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Review article

Epidemiology of life-threatening and lethal anaphylaxis: a review

Severe anaphylaxis is a systemic reaction affecting two or more organs or systems and is due to the release of active mediators from mast cells and basophils. A four-grade classification routinely places 'severe' anaphylaxis in grades 3 and 4 (death could be graded as grade 5). Studies are underway to determine the prevalence of severe and lethal anaphylaxis in different populations and the relative frequencies of food, drug, latex and Hymenoptera anaphylaxis. These studies will also analyse the risk arising from the lack of preventive measures applied in schools (personalized management protocols) and from the insufficient use of self-injected adrenalin.Allergy-related conditions may account for 0.2–1% of emergency consultations. Severe anaphylaxis affects 1–3 per 10 000 people, but for the United States and Australia figures are even higher. It is estimated to cause death in 0.65–2% of patients, i.e. 1–3 per million people. An increased prevalence has been revealed by monitoring hospitalized populations by reference to the international classification of disease (ICD) codes. The relative frequency of aetiological factors of allergy (food, drugs, insects and latex) varies in different studies. Food, drug and Hymenoptera allergies are potentially lethal. The risk of food-mediated anaphylaxis can be assessed from the number of personalized management protocols in French schools: 0.065%. Another means of assessment may be the rate of adrenalin prescriptions. However, an overestimation of the anaphylaxis risk may result from this method (0.95% of Canadian children). Data from the literature leads to several possibilities. First, a definition of severe anaphylaxis should be agreed. Secondly, prospective, multicentre enquiries, using ICD codes, should be implemented. Moreover, the high number of anaphylaxis cases for which the aetiology is not identified, and the variation in aetiology in the published series, indicate that a closer cooperation between emergency specialists and allergists is essential.

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Anaphylaxis, a term first used by Richet and Portier in 1902, is a serious and potentially lethal systemic reaction affecting two or more organs or systems (1). In English, the term embraces all the immediate signs caused by the release of active mediators from mast cells and basophils. Severe anaphylaxis is characterized by four clinical syndromes. Anaphylactic shock includes cardiovascular collapse associated with cutaneous, respiratory or gastrointestinal signs. Serious acute asthma is a particular type of anaphylaxis and is exemplified by lethal peanut allergy (2). Laryngeal angio-oedema, either isolated or associated with facial angio-oedema, is serious since it may cause asphyxia. Finally, there may be a systemic reaction affecting several target organs, with urticaria, abdominal pain, vomiting and respiratory distress. Anaphylaxis may also be classified into four grades according to severity (3, 4), severe anaphylaxis corresponding to grades 3 and 4. Grade 3 includes such serious symptoms as cardiovascular collapse, cardiac arrhythmia and severe broncho-spasm. Grade 4 includes circulatory failure, cardiac and/or respiratory arrest. Lethal anaphylaxis could be graded as 5.

Prevalence of life-threatening anaphylaxis

The prevalence of immediate allergic reactions is poorly documented. Three questions may be posed. What is the prevalence of all reactions requiring a medical assistance in the general population? What is the relative prevalence of the severe reactions? What is the relative prevalence of lethal anaphylaxis?

Epidemiological studies refer to different populations: the general population, for whom the diagnosis data are obtained through surveys or national registers (5–9), hospital populations whose files are coded according to the international classification of disease (ICD) directives (10–12), patient cohorts at emergency units (EU) (13–17), information from various networks such as The Study Group on Anaphylaxis during Anaesthesia (GERAP), and

the French Allergy Vigilance Network (4, 18). A subjective estimate of the risk of severe anaphylaxis may be made from the personalized management protocols for schools (19), and from the number of adrenalin prescriptions (20).

The available data suffer from methodological shortcomings which limit the accuracy of the estimated prevalence.

A total of 33 000 French people (a representative sample of the French population under 60 years of age, at the scale of 1/1000) answered a detailed questionnaire. This indicated that 3.2% had suffered from food allergy. About 5% were admitted to the EU and 17% required an emergency home visit from a doctor. This represented an incidence of immediate allergic reaction (requiring rapid medical intervention) for 70 in every 10 000 people (5). The rate of severe anaphylaxis is possibly much lower.

