

Incidence of anaphylaxis with circulatory symptoms: a study over a 3-year period comprising 940 000 inhabitants of the Swiss Canton Bern

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Summary

Background Diagnosis of anaphylaxis is clinically based and usually straightforward. However, data on the epidemiology of anaphylaxis, particularly the most profound and life-threatening form such as anaphylactic shock are limited and thought to be under-reported.

Objective The primary aim of this study was to investigate the incidence and the causes of severe anaphylaxis with circulatory signs in the Canton Bern, which comprises about 940 000 inhabitants or approximately one-seventh of the population of Switzerland.

Methods During a 3-year period, 1 January 1996 to 31 December 1998, all medical records (7739 documents) from the two allergy clinics of the Canton Bern have been reviewed. In addition, all seven board-certified specialists of the *Foederatio Medicorum Helveticorum* (FMH) in Allergology and Clinical Immunology of this Canton as well as all 17 hospitals with emergency units of this area have been contacted for cases with an anaphylactic event not referred to the allergy clinics.

Results Overall, 226 individuals, 106 females (47%) with a mean age of 41 years (range, 5–74 years) and 120 males (53%) with a mean age of 38 years (8 months–83 years) were diagnosed as having presented generalized, life-threatening anaphylaxis with circulatory symptoms. Altogether, these patients experienced 246 episodes of severe systemic reactions. In addition, death due to anaphylaxis occurred in three subjects. The annual incidence of anaphylaxis per 100 000 inhabitants per year ranged between 7.9 and 9.6 cases. Hymenoptera stings (58.8%), drugs (18.1%), and foods (10.1%) were the most commonly identified culprits for anaphylaxis. In 5.3% of all anaphylactic events, the cause could not be identified.

Conclusion The incidence rate of severe life-threatening anaphylaxis with circulatory signs in the Canton Bern, Switzerland, with 7.9–9.6 per 100 000 inhabitants per year is comparable to the findings of other epidemiological investigations. In most events, a causal agent or allergen could be identified by a careful allergological examination.

Keywords anaphylactic shock, anaphylaxis, anaphylaxis due to allergy, anaphylaxis to drugs, anaphylaxis to food, anaphylaxis to Hymenoptera venoms, epidemiology of anaphylaxis, fatal anaphylaxis, incidence of anaphylaxis

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Introduction

Anaphylaxis is a potentially life-threatening clinical syndrome resulting from the release of biologically active pre-formed or newly synthesized substances such as histamine, leukotrienes or prostaglandins from mast cells and basophils [1]. It affects different organs, and its most severe form results in anaphylactic shock. In many instances, an IgE-mediated mechanism can be detected, but sometimes other yet not completely understood mechanisms are causative. Detection of suspected

causes varies among different studies but may fail in up to one-third [2–6]. In some series of patients with recurrent anaphylactic episodes, the term idiopathic anaphylaxis is used to characterize a severe systemic mast cell-mediated reaction without identifiable aetiology [7].

The incidence of severe anaphylaxis may have increased in Europe and in the United States over the last decade [8], although epidemiological studies are limited. Data exist concerning certain agents such as penicillin, non-steroidal anti-inflammatory drugs (NSAIDs), radiocontrast media, Hymenoptera, or latex [1, 8, 9], and with regard to selected patient groups [5, 10–14]. Anaphylaxis may complicate the hospital course in one out of 3000 hospitalized patients [12]. Among emergency admissions, the incidence of anaphylaxis was 0.4% of a total of over 38 000 cases in an Italian [10], and

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0.04% per 55 000 cases in an English study [11]. With respect to the general population, the incidence of anaphylaxis in a Danish study was estimated as of 3.2 cases and in a German survey as of 9.8 cases per 100 000 inhabitants per year [13, 14]. In a recent and the most extensive epidemiologic evaluation of the US, Yocum et al. assessed an average annual incidence of anaphylaxis of 21 per 100 000 person-years [5].

Drugs, foods, latex, and Hymenoptera venoms are the most common reported culprits for anaphylaxis [1–10]. In a recent meta-analysis on the incidence of anaphylaxis in the US, Neugut et al. calculated that up to 16% of the population are at risk for anaphylaxis upon contact with the causative agents [8]. These estimations support the hypothesis that the occurrence of anaphylaxis is probably under-reported, which may be especially true in the case of a fatal or near-fatal course [15, 16].

The major aim of this study was to investigate the incidence and the causes of severe anaphylaxis with circulatory signs in the Canton Bern, which comprises approximately one-seventh of the population of Switzerland (approximately 7.12 Mio inhabitants).

