

Original article

The economic costs of severe anaphylaxis in France: an inquiry carried out by the Allergy Vigilance Network

Background: The prevalence of severe anaphylaxis, between 1 and 3 per 10 000, has increased sharply over recent years, with a rate of lethality of 1%. The economic burden is unknown.

Objective: The aim of this study was to estimate the economic costs of anaphylaxis, including direct costs of treatment, hospitalization, preventive and long-care measures, and the indirect cost: absenteeism.

Methods: Analysis of 402 patients of anaphylaxis declared by 384 allergists was reported to the Allergy Vigilance Network. The global cost was estimated from the national data of hospital admissions: ICD-10 coding available for 2003, 2004 and 2005.

Results: Three work/classroom days were lost per patient. Diagnosis required oral challenge with hospitalization in 18% of cases. The estimated mean total cost was 1895€ for food- and drug-related anaphylaxis (5610€ for the most severe), and 4053€ for Hymenoptera anaphylaxis. National statistics recorded 2575 patients in 2005; 22% more than in 2003. The estimated annual cost was 4 789 500 €. The possible reasons for this being an under-estimate include: data coming only from hospitalized patients, poor identification by medical teams unfamiliar with ICD-10 codes, peri-operative anaphylaxis being insufficiently declared, rush-immunotherapy and maintenance treatments for Hymenoptera anaphylaxis. Similarly, the extra cost of cow milk substitutes, as well as insurance costs where deaths are followed by litigation were not taken into account.

Conclusions: The mean cost of anaphylaxis was 1895–5610€ in nonfatal patients. The prevalence was under-estimated because of many biases, leading to under-estimation of the national cost. Further studies would be necessary to evaluate the value of preventive strategies.

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Anaphylaxis is an immunoglobulin E (IgE)-mediated allergy defined by major clinical features including cardio-vascular collapse, laryngeal angio-edema, and acute asthma requiring emergency treatment and entailing lethal risk. A positive clinical diagnosis is highly probable when one of the criteria defined by Sampson et al. is met (1–3). It occurs in children as well as in adults. The prevalence ranges from 1 to 3 per 10 000 people/year (4–9). There is a high chance of recurrence (9). Death occurs in 0.65–2% of patients (9–13). There has been a fivefold increase in frequency between 1980 and 1992 (14–17). Recently, a British study reported a 700% increase in hospital admissions for anaphylaxis between 1990 and 2007 (18). This increase in prevalence impacts the economic burden for treatment and management of anaphylaxis. Although various studies have estimated the economic cost of respiratory allergies, there have not been any for anaphylaxis (17, 19–21). A consensus exists concerning the management and treatment of allergic emergencies, together with the prevention of recurrence

(1, 2, 22, 23). The real cost must take account of all medical aspects, including indirect costs related to absenteeism and loss of productivity (24, 25). The study reported here, the first of its kind in France, is based on 402 patients of severe anaphylaxis cases documented by the Allergy Vigilance Network between January 2004 and the end of June, 2006. An extrapolation to national annual costs is then made on the basis of the frequency of anaphylaxis reported in hospitals coded according to the national classification of diseases (ICD version 10). Under-estimation of these costs will then be discussed.

Methods

Population

The study was based on 402 cases reported by the Allergy Vigilance Network: 181 in 2004, 108 in 2005, and 113 during the first semester of 2006. Data included: sex, age, type of clinical reaction, emergency management, and any hospitalization, associated factors (alcohol,

exercise, intake of aspirin, and other non-steroidal anti-inflammatory drugs, beta-blockers, or ACE inhibitors, etc.), information on food intake (estimated amount, masked allergen). They also included details of skin and laboratory tests, oral challenges, diagnosis, and proposed prophylaxis. Clinical features were classified into four categories (1, 2): (i) anaphylactic shock defined by symptoms of different organs with cardio-vascular collapse; (ii) serious acute asthma requiring emergency treatment; (iii) laryngeal angio-edema associated with respiratory distress and dysphonia or aphonia and (iv) serious systemic reaction associated with symptoms in two or more organs without change in blood pressure (26, 27).

