

Incidence of anaphylaxis in the emergency department of a general hospital in Milan

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Abstract

Objective: To evaluate incidence and causes of anaphylactic reactions in the emergency room (E.R.) of a general hospital in Milan during a 2-year period. **Methods:** We retrospectively studied the computerized records of patients discharged from an E.R. with a diagnosis of anaphylactic reaction. Anaphylaxis was established on the presence of at least two cutaneous, respiratory, gastrointestinal or cardiovascular system symptoms. **Results:** During 1997 and 1998, out of 38 685 patients referred to the E.R., 13 had severe anaphylaxis with loss of consciousness (LOC) and 127 had anaphylactic symptoms, without LOC. Of the 13 patients with LOC, a possible cause was identified in 12 (five foods, six drugs, one hair dye). In the other 127 patients anaphylaxis was related to foods in 49 cases (38.5%), drugs in 44 (34.6%), unknown causes in 29 (22.8%), hymenoptera stings in two (1.5%), and other causes in three (2.3%). **Conclusion:** The incidence of anaphylactic reactions was 0.4% and mainly affected females and atopic subjects. Foods, particularly fruits and vegetables, appeared to be the most important cause; other important causes were non steroidal antiinflammatory drugs and β -lactam antibiotics. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

The term anaphylaxis defines a systemic IgE-mediated reaction induced by a massive release of mast cell mediators targeting organs of the cutaneous, respiratory, gastrointestinal, and cardiovascular systems. Anaphylaxis is a medical emergency which requires immediate treatment because of its potential fatal outcome. This makes it particularly important to do everything to prevent anaphylactic reactions, initially by identifying the cause(s) and preventing further contact.

The main causes of anaphylaxis are closely related

to the kind of exposure, to changes in the environment and to the spread of new drugs or materials. Thus, in the 1970s penicillin accounted for about 75% of all causes of anaphylaxis [1], in the 1980s radiocontrast media started becoming one of the most important causes of severe anaphylaxis and in the 1990s latex was responsible for severe reactions among health-care workers [2]. A major step in recent years has been the identification of food allergy as a main cause of anaphylaxis. In all the epidemiological surveys conducted in the 1990s in Europe and United States food allergy was a more frequent cause of anaphylaxis than drugs or insect venom [3–5]. At least two studies reported deaths from anaphylaxis caused by eating peanuts and shrimp [6,7].

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As information is scant on the epidemiology of anaphylaxis in Italy, the present study was planned to evaluate the different causes of anaphylaxis by analyzing all cases referred to the emergency room (E.R.) of a general hospital in Milan.

2. Materials and methods

We analyzed the clinical records from the hospital's data base of all adults referred to the E.R. of the Ospedale Maggiore Policlinico in Milan during 1997 and 1998, discharged with a diagnosis of allergic and/or anaphylactic reactions.

Anaphylaxis was established on the basis of the presence of at least two major allergic symptoms or one major and two minor symptoms, involving the skin, gastrointestinal, respiratory, or cardiovascular system, as reported in Table 1. Anaphylaxis was graded as follows: grade I: slight (itching, urticaria/angioedema, rhinoconjunctivitis, abdominal pain); grade II: moderate (vomiting, diarrhea, asthma, dizziness, in addition to one or more grade I symptoms); grade III: severe [laryngeal edema, hypotension, loss of consciousness (LOC), in addition to one or more symptoms as above].

For every patient we analyzed the demographic data, including age, sex, and atopy assessed from history of pollinosis or other clear atopic manifestations and established the possible cause of anaphylaxis on the basis of the cause/effect relationship. The relationship was considered: (a) certain, when the reaction was immediate (within 1 h) and previous reactions to the same cause had occurred, or when only one food or drug had been taken before

the reaction; (b) probable, when an immediate reaction occurred but the patient had never had similar reactions to the same agent; (c) the classification "causal relationship unknown" was used when the history did not suggest any possible cause.