Methods

Medical record review

All medical records from 1 January 1996 until 31 December 1998 of the two allergy clinics of the Canton Bern (Policlinics for Allergy and Immunology, Inselspital, and Allergy Unit, Spitalbern Ziegler) have been reviewed by the investigators. In addition, all seven board-certified practitioners and specialists of the *Foederatio Medicorum Helveticorum* (FMH) in Allergology and Clinical Immunology of this Canton as well as all 17 hospitals with emergency units of this area were contacted for cases with an anaphylactic event not referred to the allergy clinics.

Definition of anaphylaxis

In this investigation, only severe systemic anaphylaxis with circulatory symptoms (hypotension, unconsciousness, or shock) consistent with a generalized mast cell-mediated reaction were included. Symptoms considered as immediate usually occurred within a period of 2 h after contact, ingestion, or parenteral injection of a potential allergen or suspected agent [1, 8]. The diagnosis of anaphylaxis was set after an allergological work-up based on history, consistent symptoms and signs of a mast cell release, and allergy testing. Patients with isolated asthmatic symptoms were not included.

Allergological work-up

Investigation of potential agents was based on history, skin, and eventually serological tests. Skin prick tests (SPTs) using commercial allergen extracts (supplied by ALK, Hørsholm, Denmark, or Allergopharma, Reinbek, Germany) were performed according to the recommendation of the European Academy of Allergology and Clinical Immunology (EAACI) [17]. Pharmedal venoms were used intra-dermally for patients with a history of bee and yellow jacket stings; scratch as well as scratch-patch testing with drugs was

performed as described previously [18]. Allergen-specific serum IgE using the CAP-FEIA system and total IgE (both from Pharmacia, Uppsala, Sweden) were determined according to the manufacturers' recommendation. In a few cases, negative investigations were followed by an open challenge test with the suspected source.

Data analysis

The incidence of anaphylaxis was calculated by using the total number of reported and affirmed anaphylaxis, and the inhabitants of the Canton Bern in the years 1996–1998 issued by the Swiss Federal Statistical Office [19]. Using the ICD10 code (D69.0, T63.4, T78.0, T78.1, T78.2, T78.3, T88.2, T88.6, T88.7, X23), fatalities due to anaphylaxis were also obtained from the same department.

Results

Data on the patients with anaphylaxis

Out of a total of 7739 medical records reviewed (6754 Inselspital; 985 Spitalbern Ziegler) in the 3-year period, 1996–1998, anaphylaxis has been identified in 215 subjects (121 Inselspital; 94 Spitalbern Ziegler); 157 patients (73.0%) were referred by general practitioners, 55 (25.6%) by hospitals, and three (1.4%) by themselves for allergy assessment. In addition, 11 subjects were evaluated outside the two allergy centres by FMH board-certified allergologists and could not be evaluated for all aspects (e.g. Table 1). Of these 226 individuals, 106 (46.9%) were females (mean age of 41 years; range, 5–74 years) and 120 (53.1%) were males (mean age of 38 years; 8 months–83 years). Altogether, these 226 patients experienced 246 episodes of anaphylaxis: 214 individuals (94.7%) had one episode, nine (4.0%) had two episodes, and three (1.3%) had three and more events of anaphylaxis.

Two hundred and ten out of the 215 (97.6%) patients investigated by the authors needed emergency medical assistance; 74 of them (34.4%) were referred to a nearby hospital for further observation subsequent to anaphylaxis. In five incidents, spontaneous remission occurred, four of them witnessed by other persons. Clinical manifestations of anaphylaxis were severe and life-threatening in all subjects. Hypotension has been documented in 160 (74.4%), and

Table 1. Organ systems involved in 215 subjects with anaphylaxis*

Organ systems	N	%
Cardiovascular total	215*	100.0
Cardiovascular alone	5	2.3
+ skin	47	21.9
+ respiratory tract	10	4.6
+ gastrointestinal tract	1	0.5
+ skin and respiratory tract	91	42.3
+ skin and gastrointestinal tract	26	12.1
+ respiratory and gastrointestinal tract	9	4.2
+ skin and respiratory and gastrointestinal tract	26	12.1
Skin total	190	88.4
Respiratory tract total	136	63.3
Gastrointestinal tract total	62	28.8

*The 11 patients evaluated by the practising allergists are not included.

unconsciousness in 120 (55.8%) subjects. A full shock was recorded in 71 (33.0%) patients, and 13 of them (6.0%) needed a cardiopulmonary resuscitation. Following the cardiovascular system (100%), skin symptoms were recorded in 190 (88.4%), respiratory symptoms in 136 (63.3%), and gastrointestinal tract symptoms in 62 (28.8%) patients (Table 1).