Analysis of economic costs

Economic costs include direct medical costs (drugs, consultations, use of emergency units, examinations required for diagnosis and hospitalizations) and nonmedical costs (transport, special diets, etc.), as well as indirect costs related to the disease such as absenteeism (25). Estimates of direct costs were based on public hospital fees and the current fees of General practitioner emergency visits Table 1. In a national project aiming to protect all school children with severe food allergy from allergens that cannot be totally avoided, two emergency kits per child are required, one at home and one at school (28, 29). All adults reporting anaphylaxis because of adverse food reaction are provided with an emergency kit. Indirect costs are related to the consequences of the disease, i.e. absenteeism and decreased productivity. Absenteeism was defined as a mean absence of 2 days at the time of the event, and of 1 day for testing after the event, i.e. an absence of 3 days. The mean costs for absenteeism of a salaried worker in France was calculated on the basis of Belgian costs, i.e. 105€/day (25). The financial conditions for sick leave were similar for the parents whose sick children required constant home care. The estimated cost of loss of productivity (33.76€/day in a single study) is very difficult to confirm, so it was not included. Moreover, loss of productivity costs can only be calculated for chronic diseases (24).

Data collection of 402 patients

Each patient report was analyzed; the data recorded included calls for emergency services (transport in ambulance and hospitalization, the treatment given, subsequent allergy consultations including skin tests, the laboratory tests performed, prescriptions for emergency kits, subsequent hospitalization for oral challenge). These data were used to calculate the costs for each patient. The costs calculated for the 402 patients were compared with national incidence as documented in the national PMSI¹ Program database (recording statistics of hospital admissions). International Classification of Diseases (ICD-10 since 1993) codes for anaphylaxis were used: T780: anaphylactic shock because of adverse food reaction, T782: anaphylactic shock, not specified, T805: anaphylactic shock because of serum/vaccine/immunization, T 886: anaphylactic shock because of adverse drug reactions, T882: anesthetic shock.

Results

Ninety-six children (38.7%) and 152 adults (61.3%) presented food allergy. Seventeen children (11.1%) and

Table 1. Estimate of the costs of medical procedures for management of anaphylaxis

<i>General Practitioner</i>	
Mean cost of emergency visit	95.90€
<i>Hospitalization</i>	
Emergency ambulance brigade called (without later hospitalisation)	200.00€
Visit to emergency unit (<5 h)	462.00€
Visit to emergency unit and hospitalization exceeding 5 h	1140.00€/day
Emergency ambulance brigade and emergency unit = equivalent costs	
Hospitalization in medical unit	779.00€/day
Hospitalization in resuscitation or intensive care unit	2115.00€/day
<i>Allergy screening</i>	
<i>Allergy tests</i>	
Prick-tests (FGRB003 or FGRB004)	28.80€ or 31.51€
IDR FGRB001, FGRB002 or FGRB005	30.49€ or 34.16€
<i>Laboratory tests</i>	
Specific IgE analysis	14.85€
Serum tryptase assay	27.00€
Serum histamine	40.50€
fx5	14.85€
CAST	56€
Basophil activation test	40€
Leukocyte histamine release test	56.70€
<i>Hospitalization</i>	
For challenge tests	779.00€/day
<i>Emergency kits</i>	
Adult (Anapen [®] _{0,3} + Ventoline [®] + Solupred [®] oro + Acrius [®])	96.95€
Child (Anapen [®] _{0,15} + Ventoline [®] + Celestene [®] + Acrius [®])	58.79€

137 adults (88.9%) were allergic to medication. Of 248 patients had food anaphylaxis, skin tests were carried out in 81% of subjects, specific IgEs in 51%, oral challenges in 12.5%. Of 154 cases of drug anaphylaxis, skin tests were carried out in 86%, *in vitro* tests for specific IgEs in 23% of subjects, cellular activation tests (basophil activation test by flux cytometry) in 11% of subjects, oral challenges in 16.8%.