The prevalence of severe anaphylaxis may be estimated by studies of national or district registers. Similar data occur in different countries: from 0.5 to 1 per 10 000 in the United Kingdom, Switzerland and the United States (7–9; Table 1). A figure of 1.5 per 10 000 was given by a multicentre epidemiological study of 481,000 hospitalized patients between 1996 and 1998 in Sweden, Budapest, Barcelona and Bombay (21).

Allergy-related emergencies could be better determined from the files of EUs. They may represent from 0.2 to 1% of attendances at EU in Australia, the United Kingdom and France (Table 1; 13–17). Severe anaphylaxis was diagnosed in 1–9 of 10 000 people attending EU in UK, Australia and the USA (13). The figures for France and Italy fall between these two extremes: 3/10 000 (16, 17; Table 2). The frequency of allergy-related emergency in children is debatable; identical to that for adults, according to the report of Bohlke, but only 0.19 per 100 000 in MacDougal's series (8, 22). This figure was contested by Clark and Ewan who, considering only nut allergy, proposed a figure at least six times higher (23).

Lethal anaphylaxis represents from 0.65 to 2% of cases of severe anaphylaxis (6, 15), i.e. 1–3 deaths per million people. A figure of 1500 deaths per year in the United States has been suggested (24).

Continuous studies have been carried out by various networks on allergy during anaesthesia and food and drugs. The French retrospective study from the GERAP established that 65.1% of 518 cases reported over 2 years were grade 3 or 4 (4). These were declared after the diagnosis had been confirmed by subsequent allergy testing, although fatal cases were not recorded. The prospective study on 328 000 subjects undergoing general anaesthesia in Spain reported no fatal cases (25). A death rate of 4.7% was recorded in Japan (26). Better knowledge of this sort of accident results in prompter treatment and nowadays the progress made in resuscitation techniques reduces the risk.

The French Allergy Vigilance Network, active in France and Belgium since 2001 and involving 326 allergists, has recorded 229 cases of severe food-mediated anaphylaxis over 3 years, 39% of which occurred in children. Four deaths were reported, two children and two adults (18).

A way of evaluating the risk of severe anaphylaxis in children has been studied by using personalized management protocols implemented in schools for severe food allergies risk. The study carried out in 2002 on the whole French school population (11 512 729 children) revealed that 6.5 of every 10 000 children followed personalized management protocols (19). There has been a fourfold increase in the absolute number of personalized management protocols since 1999 (27).

Most studies are too recent to allow changes in prevalence to be assessed although the incidence of food allergies appears to be increasing. One has suggested a possible fivefold increase in France between 1980 and 1995 (28). British studies based on CIM-9, have reported a 250% increase for severe anaphylaxis between 1995 and 1999, with food anaphylaxis progressing in parallel (10, 12).

Overall, increasing allergy and anaphylaxis worries both the public and medical body alike, to the extent that

Table 1. Epidemiological studies of anaphylaxis in hospitals

Characteristics (author, year, country)	Sheikh and Alves, 2000 and 2001 (10, 11), United Kingdom Hospitalizations coded according to ICD 9995.0	Wilson, 2000 (12), United Kingdom Hospitalizations coded according to ICD 10	MacDougal, 1998–2000, United Kingdom
Sample size	13.5 million from 1991 to 1995	1202 patients/2 years (1998 and 1999)	Paediatrics register
Frequency of allergy-related emergencies	2323–0.017% (frequency doubled between 1991 and 1995)	Frequency doubled between 1995 and 2000	
Severe anaphylaxis (grades 3 and 4)	0.005% Adults F/M : 1/2	0.011%	0.00021% (two cases/million)
Lethality	0.5% of cases of anaphylaxis		Eight deaths/10 years 1/800 000 children/year
Cause identified (%)	51	Approximately 52	
Food (%)	15	31–37	
Drugs (%)	62	16–22	
Insects (%)	11		
Other causes (%)			