Other clinical parameters analyzed were the relationship between the cause of anaphylaxis and the severity of symptoms, the time of onset of the reaction and the treatment administered in the E.R.

3. Results

In 2 years of observation (1997–1998) 38 685 patients were referred to the E.R.; 1274 (3.3%) (about 1:30) presented a suspected allergic reaction according to the national coding system. Only 140 or 0.4% (about 1:300), according to our clinical parameters, presented symptoms classifiable as anaphylaxis and 13 (about 1:3000 of total population) of these 140 had severe anaphylaxis. During 1998, 54 records were unclassifiable because of lack of data. No patients had investigations to establish or confirm the cause.

Demographic data concerning the 140 patients are set out in Table 2. There were more women ($P < 0.001$, chi-square test), and a high rate of atopy. The majority of patients (68.5%) had life threatening reactions. In 54 cases (38.5%) anaphylaxis was related to foods, in 50 (35.7%) to drugs, in 30 (21.4%) to unknown causes, in two (1.4%) to hymenoptera stings, and in four (2.8%) to other causes (rat bite, cleanser, alcohol ingestion plus exercise, hair dye). We observed that the prevalence of atopy in food allergic reactions was about 78% (42/54, $P = 0.001$) while in drug reactions the prevalence of atopy was not relevant (20/50, $P = \text{n.s.}$).

Details of the 13 cases of severe anaphylaxis, who

Table 1
Criteria of anaphylaxis

Major symptoms	Minor symptoms
Urticaria/angioedema	Abdominal pain
Dyspnea (laryngeal edema)	Itching
Loss of consciousness/hypotension	Dizziness
Rhinoconjunctivitis	
Asthma	
Vomiting/diarrhea	
Seizure	

Anaphylaxis was diagnosed on the basis of two major symptoms or one major and two minor symptoms.

Table 2
Demographic data of the 140 patients

Female/male	99/41
Age (years) (range and mean)	14–91 (38.5)
Atopy (%)	68 (48.5)
Grade I symptoms (%)	7 (5)
Grade II symptoms (%)	37 (26.4)
Grade III symptoms (%)	96 (68.5)
Previous reactions	35 (25)

Table 3
Data concerning 13 cases of severe anaphylaxis with loss of consciousness

Age and sex	Presumed cause	Atopy	Previous reactions	BP in E.R.	Symptoms	Treatment
27 M	Almond	No	No	70/?	LOC, urticaria	H, C, Hy
26 F	Tomato, corn salad	No	No	90/60	Asthma, pruritus, urticaria/ angioedema, conjunctival injection, LOC	A, H, C
56 M	Chicken egg	No	No	110/70	LOC, urticaria	Hy, C, H
26 M	Peach juice	No	No	100/70	LOC, asthma	Hy, C, H
24 M	Nuts	No	No	100/70	FA, R, asthma, LOC	Hy, C, H
28 F	Hair dye	Yes	No	?	Asthma, urticaria, LOC	A, H, C
37 F	Unknown	No	No	?	Angioedema, urticaria, LOC	Emagel, H, C
53 M	Amoxicillin	No	No	85/?	LOC	O ₂ , H, C, sodium hydrogencarbonate
41 F	Iron	Yes	No	120/80	LOC	A, H, C
22 F	Amoxicillin	No	No	85/60	Vomiting, LOC	H, Hy
69 F	Diclofenac	Yes	Yes	140/80	LOC, cyanosis	H, C, O ₂
34 F	Antimicrobial drug unknown	Yes	No	120/80	Lipothimia, vomiting, angioedema, LOC	H, C
28 F	ASA	No	No	100/70	Vomiting, diarrhea, conjunctival injection, urticaria, LOC	H, C, Hy

LOC, Loss of consciousness; BP, blood pressure; H, intravenous hydrocortisone; C, intramuscular chlorphenamine; A, subcutaneous adrenaline; Hy, hydrosaline solution, FA, facial angioedema; ASA, acetyl salicylic acid.

presented loss of consciousness and other systemic allergic features, are reported in Table 3.