Characteristics of the anaphylactic events

The temporal relationship between exposure to a suspected source and occurrence of anaphylaxis was as follows: 192 subjects (89.3%) experienced full anaphylaxis within 1 h, 12 subjects (5.6%) within 2 h, and 11 subjects (5.1%) after 2 h. The average time from exposure to the suspected source until occurrence of anaphylaxis was 28 min (range, 1–250 min). Of the 13 (6.0%) in-hospital events, eight occurred intra-operatively, one pre-operatively, and four during the hospital stay. In 80 instances (37.2%), the patient was on a drug regimen that may have caused or favoured the reaction: antibiotics (in 23 subjects (28.8%)), β -blocking agents (20 (25%)), angiotensin converting enzyme (ACE)-inhibitors (9 (11.3%)), and various drugs.

Treatment of anaphylaxis

Of the 215 patients with available data for the treatment, antihistamines and corticosteroids were given in 191 (88.8%) and 189 (87.9%) instances, respectively. Epinephrine in any form was 103 (47.9%) anaphylactic episodes. The epinephrine ampoule/syringe/needle technique (epinephrine 1:1000) was the preferred method in the emergency situations in 69 (32.1%) patients followed by the commercially available auto-injector system of EpiPen 0.3 mg (ALK-Abelló) in eight (2.7%) patients. In four incidents, the patient himself injected the auto-injector EpiPen 0.3 mg. An epinephrine inhalation aerosol and β_2 -agonist was used in 26 (12.1%) and 11 (5.1%) patients, respectively, and on two (0.9) occasions the patient needed intubation.

Table 2. Causes of anaphylaxis in 226 subjects

Cause	1996	1997	1998	Total
Total	66 (100%)	78 (100%)	82 (100%)	226 (100%)
Hymenoptera	38 (57.6)	45 (57.7)	50 (60.9)	133 (58.8)
Bee	25 (37.9)	20 (25.6)	10 (12.2)	55 (24.3)
Yellow jacket	7 (10.6)	17 (21.8)	29 (35.4)	53 (23.5)
Hornet	2 (3.0)	1 (1.3)	1 (1.2)	4 (1.8)
Not identified	4 (6.0)	7 (9.0)	10 (12.2)	21 (9.2)
Drugs	10 (15.2)	17 (21.8)	14 (17.1)	41 (18.1)
Foods	11 (16.7)	5 (6.4)	7 (8.5)	23 (10.1)
Exercise	2 (3.0)	1 (1.3)	1 (1.2)	4 (1.8)
Latex	1 (1.5)	3 (3.8)	2 (2.4)	6 (2.7)
Sperm	–	–	1 (1.2)	1 (0.4)
Mastocytosis	–	–	1 (1.2)	1 (0.4)
Cold urticaria	–	1 (1.3)	–	1 (0.4)
Specific immunotherapy	1 (1.5)	1 (1.3)	–	2 (0.9)
Snake venom	1 (1.5)	–	–	1 (0.4)
Grain dust*	–	1 (1.3)	–	1 (0.4)
Not identified	2 (3.0)	4 (5.1)	6 (7.3)	12 (5.3)

Data are given on an annual basis.

*Occupational exposure.

Causes of anaphylaxis

Agents identified as causative for an anaphylactic event are summarized in Table 2. Based on history, skin tests, and specific IgE in the majority of our study population, an insect sting as cause of anaphylaxis (133/226 (58.8%)) was diagnosed. Bees and yellow jackets were almost equally involved. In 41 cases (18.1%), a drug was identified. Approximately half of them (51.2%) reacted to NSAIDs. Propyphenazon (six of 21 cases (28.6%)) and diclofenac (five of 21 cases (23.8%)) were the NSAIDs most frequently implicated. Antibiotics were involved in eight subjects (19.5%). Except for the β -lactam antibiotics on three occasions, quinolons and sulfonamides were causative in two events each, and vancomycin in one case. Foods were the third important cause for anaphylaxis with celery as the principal source in 11/23 (47.8%) episodes. In addition, in two of four subjects, a food-dependent, exercise-induced anaphylaxis to celery and mango, respectively, was suspected. Latex anaphylaxis occurred in relation to contact to gloves (three), condoms (two), and in one case following urinary catheterization. In two subjects, specific immunotherapy with standardized grass-rye pollen mixtures (ALK, Hørsholm, Denmark) was causal. In spite of an intense search, no source could be identified in 12 subjects (5.3%) based on history, medical documents, or allergy tests. In total, 11 challenges were performed with alternative drugs in seven and foods in four subjects; all challenges were negative.