Table 2. Epidemiological studies of anaphylaxis in emergency units

Characteristics (author, year, country)	Brown et al., 2001 (15), Australia (SAU) (cases coded according to ICD 9)	Stewart and Ewan, 1996 (14), United Kingdom (SAU)	Bellou et al., 2003 (17), France (SAU)	Pastorello et al., 2001 (16), Italy	Helbling et al., 2004 (6), Switzerland
Sample size	62 000 patients/year	55 000 patients/year	32 000 patients/year	38 685 patients in 1997 and 1998	940 000 patients
Frequency of allergy-related emergencies	0.22% (144)	0.04%	1% (324)	0.36% (140)	
Severe anaphylaxis (grades 3 and 4)	0.09% (60) Adults F/M : 3/2	0.016% (24)	0.037% (12)	0.03% (12)	0.02% (226)
Lethality	0.70% of cases of anaphylaxis = 0.01% des patients				1.3% of cases of anaphylaxis (three patients)
Cause identified (%)	73	Eight of nine	49	77	94.7
Food (%)	17	Three cases	9.5	38.5	10.1
Drugs (%)	28	Two cases	7.7	34.6	18.1
Insects (%)	17	Three cases	24	1.5	58.8
Other causes (%)				2.3	

prescription of adrenalin far exceeds the objective risk of severe anaphylaxis. In the United Kingdom, adrenalin prescriptions increased sevenfold for cohorts born between 1990 and 1992 compared with those born between 1981 and 1983 (29). In a Canadian population of over 1 million, the prescription rate corresponded to about 1% of the population, with a peak of 5% in males aged 12–17 months (100–500 for 10 000 children) (20).

Features of sublethal and lethal anaphylaxis dependent upon aetiology

Food allergies

In 1905, Finkelstein reported the death of a baby re-challenged with milk. The death of an 18-month-old child during re-challenge with peas was also reported by von Starck in 1926 (30, 31). From as early as 1988, attention was drawn to peanuts, fruit with shells and soya (32–34). Then death following inhalation of steam from shrimp and milk powder cooking was reported (35, 36). From 1997, the risk of transmission, or onset of food anaphylaxis following liver transplant was identified, and deaths were reported (37, 38). Between 2002 and 2003, the Allergy Vigilance Network recorded three deaths associated with peanut, soya and goat milk proteins (18). Severe anaphylaxis may also be caused by rare allergens such as boar meat, limpets, royal jelly, camomile and boldo, alcohol, caffeine, gum arabic (39–46). The risk of severity is shared by all foods (Fig. 1).

The most commonly affected age groups are adolescents and young adults (2, 47, 48). This higher prevalence than with adults may be related to the considerable increase in peanut allergies reported for children 10 years ago, and the severity in adolescents today may indicate an increase in persistent allergies. There is a serious risk of asthma in patients with food allergy. All the subjects in Bock's series were asthmatic (48). In a case-controlled study, half the children with life-threatening asthma had a food allergy, compared with 10% in the control group (49). About 86% of deaths because of food-induced anaphylaxis reviewed by Pumphrey presented with dyspnoea followed by respiratory arrest (50). Exercise could be an aggravating factor (51). However, no fatal cases of exercise-induced wheat-related anaphylaxis have been reported, despite the relative frequency of allergy to wheat. Masked allergens cause many cases of severe anaphylaxis (32, 50). They concern 13% of the cases reported by the Allergy Vigilance Network (18).

Severe drug-induced anaphylaxis

The lethal risk related to penicillin has been long known. There is renewed interest in this subject because injectable antibiotics are responsible for a large number of incidences of anaphylaxis during anaesthesia (15%), taking the third position after curare and latex (4, 52). They take the first position in cases declared to the Allergovigilance Network (Fig. 2). Deaths reported recently involved iodine contrast agents, rocuronium, protease inhibitors such as gabexate mesylate (53), aprotinin, cisplatin, nonsteroidal anti-inflammatories (NSAID; diclofenac, ketorolac), clindamycin, hydrocodone, methylprednisolone, dexrazoxane, and agents used for investigations such as patent blue, fluorescein, etc. (54–65). All routes of administration are potentially lethal: intra-articular (66), intra-uterine (67), intra-lymphatic (64), inhalation (68, 69), rectal (70, 71), topical skin application (72–74), and even prick-tests (75). Anaphylactoid reactions without defined immunological data have been associated with similar risk: angiotens in converting enzyme (ACE) inhibitors (76, 77), acetylcystein (78), nonhuman monoclonal antibodies (79, 80). Deaths involving latex are rare (68, 71).

