

# Epidemiology of insect-venom anaphylaxis

Beatrice M. Bilò and Floriano Bonifazi

Department of Internal Medicine, Immunology, Allergy and Respiratory Diseases, Azienda Ospedaliero-Universitaria, Ospedali Riuniti, Ancona, Italy

Correspondence to Beatrice M. Bilò, Department of Internal Medicine, Immunology, Allergy and Respiratory Diseases, Azienda Ospedaliero-Universitaria, Ospedali Riuniti, Ancona, Italy  
Tel: +39 071 5963804; fax: +39 071 5963253;  
e-mail: b.bilo@ospedaliriuniti.marche.it

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## Purpose of review

Knowledge of the epidemiology, natural history and risk factors of insect-venom allergy is crucial for improving the clinical management of allergic patients. This review focuses on the recent research on these aspects of Hymenoptera-sting anaphylactic reactions.

## Recent findings

The latest data from population-based studies of anaphylactic reactions due to Hymenoptera stings, as well as those extrapolated from studies of epidemiology of anaphylaxis due to any cause are reviewed. The topic of biphasic anaphylactic reactions due to insect stings is also examined. Although no parameter has been identified that can predict which sensitized individuals will have a future anaphylactic reaction, several factors associated with the severity of a systemic resting reaction are known and emphasized here.

## Summary

As half of individuals with fatal sting reactions had no documented history of previous systemic reaction, we need to further improve the knowledge of the natural history and risk factors, especially in asymptomatic-sensitized individuals. Moreover, and no less important, the epidemiological studies on sting anaphylaxis conducted in the 2000s continue to reveal the poor management of allergic patients and the startling lack of awareness of the efficacy of venom immunotherapy. These findings indicate the urgent need to educate the general population and doctors on the management of venom-allergic patients.

## Keywords

anaphylactic reaction, biphasic anaphylactic reaction, Hymenoptera venom allergy, mortality, risk factors

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## Introduction

Stinging insects of the order Hymenoptera cause anaphylaxis [1,2]. Worldwide the culprit Hymenoptera belong to the suborder *Aculeate*, which are made up of the superfamilies of *Apoidea* (*Apis mellifera*, *Bombus* spp.) and *Vespidae* (Vespininae and Polistinae subfamilies). However, several of the European species of the vespidae family differ from those found in the USA (Table 1). Furthermore, popular names for vespids in the USA and Europe are different and may lead to confusion (Table 1). Also, in the USA stinging Hymenoptera include the fire ant (*Solenopsis invicta*), and although fire ants may be seen in Australia, the jack jumper ant (*Myrmecia pilosula*) seems to cause more problems.

Allergic hypersensitivity can cause large local reactions (LLRs) or systemic reactions, which are mostly IgE mediated. Systemic reactions result in cutaneous, respiratory or vascular symptoms and signs, either singularly or in any combination, and may involve the less-common

target tissues like the intestines, heart and uterus. Allergic sting reactions are responsible for significant morbidity and deterioration in health-related quality of life, especially as the emotional distress can lead to extreme avoidance behavior [3]. Fatal reactions after a single Hymenoptera sting may occur. This review focuses on the epidemiology of systemic reactions caused by Hymenoptera stings other than ants, and especially anaphylactic reactions, and on the natural history and risk factors for their development.

## Epidemiology of Hymenoptera venom allergy

Depending on the country's climate, 56.6–94.5% of interviewees remember being stung by a Hymenoptera insect at least once in their lives [4]. The prevalence of sensitization (indicated either by a positive skin test or by the detection of specific IgE in patients with no previous case history or both) is estimated at between 9.3 and 28.7% in the adult population [1], which is related to the

**Table 1 Vespid species in the USA and Europe**

| Genus          | Europe                        |              | USA                                  |                 |
|----------------|-------------------------------|--------------|--------------------------------------|-----------------|
|                | Species                       | Popular name | Species                              | Popular name    |
| Polistes       | Gallicus<br>Dominulus         | Wasp         | Annularis<br>Fuscatus<br>Exclamans   | Paper wasp      |
| Vespula        | Vulgaris<br>Germanica<br>Rufa | Wasp         | Vulgaris<br>Germanica<br>Maculifrons | Yellow jacket   |
| Dolichovespula | Media<br>Saxonica             | Wasp         | Maculata<br>Arenaria                 | Hornet          |
| Vespa          | Crabro<br>Orientalis          | Hornet       | Crabro                               | European hornet |

degree of exposure to stings (in 30–60% of beekeepers) and to the insect distribution and behavior [4]. The prevalence of LLRs in the general population ranges from 2.4 to 26.4%, up to 38% in beekeepers [1]. The causes of such a wide variation are not known, although a different definition of the LLR and the degree of exposure could be involved [4].

