyspnea and 6 occurrences of collapse. The BP and HR that we reported were the ones reported during the acute episode. Some of the patients, during their acute attacks, were assisted outside the hospital in an emergency medical setting (EMS), and then transferred to the hospital ER, by which time some of the symptoms were already resolved. In some pa-

Table 1. Characteristics of the 107 Patients and Symptoms at Presentation of the 113 Episodes of Anaphylaxis

	Mean ($\pm$ SD)	N (%)
Male		59/107 (55%)
Female		48/107 (45%)
Age	42 ($\pm$ 18) years	
History of atopy		
Positive		55/107 (51%)
Negative		45/107 (49%)
Urticaria/angioedema		102/113 (90%)
Respiratory		88/113 (78%)
Cardiovascular		34/113 (30%)
Gastrointestinal		16/113 (14%)

Table 2. Etiologic Agents and Frequency of Occurrence in 113 Episodes of Anaphylaxis

Agent group	N (%/113)	Specific agent	N (%)
Drugs	52 (49%)	NSAID	18/52 (35%)
		Antibiotics	25/52 (48%)
		Unidentified	9/52 (17%)
Venom	31 (29%)	Hornet	2/31 (6 %)
		Bee	8/31 (26%)
		Wasp	13/31 (42%)
		Unidentified	8/31 (26%)
Food	9 (8%)	Miscellaneous	
Specific immunotherapy	7 (6%)	Grass mix	5/7 (72 %)
		Dust mite	2/7 (28 %)
Idiopathic	6 (6%)		
Exercise-related	2 (2%)		

tients in the outpatient EMS, the BP and the HR were not recorded.

Cardiac symptoms were inversely correlated with the BP levels, both maximal and minimal ($P < 0.0001$) and with the numbers of eosinophils ($P = 0.014$). All patients were treated in the ER; some of them received treatment before arriving in the ER in an EMS. The frequency of administered drugs is reported in Table 3, only two patients (2%) did not receive any therapy. Although 53 (47%) patients received only corticosteroids and anti- H_1 , 10 (9%) received only corticosteroids and two (2%) only anti- H_1 , remarkably, none of the patients received epinephrine without any other treatment. Epinephrine was used in only 16 patients (15%). However, epinephrine was administered more often in patients with cardiac symptoms ($P = 0.002$).

ETIOLOGIC AGENTS PROVOKING ANAPHYLAXIS

Drug-Dependent Anaphylaxis

Drugs were the most probable cause of anaphylaxis in 52 patients. Twenty-

five of these 52 episodes involved antibiotics (such as cephalosporins in 8 [ceftriaxone in 3, cefotaxime in 3, cefoperazone in 1, ceftazidime in 1], tetracyclines in 3, trimethoprim-sulfamethoxazole in 3, penicillins in 7 [diamino-penicillin in 1, bacampicillin in 2, ampicillin in 3, amoxicillin in 1], aminoglycosides in 2, not specified in 2). Eighteen of 52 involved NSAIDs (acetyl salicylic acid in 7, acetaminophen in 1, pyrazolone in 5, diclofenac in 4, piroxicam in 1). In nine patients the anaphylaxis was clearly related to a drug but, from the records, it was impossible to identify the specific drug. None of the patients with cephalosporin-induced anaphylaxis had histories of penicillin allergy. The mean age $\pm$ SD for patients in this group was 46 ± 18 (range 13 to 76) years and the female: male ratio was 28:24. These 52 anaphylaxis episodes occurred among older patients ($P = 0.015$) compared with the other etiologic agents. The initial symptoms of the 52 episodes more often involved the cardiovascular system (two-sided Fisher exact test, $P = 0.0064$), and the patients more often had lower MaxBP and MinBP levels ($P = 0.006$ and 0.009 , respectively) as well as higher HR ($P = 0.031$). A multiple logistic regression showed that the cardiac symptoms and age are independently associated with drug-related anaphylaxis ($P = 0.025$ and $P = 0.05$, respectively). Patients with drug-related anaphylaxis received both epinephrine (two-sided Fisher exact test, $P = 0.0046$) and oxygen (two-

sided Fisher exact test, $P = 0.0143$) more often and received the anti- H_1 (two-sided Fisher exact test, $P = 0.0075$) less frequently.

Hymenoptera Venom-Dependent Anaphylaxis

Hymenoptera venoms were the most probable etiologic agents in 31 episodes of anaphylaxis. The mean age $\pm$ SD was 45 ± 18 (range 18 to 90) years and the female: male ratio was 7:24 (two-sided Fisher exact test, $P = 0.0031$). The patients with hymenoptera venom anaphylaxis more frequently had no personal atopic history (two-sided Fisher exact test, $P = 0.012$), especially for allergic rhinitis (two-sided Fisher exact test, $P = 0.045$), urticaria/angioedema (two-sided Fisher exact test, $P = 0.0143$). The most common treatment for these patients was anti- H_1 (two-sided Fisher exact test, $P = 0.0017$).