In contrast to food anaphylaxis, drug anaphylaxis is characterized by a high frequency of cardiovascular collapse with rapid onset (within minutes), especially in

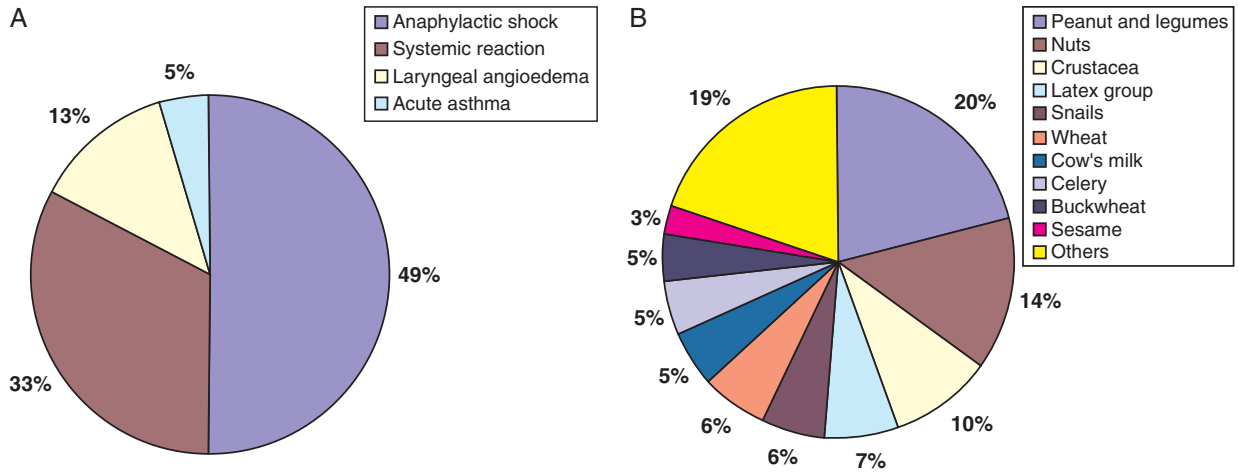

Figure 1. Clinical aspects and allergenic foods in life-threatening food anaphylaxis. Records of the Allergo Vigilance Network (2002, 2003, 2004 first semester).

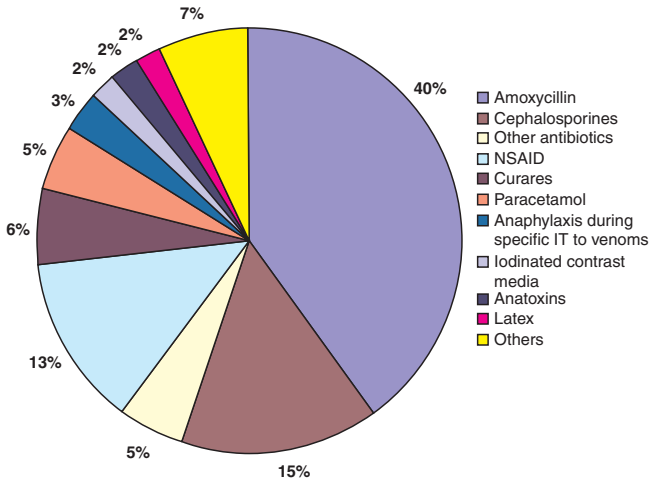

Figure 2. Aetiologies of 100 cases of life-threatening drug anaphylaxis registered by the Allergo Vigilance Network over 2003/2004 (%).

older patients (81). The risk factors for death include cardiopathy associated with β-blocker therapy (82, 83). A multicentre case–control study carried out in hospitals in Sweden, Spain, Hungary and India, established a grading of anaphylactic risk according to drug classifications: out of 10 000 patients treated, 0.5–1.5 received antibiotics and NSAIDs, 3.2 penicillin, 3.5–9.5 iodine contrast agents, dextran and pentoxyfilline, 37.8 streptokinase (82). There was a marked difference in grading for vaccines and modified starches as opposed to protease inhibitors and protamine (84, 85; Table 3).

Severe anaphylaxis during anaesthesia

This condition has a special place amongst drug allergies since it is regularly followed up by the GERAP (4). Muscle relaxants (58.2%) remain the most common cause with rocuronium the most implicated, followed by latex (16.7%) and antibiotics. The incidence of anaphylaxis to antibiotics has increased sevenfold since the first survey carried out from 1984 to 1989 (4).