#### Population-based studies of systemic reactions due to insect stings

The prevalence of Hymenoptera-sting systemic reactions in the general population has been the subject of various population-based studies. However, only a few studies on insect-venom anaphylaxis have been published recently. In the USA, the prevalence of systemic reactions among adults ranges from 0.5 up to 3.3% [2]. European epidemiological studies report a prevalence of systemic reactions between 0.3 and 7.5% [1]. Table 2 shows studies on the prevalence of systemic reactions over the last decade, among which anaphylactic shock was reported in 0.6–42.8% of cases [5–11]. The small number of patients with systemic reactions may account for this wide percentage range. In children, prevalence rates of systemic reactions are lower, ranging from 0.15 to 0.8%. Either skin testing or specific IgE or both are positive in 50–100% of adult patients with systemic reactions (Table 2); one Italian

study [7] that showed a 7% skin test positivity reflects a pediatric population in which only prick skin testing was done.

The degree of variability of systemic reactions prevalence can essentially be accounted for by three influencing factors: the lack of universal consensus on the definition of anaphylaxis with consequent use of different classifications [12<sup>••</sup>], the data collection technique, and the degree of exposure to stings [4].

Among the various classifications of the degree of the severity of insect-sting systemic reactions, the most frequently used were those by Mueller and Ring [1]. However, the former does not take into account that cutaneous symptoms might be absent and that an isolated cardiovascular shock might be the only allergic manifestation after an insect sting [13]. The latter considers cardiovascular compromise to be more severe than respiratory compromise, focusing almost entirely on the severity of cardiovascular collapse. The use of a consistent and single definition of anaphylaxis like the recent one arising from the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network symposia [14,15] would allow for the uniform reporting of cases and more accurate picture of the severity of insect-sting reactions, after its validation by means of prospective multicenter clinical trials.

With sting exposure, the prevalence of systemic reactions among beekeepers is high and falls between 14 and 32% [16]. A self-administered questionnaire was completed by 494 Turkish beekeepers reporting systemic reactions were present in 6.5% of participants and anaphylactic reaction in 2% of them [17]. According to these authors, this low prevalence of systemic reaction might be due to the protective effect of a high frequency of bee stings [17].

Bumblebee anaphylaxis is a rare phenomenon due to the nonaggressiveness of these insects, except for occupationally exposed people, like gardeners, workers in

**Table 2 Prevalence of systemic sting reactions obtained by questionnaire: Epidemiological studies in Europe for the last decade**

| References                   | Country | Study population                  | Number of patients | Systemic reactions (%)  | Reaction severity classification | Skin test and/or serum IgE positivities in systemic reactors (%) |
|------------------------------|---------|-----------------------------------|--------------------|-------------------------|----------------------------------|------------------------------------------------------------------|
| Grigoreas <i>et al.</i> [5]  | Greece  | Hellenic air force                | 480                | 3.1                     | Mueller modified                 | 77.3 (IDT)                                                       |
| Incorvaia <i>et al.</i> [6]  | Italy   | Conscripts                        | 701                | 2.7 (10.6) <sup>a</sup> | Mueller                          | Not done                                                         |
| Novembre <i>et al.</i> [7]   | Italy   | School children                   | 1175               | 0.34                    | Not known                        | 7 (PT) (all reactors)                                            |
| Fernandez <i>et al.</i> [8]  | Spain   | Rural area population             | 1600               | 2.3 (42.8) <sup>a</sup> | Mueller                          | 57.6 (serum IgE)                                                 |
| Navarro <i>et al.</i> [9]    | Spain   | Working population (Ford factory) | 1064               | 2.3 (0.6) <sup>a</sup>  | Mueller                          | 100 (IDT and serum IgE)                                          |
| Fernandez <i>et al.</i> [10] | Spain   | Rural area population             | 145                | 2.8 (25) <sup>a</sup>   | Mueller                          | 50 (serum IgE)                                                   |
| Onbaşı <i>et al.</i> [11]    | Turkey  | General population                | 709                | 5.4 (1.2) <sup>b</sup>  | Not known                        | Not done                                                         |

IDT, intradermal testing; PT, prick testing.

<sup>a</sup>Systemic IV grade reaction (Mueller classification) (%).

<sup>b</sup>Severe systemic reaction (%).

**Table 3 Insect-sting anaphylaxis: data extrapolated from the latest emergency departments visits for anaphylaxis due to any cause of anaphylaxis**

| References                                | Country     | Type of study                   | Period of study (years) | Study population     | Number of cases of anaphylaxis | Insect sting (%) | Number of fatalities |
|-------------------------------------------|-------------|---------------------------------|-------------------------|----------------------|--------------------------------|------------------|----------------------|
| Mullins [19]                              | Australia   | P                               | 6                       | Children and adults  | 432                            | 20.4             | 0                    |
| Helbling <i>et al.</i> [13]               | Switzerland | R                               | 3                       | Adults               | 226                            | 59               | 3 <sup>a</sup>       |
| Peng and Jick [20]                        | UK          | P                               | 6                       | Children and adults  | 675                            | 32               | 1 <sup>b</sup>       |
| Bohlke <i>et al.</i> [21]                 | USA         | R                               | 6                       | Children             | 67                             | 22               | 0                    |
| Thong <i>et al.</i> [22]                  | Singapore   | R                               | 3.8                     | Adults               | 67                             | 32.8             | 0                    |
| Mehl <i>et al.</i> [23]                   | Germany     | R                               | 1                       | Infants and children | 103                            | 13               | 0                    |
| Yang <i>et al.</i> [24]                   | Korea       | R (inpatients, outpatients, ED) | 6.6                     | Children and adults  | 138                            | 11.8             | 1 <sup>a</sup>       |
| De Swert <i>et al.</i> [25 <sup>•</sup> ] | Belgium     | P                               | 2                       | Children             | 64                             | 7.3              | 0                    |

ED, emergency department; P, prospective; R, retrospective.