A probable cause was identified in 12/13 patients. Six reactions were related to drugs, amoxicillin in two, unknown in one, two cases were related to non-steroidal antiinflammatory drugs (NSAIDs) [diclofenac, acetyl salicylic acid (ASA)] and one case occurred after iron infusion. Five reactions were related to food, two to nuts, one to peach juice, one probably to chicken egg and one after tomato and

corn salad. One patient had anaphylactic shock 20 min after using a hair dye. The cause of one reaction was unknown.

In the other 127 patients (Table 4), anaphylaxis was related in 49 cases to foods, in 44 to drugs, in 29 to unknown causes, in two to hymenoptera stings, and in three to other causes (rat bite, cleanser, alcohol ingestion plus exercise). The table shows also the time elapsed between exposure and onset of symptoms. The onset time was sooner (within 30

Table 4
Causes of anaphylaxis in the 127 patients and onset time of symptoms

Causes of anaphylaxis	Foods	Drugs	Hymenoptera	Other	Unidentified
No. patients	49 (38.5%)	44 (34.6%)	2 (1.5%)	3 (2.3%)	29 (22.8%)
Onset within 30 min	36	8	2	1	6
Onset within 60 min	11	21	/	1	8
Onset from 1 to 6 h	2	15	/	1	10
?	/	/	/	/	5

min) in patients with anaphylaxis related to foods and hymenoptera sting than in those with anaphylaxis related to drugs (within 60 min).

Table 5 grades the anaphylaxis in relation to the cause: the majority of the patients presented serious symptoms.

Of the 49 food reactions 25 (51%) were certainly related to a specific food as the sensitization was already known, and nine (18.3%) were probably related to a food that had been ingested just before the reaction although the patient had had no previous reactions to it; 15 (30.6%) were considered as food reactions because they had arisen after a meal but it was impossible to identify the culprit food.

Thirteen of 44 (29.5%) drug reactions were confirmed as the patients had had previous reactions to the same agent, and 31 of the 44 (70.4%) were probably drug related as a specific drug had been taken just before the reaction.

In five out of 127 patients (4%) anaphylaxis was related to other causes (exercise, cleanser, rat bite, two to hymenoptera sting). In each of these patients symptoms were immediate but no previous reaction to the same agent had occurred.

The foods causing anaphylaxis are reported in Table 6; the most frequent were fresh fruits and vegetables followed by seafood and nuts.

NSAIDs were the first causal agent of anaphylactic reactions to drugs, followed by antimicrobial drugs (β -lactams) (Table 7). Other causes of anaphylaxis and the number of cases related to unknown causes are shown in Table 8.

Treatment consisted mainly of intravenous hydrocortisone plus intramuscular chlorphenamine; only eight patients (5.7%) needed adrenaline. In two

Table 5
Anaphylaxis grading in the 127 patients

Causes of anaphylaxis	Grade I	Grade II	Grade III	
			Total	L.E.
Foods	6	13	30	17
Drugs	1	15	28	19
Unidentified	0	7	22	14
Hymenoptera stings	0	1	1	1
Rat bite	0	1	0	
Exercise	0	0	1	1
Cleanser	0	0	1	

L.E., Laryngeal edema.