The direct cost of severe anaphylaxis ranged from 74.88€ (emergency visit during working hours accompanied by emergency treatment such as injection, not followed by allergy screening because the patient had known allergy) to 4445.47€ (night-time emergency visit with emergency treatment, emergency ambulance brigade called and patient sent to an emergency unit, 1 day's hospitalization in the resuscitation unit, allergy screening after the event with a battery of skin tests, one or several IgE-specific analyses, tryptase assay, 2 days of hospitalization for re-challenge and two emergency kits for children). Eighteen percent of patients required further hospitalization for challenge tests. The mean direct cost was 1580€/patient. The seven most severe cases (seven prelethal cases/402) had costs of 2115€/day. The mean indirect cost was based on mean absenteeism of 3 days, i.e. 315€. The total cost was 1895€. Data collected from the national database using ICD-10 codes (data validated by the French technical agency for hospitalization infor-

¹Programme de médicalisation des systèmes d'information – information system medicalization.

Table 2. Hospital statistics for 2003–2005 according to anaphylaxis coding

ICD 10 code	Classification	2003	2004	2005
T780	Anaphylactic shock due to adverse food reaction	153	212	236
T782	Anaphylactic shock, not specified	1426	1708	1703
T805	Anaphylactic shock due to serum/vaccine/immunization	16	15	11
T886	Anaphylactic shock due to adverse drug reactions	446	553	535
T882	Anesthetic shock	69	78	90

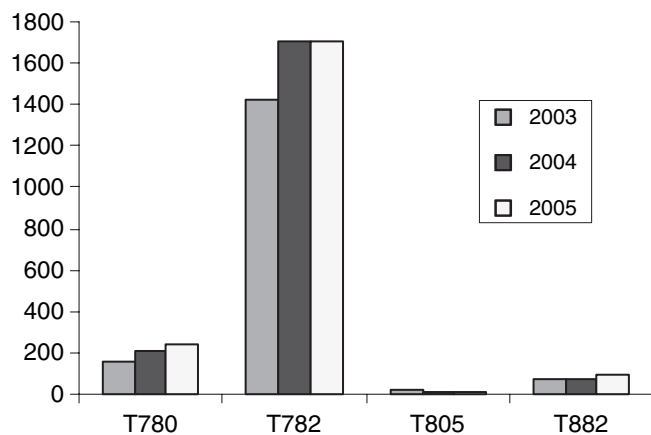


Figure 1. Frequency of different types of anaphylaxis according to ICD-10 codes.

mation: *Agence technique de l'information de l'hospitalisation*) evidenced 2575 cases in 2005 (Table 2, Fig. 1). There was a 22% increase between 2003 and 2005. On the basis of 2575 cases, the annual national cost has been extrapolated from our data and may reach 4 789 500€.

Discussion

There is a general consensus on calculating the direct costs for the prevention and treatment of allergic emergencies and on the need for allergy screening tests (1, 2, 23). Emergency treatment always requires adrenalin. Corticosteroids are only complementary and the efficiency of histamine H1 antagonists, though widely prescribed, has never been studied (30) by randomized studies. It is, however, a standard practice to recommend a combination of three drugs (22). The duration of hospitalization should be from 8 to 10 h to treat biphasic reactions which occur in 6–19% of patients (14, 31). All authors record the insufficient use of adrenalin, even in emergency units (used only in 24–33% of cases). According to the Allergy Vigilance Network, adrenalin was used in 32% of patients in 2006 (26, 27). This insufficiency affects both the seriousness and recurrence of anaphylaxis and is a source of increased costs (32).

Because of the risk of recurrence, there is a consensus on the need for emergency kits containing two preloaded syringes for self-injection. These kits also often contain an immediate-acting beta agonist, corticosteroids (orodis-

persible tablets or drops), and an anti-histamine (29). The daily prescription of a long-acting beta-agonist for asthmatic children with food allergy with a history of broncho-spasm, or who suffered broncho-spasm during oral challenge, was not taken into account in our study, because a consensus on such a decision has not yet been established. The prescription of a long-acting beta-agonist might be justified even in the case of a mild asthma, as death because of anaphylaxis is often related to serious acute asthma (11). Similarly, with regard to prevention, it is impossible to evaluate the costs of food substitutes for infants allergic to cow's milk. The cost of milk protein hydrolysates and amino acid formulas are covered by the French health insurance, but those of allergen-free foods marketed by the food industry for older children are borne entirely by families. Finally, this study did not take into account the recommendation for an annual consultation and allergy tests in the event of anaphylaxis because of adverse food reactions (33).