A prospective study carried out in 20 hospitals in Catalonia from 1996 to 1997 collected data from over 328 000 anaesthetized patients. One case per 10 000 patients was recorded. About 56% were grade 3 or 4, with high urinary methyl-histamine and/or tryptase levels in 91% of grade 4 patients. No case of fatal anaphylaxis was reported (25).

Severe anaphylaxis induced by Hymenoptera

This condition has appeared in all major studies and represents from 11 to 29% of aetiologies, Switzerland excepted (58%) (Tables 1 and 2). Deaths occur in a range from 0.09 to 0.45/year/million (86). Anaphylaxis caused by the stings of the hornet (*Vespa crabro*) is much

Table 3. The rate of severe anaphylaxis depends on the type of drugs

Authors	Drugs	Number of patients treated	Anaphylaxis (%)	Lethality
Gupta et al. (113)	Protamine	1125	1	36% cases of anaphylaxis
Cochrane and Bomyea (56)	Iodine contrast agents	>90 000 injections	0.05 (all grades)	Yes
Laxenaire et al. (85)	Modified starches	5231 intravenous infusions	0.05 (0.01% grades 3 or 4)	No
Bolkher	Vaccines	>7 640 000 doses	0.65–1.5/million doses	No

more severe than that due to bees and *Vespula* species (87). An interesting point is the particular risk related to mastocytosis (88), and the fact that specific immunotherapy, normally very efficient, has not prevented death (88, 89).

Severe anaphylaxis related to ants, ticks, rattlesnake and hamster bites

Severe anaphylaxis related to the bites of Uruguayan and Brazilian ants (*Solenopsis richteri* and *S. invicta*) in the USA, and Australian ants (*Mirmecia pilosula* and *M. forficata*) has been reported. About 17% of the inhabitants of Georgia are sensitized to ants (90). About 32 deaths were recorded over 3 years, mostly in Florida and Texas, and about 10 in Australia (90–92). Anaphylaxis to ticks (*Ixodes ricinus*, *Argas reflexus*, *Rhiphicephalus*) may be more common than suspected (93–95). A single case of anaphylactoid shock to a rattlesnake bite draws the attention to the danger of removing the pressure band, allowing venom proteins to reach the systemic circulation (96). The popularity of various pets, such as hamsters, raises new risks of anaphylaxis after their bites, because of a sensitization to salivary proteins (97).

Only one fatal case of idiopathic anaphylaxis has been recorded (98).

Severe anaphylaxis due to inhalants

Cases of systemic anaphylaxis associated with acute laryngeal angio-oedema or respiratory arrest have been triggered by inhalation of grass or cereal pollens (99–101). A case of alpine slide anaphylaxis was the consequence of a direct exposure to grass pollens through abraded skin (102).

Severe anaphylaxis linked to parasitic diseases

Echinococcus granulosus forms hydatid cysts commonly in liver and lungs. The rupture of these cysts induces a potentially lethal anaphylaxis (103). Other cases have been described linked to sensitization to *Anisakis simplex*, a parasite of fish (104).

Discussion

Differences in the figures of various authors regarding the prevalence of severe anaphylaxis can be explained by the fact that there is no consensus on the definition of the condition. For some, acute asthma, a fall in blood pressure and acute dyspnoea because of laryngeal angio-oedema can be classified as *severe* anaphylaxis, since those conditions can be fatal if not treated. For others, the event must include cardio-respiratory arrest and require at least two doses of adrenaline (22). Furthermore, it is of interest that of all the immediate-type allergic reactions, the relative risk of severe anaphylaxis for patients attending the EU is different in Anglo-Saxon and Latin countries. In Anglo-Saxon countries, 29–41% of patients attending EU presented with severe anaphylaxis, compared with only 3.7–8% of French and Italian patients (Table 1). These statistics seem to indicate different behaviour patterns amongst patients.

However, it seems that there is range of 0.5–3 cases of severe anaphylaxis for every 10 000 people, and a death rate of 1–3 per million. These figures are compromised by deaths that are not always identified as anaphylaxis. For example, in a case of allergy after liver transplant, it was discovered later that the donor had died of food-induced anaphylaxis (105). There are also cases of sudden death possibly related to anaphylaxis, given the high level of tryptase (106).