Table 6
Causes of anaphylaxis – foods: 49

Seafoods	13 (26.5%)
Fish	8 (16.3%)
Crustacea	4 (8.1%)
Mussels	1 (2%)
Fresh fruits and vegetables	15 (30.6%)
Apple	2 (4%)
Lemon	2 (4%)
Pineapple	2 (4%)
Peach	1 (2%)
Carrot, plum, grapefruit, cabbage, fennel, celery, pear, ribs	1 (2%)
Nuts	4 (8.1%)
Almond	2 (4%)
Hazelnut	2 (4%)
Yeast	2 (4%)
Chicken egg	1 (2%)
Salami	1 (2%)
Unidentified	15 (30.6%)

Table 7
Causes of anaphylaxis – drugs: 44

NSAIDs	22 (50%)
ASA	6 (13.6%)
Propyphenazone	5 (11.3%)
Ketoprofen	4 (9%)
Nimesulide	3 (6.8%)
Acetaminophen	2 (4.5%)
Aminophenazon, tenoxicam, noramidopyrin	1 (2.2%)
Antimicrobial drugs	12 (27.2%)
β -Lactams (amoxycillin)	9 (20.4%)
Chlarythromycin	2 (4.5%)
Ceftriaxone	1 (2.2%)
Other drugs	10 (22.7%)
Muscle relaxants	2 (4.5%)
Ferric gluconate	1 (2.2%)
Local anesthetics, methylethylgometrins, fluorangiography, bechic, vitamins	1 (2.2%)
Combinations of drugs	2 (4.5%)

Table 8
Causes of anaphylaxis – other causes: 34

Hymenoptera stings	2 (5.8%)
Exercise	1 (2.9%)
Cleanser	1 (2.9%)
Rat bite	1 (2.9%)
Unidentified causes	29 (85.2%)

patients oxygen was used in association with adrenaline and corticosteroids. Two patients were admitted to hospital.

4. Discussion

The present study found that an anaphylactic reaction accounted for 140 (0.4%) out of the 38 685 attendees seen for medical problems in the E.R. of our regional hospital in Milan. This high prevalence appears to be in contrast to that found in the other studies. In the study by Stewart and Ewan [3] the prevalence was 43.4/100 000 patients seen in casualty attendance and in the one by Yocum et al. [8] was 30/100 000 residents in Olmsted county. Nevertheless we might assume the existence of a real difference in prevalence; we have to underline that different diagnostic criteria could be at the basis of the discrepancy. In our study in fact we personally analyzed all the medical records of patients discharged by the E.R. just with the diagnosis of allergic reaction and following our prefixed diagnostic criteria, we redefined as anaphylaxis all the reactions involving at least two apparatus among the ones, cutaneous, gastrointestinal, respiratory and cardiovascular. So we found a prevalence of 333/100 000 reactions; this is a very high figure that may be provocative but may demonstrate that the real prevalence of anaphylaxis is very underestimated.

A main finding here concerns the prevalent causes of anaphylaxis. Our analysis similarly to the English study, evaluated retrospectively all computerized records of patients who came to the E.R. for a generalized allergic reaction, so the etiologic diagnosis was made on the basis of the clinical history while in the English study [3] the patients were recruited only on the basis of the computerized diagnostic index. Although the patients were not seen by an allergist, in the majority of cases the history enabled us to formulate an almost certain diagnosis because of the short interval between exposure and symptoms and the history of previous exposure and reactions to the suspected causal agent.

Food allergic reactions accounted for 54 (38.5%) out of the 140 reactions. This figure was higher than drug reactions which accounted for 50 (35.7%) of the 140, and any other cause. This result is in line

with at least three previous studies. Stewart and Ewan [3] found 29% of food reactions, 21% of drug reactions and 25% of insect venom reactions; Yocum and Kahn [4] found 33% food, 13% drug and 14% insect venom reactions; and Pumphrey and Stanworth [5] found 60% food, 9% drug, and 16% insect venom reactions.

All these reports indicate that food allergy is currently the main predisposing factor to anaphylactic reactions.

Considering the culprit foods, among the 13 patients with life-threatening reactions, nuts were the most frequent food. In all the studies cited, peanut and other nuts were also responsible for most of the severe cases of anaphylaxis. It thus seems confirmed that the majority of severe reactions – even deaths – for allergic reactions to food involve nuts [9]. As reported elsewhere allergic reactions to peanuts and nuts are in fact always potentially life-threatening and have already been responsible for five of seven near-fatal and 10 of 13 fatal food-induced anaphylactic reactions [6,7].