Recurring anaphylaxis

Before the allergological work-up, six out of 215 individuals (2.8%) experienced at least one prior episode of anaphylaxis. After the identification of the causal agents, four subjects (1.9%) faced anaphylaxis again: in two cases, anaphylaxis was caused by an inadvertent re-exposure to the same source, in one subject by a self-experiment, and in the fourth patient the cause remained unidentified. Sperm allergy was recognized in a 36-year-old atopic woman. Although she knew the origin and was aware of protective measures, she experienced several allergic reactions of various intensity following sexual intercourse. Repeated episodes of anaphylaxis were also reported in a 25-year-old atopic woman with cold urticaria.

Prevalence of atopy

Eighty-five out of 215 subjects (39.5%) who experienced anaphylaxis were atopic based on personal and family history, and SPT reactivity to inhalants (≥ 2 positive tests). With regard to the causal agents, the distribution of atopy in our study population was as follows: 40 of 129 (31.0 %) Hymenoptera sting reactors, 15 of 40 (37.5%) drug reactors, 12 of 19 (63.2%) food reactors, nine of 12 (75.0%) patients without identification of the source, three of four (75.0%) latex reactors, both subjects on immunotherapy, one out of four exercise reactors, and the subjects with sperm allergy, cold urticaria, grain-dust, and the snake venom allergy.

Incidence of anaphylaxis

Annual occurrence of all the 249 recorded anaphylactic episodes was as follows (Table 3): 74 events (29.4%) in 1996, 86 events (34.1%) in 1997, and 92 events (36.5%) in 1998.

Table 3. Annual prevalence of life-threatening anaphylaxis and incidence per year for the Canton Bern

Prevalence	1996	1997	1998	Total
Cases	74	86	89	249
Death due to anaphylaxis	–	–	3	
				Average
Incidence per 100 000 citizens	7.9	9.2	9.6	8.9
Hymenoptera stings	4.1	5.2	5.5	4.9
Drugs	1.3	1.9	1.5	1.6
Food	1.4	0.5	0.9	0.9
Various triggers	1.1	1.6	1.7	1.5

During the 3-year period, death due to anaphylaxis occurred in three subjects living in the Canton Bern, all in the year 1998 (19): an 84-year-old woman died after the administration of a radiocontrast material, a 73-year-old man succumbed intra-operatively following an anaphylactic shock, and a 53-year-old man died of anaphylaxis due to an unknown cause. The population-based case-fatality rate in our study was 0.0001% per year for the Canton Bern and was somewhat lower than for the rest of Switzerland (0.0004%). Whereas three fatalities occurred within the area investigated, 24 incidents were recorded in other parts of Switzerland [19]. With reference to entire Switzerland, 24 subjects died of anaphylaxis during this observation period: 13 subjects (10 males and three females) died due to Hymenoptera stings (yellow jackets (nine), bee (one), not identified (three)), seven due to other causes but mainly in relation to drugs (five males and two females; radiocontrast material (two), β -lactam antibiotics (two), ACE-inhibitor (one), not specified (two)), and four in relation to general anaesthesia.

Discussion

In this 3-year retrospective survey of the second largest Canton of Switzerland, the incidence of severe life-threatening anaphylaxis with eight to 10 per 100 000 inhabitants per year is within the range of investigations from other areas [5, 8, 13, 14]. A major difficulty in comparing indisputably most of these studies is the definition of anaphylaxis used. Anaphylaxis is a clinical diagnosis comprising a combination of circulatory, dermatological, respiratory, and gastrointestinal symptoms. In Switzerland, the term 'anaphylaxis' is almost exclusively used for generalized reactions with hypotension and/or anaphylactic shock. With the exception of five subjects who experienced circulatory manifestations only (cause: yellow jackets in four cases, gelatin colloid solution in one case), in all other patients at least two organ systems were involved in all other episodes of anaphylaxis.

We believe that our investigation comprises most if not all patients with anaphylaxis of our region. This assumption is based on the severity of the clinical reaction, the fact that treating physicians transfer the patients with anaphylaxis to an allergological work-up that is supported by the low pre-analytic anaphylactic events of less than 3%. Therefore, most patients with anaphylaxis will be seen by an allergologist in this part of Switzerland.