There is agreement on the need to carry out allergy tests within an optimal period of 3 months to confirm the anaphylactic nature of the event and to identify the causative allergen, which is the only way to implement adequate corrective measures (1–3). For anaphylaxis because of adverse food reaction, testing usually requires two consultations for skin tests to airborne allergens (orientation towards possible cross-reactions) and to food allergens. Identification of *in vitro* specific IgE may require five tests (34). Tryptase assay is recommended to detect underlying mastocytosis (35). For anaphylaxis because of adverse drug reactions, two series of skin tests are often necessary, one for diagnosis and one to study possible cross reactivity, to inform the patient on the replacement of compounds of the same family (i.e. curares, beta-lactamines, iodinated contrast agents). As tests for anti-drug IgE are limited to beta-lactamines and to quaternary ammoniums ions (for curares), cellular activation tests are more used than in food anaphylaxis (basophil activation test, histamine release test, cellular allergen stimulation test) (36). For food and drug anaphylaxis, patients are often hospitalized to carry out oral challenge tests. This was the case for 57 of patients in this study.

The prevalence of anaphylaxis to Hymenoptera is estimated at 0.85% in France (37). Related costs are higher because a tryptase assay is also recommended to detect a mastocytosis (35, 38, 39). The costs of rush immunotherapy (24 h hospitalization: 779€) and monthly

immunotherapy injections for 5 years [1260€ with annual allergy tests (31.5€)] must be added, i.e. a total of 4053€. In the event of associated mastocytosis, immunotherapy has to be continued indefinitely because of the risk of fatal recurrence (39). Depending on the guidelines followed, patients of peri-operative shock, related to anesthesia require two to three laboratory tests during the event (tryptase and histamine assays, screening for IgE specific to curares or latex) (40, 41). The cost of peri-operative shock is higher than calculated costs because it often prolongs stay in the intensive care unit and possibly postpones surgery. One study evaluated the real cost of an injection of succinylcholine, taking into account anaphylaxis to succinylcholine, and hypothesized that it is more than 20 times the cost of the vial (42).

Indirect costs are difficult to estimate. There is no standard method for measuring productivity in the work place as a function of profession, type of activity and their capacities. It is therefore difficult to estimate the economic loss caused by poor performance at work. We estimated that anaphylaxis corresponded to a 3 day sick leave, and we based this on the mean duration of hospitalization for allergic diseases (1.5 days according to the French technical agency for hospitalization information: *Agence technique de l'information de l'hospitalisation*) (43). The agency classified hospitalization of homogeneous patient groups (HPG) as follows: 21M04Z: allergic reactions NOS, age <18 years, 21M05Z: allergic reactions NOS, age >17 years (the number 21 indicates that the HPG belongs to the major diagnostic category (MDC) number 21 entitled: 'Trauma, allergies and poisoning'. The letter M indicates the medical (and not surgical) character of the HPG, 04 signifies that it is HPG No. 4 in the MDC, Z refers to the absence of associated co-morbidity). The mean 3 days absence retained for severe anaphylaxis includes the day of the event, following hospitalization for 12–24 h and return home, which seems correct.

The overall cost of severe anaphylaxis is 1895€/patient. Although it is not easy to compare the cost of an acute disease with that of a chronic allergic condition, it is known in the US that the current annual cost of allergic rhinitis is 296€ and of asthma 4912€ (19, 20). However, this cost does not take into account the routine prescription of auto-injectable syringes of adrenalin found in many emergency kits of school children participating in a project to protect them from the risk of anaphylaxis: more than 7500 children in France took part in this project in 2004. The costs of food substitutes in the event of anaphylaxis because of cow's milk and to wheat-gluten flour do not fall within the scope of this study, even though milk protein hydrolysates and amino acid formulas are covered by the French health insurance, as are gluten-free foods in the event of prior agreement between the patient and the national insurance system. Finally, this cost estimate does not take into account compensation in the event of litigation following fatal anesthetic anaphylaxis (44). Finally the impact of anaphylaxis on

quality of life is hardly appreciated. Financial consequences of different ways of life (interruption of the maternal occupation, buying alternative but expensive food products, etc.) remain beyond any possibility of evaluation (45).