Food-Dependent IgE-Mediated Anaphylaxis

Nine patients had anaphylaxis with foods as the etiologic agents. In six patients the anaphylaxis could be attributed as follows: 1 to mustard, 1 to mussels, 1 to shrimp, 1 to soy, 1 to peanuts, and 1 to fish. In 3 patients, multiple kinds of food had been consumed, so no clear relationship was identified. The mean age $\pm$ SD (range) was 31 ± 13 (16 to 51) years and the female: male ratio was 4:5. The initial symptoms of the nine episodes never involved the cardiovascular system (two-sided Fisher exact test, $P = 0.05$).

Specific Immunotherapy (SIT)-Induced Anaphylaxis

SIT-induced anaphylaxis occurred in 7 patients and the male: female ratio was 4:3. Usually these patients were younger with a mean age $\pm$ SD of 25 ± 7 (range 17 to 36) years ($P = 0.032$). All the adverse episodes, save one, occurred within 30 minutes of immunotherapy administration. Five patients had asthma during the acute anaphylactic attack. Patients with SIT-induced anaphylaxis more frequently, as expected, have a positive personal

Table 3. Therapies Used in 107 Patients with Acute Anaphylaxis

	N (%)
Corticosteroids	103/113 (91%)
Antihistamines	82/113 (72%)
Epinephrine	16/113 (15%)
Intravenous fluids	25/113 (22%)
β_2 -agonists	3/113 (3%)
Oxygen	9/113 (8%)

atopic history (two-sided Fisher exact test, $P = 0.0001$), especially for allergic rhinitis (two-sided Fisher exact test, $P = 0.0008$) and asthma (two-sided Fisher exact test, $P = 0.0055$). A multiple logistic regression showed that these probabilities were independent ($P = 0.013$ for asthma and $P = 0.002$ for rhinitis). Frequently these patients had higher levels of total IgE ($P = 0.009$).

DISCUSSION

Anaphylaxis is a potentially life-threatening allergic reaction that involves one or more of the following: the upper airways (epiglottis angioedema) the cardiovascular system (hypotension, dysrhythmia), the skin (urticaria, angioedema, pruritus, flushing), and the gastrointestinal system (vomiting, diarrhea).^{4,5}

Many agents can trigger an anaphylactic reaction, such as foods, drugs, insect venoms, heterologous sera, inhalant allergens injected during hypersensitization therapy, and radiocontrast media.⁴ Despite the severity of this reaction, there are few studies that document a large series of patients. Most studies involve patients with a past episode of anaphylaxis, who were referred to an outpatient center for allergological evaluation. These studies usually elucidate the most frequent causes of anaphylaxis and the atopic status of the patients.^{6,7}

In our study we have collected details of 113 anaphylactic reactions in 107 adults. These details delineated the clinical features of acute, severe anaphylaxis that required admittance to the hospital for at least 24 hours in an outpatient nonselected population. We have tried to elucidate the differences in the clinical presentations of anaphylaxis triggered by different agents. Indeed, we have previously observed in children referred to an outpatient unit for anaphylaxis that anaphylaxis triggered by different agents may have different clinical presentations.⁸ Unfortunately, unlike the study on children,⁸ in this study, we can not make any definitive statements because the etiologies of the anaphylactic reaction were only presumed, based on the

medical chart review, without any corroborative specialty consultation, diagnostic testing, or challenge.

In this study, men and women were equally represented, as has been observed in other studies.^{8,9} With a few exceptions, such as latex-, aspirin-, and muscle relaxant-induced anaphylaxis, which occur more frequently in women and hymenoptera venom-induced anaphylaxis, which occurs more often in men,^{10–12} sex in adults is not considered a risk factor for anaphylaxis.¹³ In our study, only hymenoptera-induced anaphylaxis was more common in male patients, as previously reported.^{8,14}

About half of the studied patients had a personal history of atopic disease (urticaria/angioedema, atopic eczema, asthma, and allergic rhinitis). Atopy is generally considered a risk factor for ingested antigens, exercise-induced anaphylaxis, idiopathic anaphylaxis, and latex reactions.^{8,15–19} The role of atopy is not clear in venom-induced anaphylaxis; some authors do not recognize atopy as a risk factor for venom-induced anaphylaxis,^{8,13} whereas others believe that atopy can be important in the more severe reactions.²⁰ However, in our study, atopy was less frequent among patients with hymenoptera-induced anaphylaxis, as previously reported.^{6,8,21,22}