The wide use of these foods, and the “cross-contamination” in bakeries, restaurants, and food processing lines, make avoidance difficult and accidental ingestion common [10]. It is of particular interest that in our study hazelnuts, almonds and walnuts but not peanuts were mainly responsible for anaphylactic reactions. In other countries (United States, UK) peanuts are the food that causes anaphylaxis most, in children and adults, probably because of its wider consumption from childhood. In Italy peanut intake is lower (0.68 kg per person/year [11]) than in the United States (3.5 kg per person/year [12]) and this may explain the lower incidence of life-threatening reactions.

Looking at the other 49 food reactions, the main feature of our study is the high prevalence of anaphylactic reactions to fresh fruit and vegetables. This does not appear in studies conducted in Northern Europe and seems peculiar to the Mediterranean Area. In fact in Israeli and Spanish studies too [13,14], fresh vegetables and fruit, particular peach, have been reported as a cause of anaphylaxis. Our study identified peach, apple and pineapple among the culprit fruits. Peach, can thus be considered the most common cause of severe food allergy in adults in the Mediterranean Area. This may be related to

the high consumption of this fruit in Southern Europe but also to the usually mild nature of the symptoms [15] that induce the people to continue eating them. Moreover avoidance of the allergen is difficult because of the cross-reactivity among vegetable and fruits. In fact we recently identified a cross-reactive allergen present in all the fruit belonging to the *Rosaceae* family [16].

In our study seafood was the second most important food, responsible for 26% of anaphylaxis, in line with the study conducted in our area by Novembre et al. [17], in which seafood seemed to be the most important etiologic factor triggering anaphylaxis in children. We could not verify by specific IgE detection whether these reactions were truly allergic or allergy-mimicking. Adverse reactions to seafood are common and may cause a variety of symptoms that are difficult to pinpoint. These reactions include allergic or infectious diseases with fever, abdominal pain and diarrhea, and toxic reactions such as Scombrototoxicosis mimicking an IgE-mediated reaction [18,19].

Drugs accounted for 35.7% of the episodes in our study, with 24/50 (48%) reactions related to NSAIDs and 15/50 (30%) to antibiotics, β -lactams being the most frequent (11/50, 22%). This is similar to the findings by Stewart and Ewan [3] and Yocum and Khan [4] but contrasts with Pumphrey and Stanworth's study in which all drug reactions were due to muscle relaxants [5]. In the general population, β -lactams are responsible for 60% of allergic reactions to antimicrobials [20], muscle-relaxants accounts for 43% of anaphylactic reactions to drugs [21] and NSAIDs cause 1/3 of the cases of cutaneous reactions [22] but figures on anaphylaxis are scant.

In our study, very few reactions were due to hymenoptera venom. This contrasts with our previous findings of a prevalence of 2.7% in the general population [23]. However this figure was obtained from an epidemiological study in a specific area. Our hospital is in the centre of Milan and the population mainly lives in town, so it is less likely to be stung.

In this study, as in the studies by Stewart and Ewan [3] and Yocum and Khan [4] there was higher prevalence of anaphylactic reactions among females (71%); the real cause of this is not known. A personal history of atopic disease was found in

48.5% of the patients, in agreement with previous studies [3–5]. Patients with food anaphylaxis were highly atopic, with a clinical history of allergy to several foods; the association between atopy and food anaphylaxis has already been reported [5]. In patients with drugs anaphylaxis, this association was not found according to literature data.

In conclusion, foods, in particular fresh fruit and vegetables, seem to be the most important cause of recourse to the E.R., at least in our area. We are now planning an operative system in the Milan area by which all patients coming to the E.R. because of an anaphylactic reaction will be referred to an allergy department. This will enable us to calculate the incidence of anaphylaxis more precisely from the epidemiological viewpoint.

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