Hymenoptera stings caused most of the anaphylactic events in our series and exceeded all other identified sources by far. In our previous study comprising 118 patients, Hymenoptera stings ranked on the second place as a cause for life-threatening anaphylaxis with 23.7% [4]. Because of the participation of the main Swiss centre for Hymenoptera allergy, the Spitalbern Ziegler, this marked difference is partly explained [20]. On the other hand, almost half (43%) of the Canton Bern is a rural area and harbours twice as much beehives as any other canton, which might account for the overwhelming number of Hymenoptera sting anaphylaxis. According to the Swiss Beekeeper Association (Verein Deutschschweizerischer und Rätomanischer Bienenfreunde), about 43 300 beehives, and an average of approximately 1299 million bees (30 000 bees/hive) have been registered for the Canton Bern in the period from 1996 to 1998 [21]. During this 3-year period, 11 deaths were due to Hymenoptera stings. The estimated mortality from Hymenoptera stings is 0.45/Mio and year, and the estimated lethality is one in every 100 000 insect sting-allergic subjects per year [20, 22]. Both characteristics have been constant since decades in Switzerland.

NSAIDs were causal for most drug-induced anaphylaxis, which is in agreement with recent studies [2, 4, 5, 9]. Other important causes even for fatalities were β -lactam antibiotics and radiocontrast material. Irrespective of the identified cause, in about one-third of our series anaphylaxis was linked to the concomitant use of medications. Although not considered as causal agents, β -blockers (9%) and ACE-inhibitors (4%) were rather frequently involved in anaphylactic incidents. Of these, particularly the β -blocking agents are thought to raise the risk of anaphylactic reactions [1, 8, 23].

Foods are quite common causes of anaphylaxis. The incidence of food allergy depends not only of the age group but also on the cultural eating habits [1–8, 16, 23]. Overall peanuts, tree nuts, shellfish, fish, milk, and eggs are considered the leading causes of severe food-induced anaphylaxis. In children and adolescents with brittle asthma, peanuts and tree nuts are the main food identified for fatal or near-fatal allergic reactions [16]. In Switzerland, however, peanuts and tree nuts rarely cause life-threatening episodes in asthmatic children. This might be due to a different management of asthmatic children, and different feeding standards in childhood. In both our series, celery is by far the most important vegetable causing anaphylaxis with circulatory signs [4]. In Central Europe, this vegetable is the principal food causing severe allergic reactions, resulting particularly in generalized urticaria and hypertension but rather rarely in asthma. In adults, celery allergy preferentially is associated with sensitization to mugwort or birch as in our series [4, 24, 25]. In comparison with other reports [1, 3, 8, 15, 16, 26], in our study, no fatality could be definitively correlated to foods, although a systematic search of the Swiss Federal Statistical Office has been completed.

Despite educational campaigns, particularly in health-care settings, latex allergy still incorporates an unpredictable risk affecting more and more non-occupationally latex-exposed individuals [27, 28]. The implicated material – gloves, condoms, and urinary catheters – remains up till now the main source for allergic reactions to latex itself [1, 8, 23, 27, 28]. In addition, cross-reactivity to food such as banana, or chestnut also accounted for some food-induced reactions.

Idiopathic anaphylaxis is an exclusion diagnosis [7, 23]. In comparison with many other studies [2, 5, 7], the percentage of idiopathic anaphylaxis in our series is quite insignificant. As in the previous study, more than 90% of all anaphylactic episodes could reasonably be explained [4]. Whereas others argue that in some studies exercise-induced or multifactorial events were diagnosed as idiopathic, we believe that the search for identification of the cause has not been forced intensively or the interpretation was not straightforward enough. Although the occurrence of exercise-induced anaphylaxis is not rare, most episodes do not end in the full picture of anaphylactic shock [29].

A thorough allergy work-up is essential for all kinds of anaphylaxis. Based on this analysis, the rate of recurrent anaphylaxis with 3% and 2%, respectively, prior and subsequent to the allergological evaluation seems minimal. While all emergency physicians are instructed to consider epinephrine as the drug of choice for treatment of anaphylaxis [23, 26, 30, 31], epinephrine has been used in only half of our patients for the treatment of acute anaphylaxis. This might be explained by the assumption that in many instances clinical symptoms of anaphylaxis were considered as rather mild or already on the way of spontaneous recovery.

Atopy is thought to be a risk factor for anaphylaxis [2, 5, 10, 26]. While in studies on Hymenoptera or drug allergies no correlation to atopy has been found [5, 20, 32], other studies indicate an association with latex or food allergy [3, 4, 23, 26, 27].

In summary, the incidence rate of anaphylaxis of the Canton Bern, Switzerland, with eight to 10 per 100 000 inhabitants per year is within the range of that reported for other countries considering life-threatening severe allergic reactions only. In most events, a causal agent or allergen has been identified, indicating the necessity of a thorough investigation by a trained allergologist. Whereas the main culprits of anaphylaxis were the same as in comparable studies, Hymenoptera sting allergy by far exceeded all other causes in our series.

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