The estimate of national annual costs is greatly under-estimated for many reasons

If we retain the prevalence of severe anaphylaxis as 1–3/10 000, the probable number of cases is 6000–18 000. It is not possible to relate this figure to the year. However, the patients recorded in hospital statistics under-estimate the true situation. The recording of 78 and 90 anesthetic shocks for 2004 and 2005 (respectively) does not correspond with the findings of the Study Group on Anesthetic Anaphylactoid Reactions (*Groupe d'Etudes des Réactions Anaphylactoides Peranesthésiques*) that recorded more than 350/year (40). Similarly, hospital statistics reported 236 patients of anaphylaxis because of adverse food reaction, and for the same year the Allergy Vigilance Network reported 108, limiting reports to patients consulting 384 allergists. Approximate coding is also a cause for under-estimation: there were 3300 patients reported as T782 (anaphylactic shock, not specified). This code can include severe anaphylaxis corresponding to current criteria. From figures available in France, it is clear that anaphylaxis is greatly under-estimated. There are many reasons for this, either diagnosis is incorrect or codes are insufficiently known in emergency units (46).

The dramatic increase in anaphylaxis, evoking a genuine epidemic (47), indicates the necessity for more stringent quantitative assessment by means that are complementary to hospital statistics that use ICD-10 codes which are too limited for a comprehensive classification of allergy. Various ICD-9 codes which included useful information have completely disappeared (46). Moreover, severe anaphylaxis includes phenomena other than anaphylactic shock defined by cardio-vascular collapse. The fact that most deaths are caused by serious acute asthma (48) is difficult to assess as the ICD code for serious acute asthma (J46) makes no reference to etiology, and so it is currently impossible to identify those cases related to food-induced anaphylaxis. The same applies to the ICD code for angio-edema (T78.3) which groups together hereditary angioneurotic edema and angio-edema of different localizations and etiologies, and provides no information on the particular risk of laryngeal angio-edema. Modifications could be proposed for the ICD 10 code, backed by scientific allergological societies. Medical networks, such as the Allergy Vigilance Network, are now indispensable for regular updating of anaphylaxis data, complementary to epidemiological studies. This quantitative evaluation is necessary to estimate the full economic burden of anaphylaxis. This cost estimation will provide the future basis for assessing preventive strategies, for which costs and savings will have to be calculated.

Some economic studies have been published in American journals such as estimation of the least expensive antibiotic strategy during cardio-vascular surgery for patients allergic to penicillins and cephalosporins (49). Allergy tests could limit the use of vancomycin, which is an expensive drug, to 16% of cases (50). For idiopathic anaphylaxis, daily treatment with anti-histamines and corticosteroids considerably reduces emergency hospitalizations, thus reducing disease-related costs (51).

Conclusion

The cost of severe anaphylaxis, calculated from specific information collected by the Allergy Vigilance Network, is particularly high: 1895€. Under-reporting of patients using ICD codes is certain, and this results in under-estimating national costs, that this study has calculated at only 4 789 500. In France, the number of patients have increased by 22% between 2003 and 2005; in the UK there has been a 70% increase, suggesting that a similar evolution may occur in other European countries. Accurate etiological diagnosis is necessary to prevent recurrence, and in France the costs of first

intention allergy tests is low: <100€ (two consultations and skin tests). The cost of allergy consultations is negligible, compared with costs related to visits to emergency units and/or hospitalization in intensive care units. In the rapidly changing environment of severe anaphylaxis, allergologists have become key players in public health, and all economic cost strategies must necessarily take account of the data they provide. Studies carried out in other European countries with completely different health systems would be useful, as we could then compare management of severe anaphylaxis, and use them as a basis for general agreement on harmonizing practices for a disorder that is sometimes life-threatening.

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