In the present investigation, drugs accounted for half of the patient histories examined. The drugs more frequently involved were NSAIDs and antibiotics. NSAIDs have previously been reported as one of the leading causes of anaphylaxis.⁶ We have previously seen that both NSAIDs and antibiotics were very important causes of anaphylaxis in children.⁸ Remarkably, cephalosporins were more frequently involved in this type of reaction, compared with penicillin and its derivatives. We have observed the same phenomenon also in children who live in the same area.⁸ Only a small number of epidemiologic studies have been performed on the role of drugs as an etiologic factor of anaphylaxis.⁷ In outpatient populations, the percentage of anaphylaxis attributable

to drugs is between 20% and 30%.^{6,23} We found a higher incidence of drug-related anaphylaxis, that was similar to the ones that Sorensen et al²⁴ reported, in a retrospective study on cases of anaphylactic shock in an outpatient population during a 13-year period.²⁴ These differences might be because of the greater severity of anaphylaxis induced by drugs and emergency treatment was required more often. Indeed, we found that patients admitted for drug-induced anaphylaxis more often experienced cardiovascular symptoms, such as hypotension and tachycardia and more often received epinephrine and oxygen. The lower incidence that Dibs and Baker²⁵ found in 50 pediatric cases of anaphylaxis admitted to an urban children's hospital pediatric emergency department, operating suites, and inpatients' unit, was attributable perhaps to a lower prevalence of drug allergy in children compared with adults.^{6,13} In addition, in our study, the frequency of drug-related anaphylaxis was higher in older patients. Further, we found few cases of food-induced anaphylaxis, with a percentage similar to the one found by Sorensen et al,²⁴ which may explain the relatively high frequency of drug-related anaphylaxis. This low frequency of food-induced anaphylaxis could be due to less severe anaphylaxis due to ingested antigen, compared with injected antigen.¹³ Indeed, in our study, food-induced anaphylaxis never involved the cardiovascular system. In addition, food anaphylaxis rarely caused cardiovascular symptoms in children.⁸ Further, in children, food-induced anaphylaxis accounted for almost up to 60% of patients in an outpatient population referred to an ambulatory unit,⁸ whereas it accounted for only 25% in children admitted to an ER.²⁵ The foods most frequently identified in our investigation were fish, shellfish, and crustaceans, as previously reported in children living in a similar area and therefore with similar alimentary habits.⁸

We found seven cases of SIT-induced anaphylaxis. Four of them were patients with asthma, and asthma is a known risk factor for SIT-induced ana-

phylaxis.²⁶ Further, 5 of the 7 had asthma symptoms during the anaphylaxis attack. In three patients, the SIT injection was administered at home and not by a medical doctor. It is commonly known that a doctor should always administer SIT, and epinephrine and other emergency devices should always be available. Remarkably, none of the 7 patients received epinephrine, which is without doubt the first choice in treatment in SIT-induced anaphylaxis.²⁶

We also found an inverse correlation between the numbers of eosinophils and cardiovascular symptoms. This phenomenon could be because of the prevalent role of mast cells and their mediators in cardiac symptoms during anaphylaxis,^{27,28} whereas eosinophils, together with mast cells, might be more important for respiratory, gastrointestinal, and skin manifestations.^{29–32}

The two best markers of acute anaphylaxis are serum histamine and tryptase.^{33–35} In our study, tryptase was not measured, because in the years studied, the hospital laboratories did not measure tryptase as part of an urgent examination. In some of the patients examined, the c3 and c4 fractions of complement were measured, because alterations in complement levels during anaphylaxis have been described.^{36,37} We did not find any alterations in either c3 or c4 levels.

The locations where the anaphylactic reactions occur is very important for access to adequate therapy.³⁸ In our study as well as others,^{8,25} home was the most frequent location for occurrence of an anaphylaxis. Because of this, all family members should be adequately informed on medical treatment. In particular, the home administration of epinephrine should be encouraged^{42,39} as epinephrine is absolutely the first choice drug in anaphylaxis treatment.^{38,40–42} In one study, epinephrine in acute anaphylaxis was used in up to 88% of cases,²⁵ but, in an Italian study in children, it was largely underused.⁸ Use of epinephrine in the treatment of anaphylaxis should be emphasized because, in the present study, only 15% of patients received epinephrine, whereas the most com-

monly used treatment was corticosteroids. Further, adrenaline should not be used if strictly cardiovascular symptoms are present, as seems to be the case in our study, but also in the presence of respiratory symptoms.

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