An increased prevalence over recent years may be related to improved diagnosis because of the recording of disease in hospitalized patients with classification according to CIM-9 and -10. Moreover, in an ageing population, there are more frequent intakes of drugs. There is also an increased risk of allergy due to new food proteins technologies, tending to increase the incidence of food allergy and severe anaphylaxis.

Although great progress has been made with regard to anaphylaxis during anaesthesia, the identification of the causes remains variable, even in large cohort studies (6, 14–16, 85; Tables 1, 2, 4).

The fear of the risk of anaphylaxis probably explains why adrenalin prescriptions have increased, but a sound basis for this prescription is questionable. It is certain that there is a marked over-estimate of the risk of severe anaphylaxis. If adrenalin is prescribed 200 times for each real risk, the drug's benefit/risk ratio may change fundamentally. However, it is unfortunately also very true that at the time of the emergency adrenalin is often not available (6, 9, 107–111). It is noteworthy that in 28% of cases, death results from cerebral anoxia following collapse within a few hours to 3 days and not treated by adrenalin in a timely fashion (47, 48, 50). This underlines how much information and training is necessary for emergency staff, other health professionals and the general public with regard to first-line treatment of anaphylaxis. Special attention has to be paid by school personnel in charge of children at high risk of food anaphylaxis (112). Emergency plans, including comprehensive guidelines, should be set in all countries. The French school population includes 11 million children. One of 1500 benefits from a care management project and so far no lethal cases have been recorded in schools (19).

The available data are contradictory, on the one hand, it seems that there is a steady increase in the frequency of *severe* anaphylaxis, but diagnosis is now better and more frequent, which is not the case for lethal anaphylaxis. This affects 1–3 per million people and when applied to the population of a country-like France suggests a

Table 4. Causes of severe anaphylaxis.

Author, year, country	Dibs and Baker, 1997 (107), USA	Yocum et al., 1999 (108), USA	Cianferoni et al., 2001 (109), Italy	Pumphrey, 2000 (50), United Kingdom	Mullins, 2003 (9), Australia
Sample size	50 children retrospective study over 5 years	154/cohort of 1255 patients followed up from 1983 to 1987	107 patients retrospective study over 11 years	164 patients National statistics 1992–98	
Causes identified (%)		68		80.8	91.6
Food (%)	25	36		25	61
Drugs (%)	16	17	49	50 (half during anaesthesia)	8.3
Insects (%)	15	15	29	25	20.4
Latex (%)	27			3.4	

widespread ignorance of cases not benefiting from diagnosis. The proposed rate of 0.002% in the American population (20 per million people) must be corroborated by large-scale prospective studies (24), but it suggests underlining the importance of diagnosis to all doctors.

Conclusions

There is a definitive agreement on the figures for incidence of *severe* anaphylaxis (1–3 per 10 000 people) and for lethal anaphylaxis (1–3 per million people). Risk related to children cannot be assessed accurately since there are insufficient studies in this population. Although allergy to latex is rarely lethal, food and drug allergies provide the most data. Unlike allergies related to Hymenoptera, where specific immunotherapy can effectively counteract the risk of recurrence, there is currently no prophylaxis or specific treatment for food and drug allergies.

Emergency health care professionals and patients should be better informed, so that emergency treatment can be followed by a complete allergy diagnosis. Close cooperation between emergency health care professionals and allergists is essential and should evolve gradually in the same way as that between anaesthetists and allergists. Such cooperation could allow in-depth analysis, seeking factors predictive of seriousness. A high level of sensitization has not been correlated with the severity of allergic reactions. Other possible factors might identify particularities of the organism, prevailing over the specific nature and the dose of food allergens.

More accurate epidemiological data should now become available from the coding of hospital files using ICD 10: T 78.0 C A food, T 88.6 C A medicinal products, T 80.5 C A serum, T 78.2 C A not specified (idiopathic), J 46 serious acute asthma, T 78.3 laryngeal oedema. This should enable close comparison of countries, based on prospective, multicentre studies. Limiting these studies to hospital populations would be, however, insufficient. Complete data regarding severe anaphylactic reactions could be obtained from networks to which all allergists might report cases with their aetiologies. The Allergy Vigilance Network, now including 326 French and Belgian allergists, has been implementing this process since its foundation in 2001 and might open the way to a European network (18).

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