<sup>a</sup> Mortality not due to an insect sting.<sup>b</sup> Unknown cause of fatal anaphylaxis.

tomato horticulture or on bumblebee farms; however, epidemiological data are lacking [18].

#### Data extrapolated from studies of epidemiology of anaphylaxis due to any cause

Another way of assessing the extent of insect anaphylaxis is to extrapolate data from population-based studies, hospital admissions and emergency department (ED) visits due to any cause of anaphylaxis.

By analyzing the latest population-based studies of anaphylaxis due to any cause [19–24,25<sup>•</sup>], insect-sting-induced anaphylaxis is responsible for 7.3–59% of the total number of cases reported, being a more frequent cause in adult than in pediatric populations (Table 3).

As opposed to the majority of studies that reveal food being the main cause of anaphylaxis, a study by Helbling *et al.* [13] reports insect stings as the principal cause of anaphylaxis, followed by drugs. This may be due to the fact that the study was performed by the two main Swiss centers for insect venom and drug allergy, and that Canton Bern is a rural area and harbors twice as many beehives as any other canton, which may account for the

overwhelming number of Hymenoptera-sting anaphylaxis cases [13].

Looking at the last decade, ED studies of anaphylaxis due to any cause [26–34], the percentages of prevalence of insect-sting anaphylaxis range from 1.5 to 34% (Table 4). The lowest level was documented in Italy [28], but the study was performed in a hospital in the center of Milan, where the likelihood of being stung is slight. On the contrary, confirming the close relationship between reactions and exposure to the *Myrmecia* ant, Brown's study [30] shows a higher percentage of insect stings as being the cause of anaphylaxis in Australia.

Many factors could explain the divergent estimates of the occurrence of anaphylaxis due to insect stings: the lack of the definition of the best criteria for diagnosing anaphylactic reactions, different populations studied, different methods of identification of cases [different International Classification of Disease (ICD)-9 codes and other system codes], different geographic locations, different allergen exposure [12<sup>••</sup>], and also different interests of the local Allergy Units [13]. Moreover, in ED studies, cause of anaphylaxis is based on ED assessments rather than

**Table 4 Insect-sting anaphylaxis: data extrapolated from the latest emergency departments visits for anaphylaxis due to any cause of anaphylaxis**

| References                           | Country                        | Type of study | Period of study (years) | Study population    | Number of cases of anaphylaxis | Insect sting (%) | Number of fatalities |
|--------------------------------------|--------------------------------|---------------|-------------------------|---------------------|--------------------------------|------------------|----------------------|
| Cianferoni <i>et al.</i> [26]        | Italy                          | R             | 11                      | Children            | 107                            | 29               | 0                    |
| Brown <i>et al.</i> [27]             | Australia                      | R             | 1                       | Adults              | 142                            | 17.5             | 1 <sup>a</sup>       |
| Pastorello <i>et al.</i> [28]        | Italy                          | R             | 2                       | Adults              | 140                            | 1.5              | 0                    |
| Bellou <i>et al.</i> [29]            | France                         | R             | 1                       | Adults              | 12                             | 25               | 0                    |
| Brown [30]                           | Australia                      | R             | 9                       | Children and adults | 1149                           | 30               | Not known            |
| Smit <i>et al.</i> [31]              | Hong Kong                      | R             | 6                       | Children and adults | 282                            | 7.1              | 0                    |
| Braganza <i>et al.</i> [32]          | Australia                      | R             | 3                       | Children            | 57                             | 5.3              | 0                    |
| Jirapongsananuruk <i>et al.</i> [33] | Thailand (hospital admissions) | R             | 5                       | Children and adults | 101                            | 11               | 1                    |
| Simon and Mulla [34]                 | Texas (hospital admissions)    | R             | 1                       | Children and adults | 464                            | 34.1             | 4 <sup>b</sup>       |

R, retrospective.

<sup>a</sup> Mortality due to a bee sting.<sup>b</sup> Two fatalities due to ant bites.

allergist review with confirmatory skin testing and serum specific IgE antibodies.

### Emergency department admissions due to insect stings

The only multicenter study of ED visits for insect-sting allergies was performed in 15 North American EDs [34], using the ICD-9-Clinical Modification (ICD-9-CM) code. According to Brown's classification, 259 (42%) of ED patients had a systemic reaction; among them, 70 (27%) had mild systemic reactions, 143 (55%) moderate systemic reaction and 46 (18%) severe systemic reactions [35].

According to that study, although the use of ICD-9-CM codes identified 87% of patients with insect-sting allergy versus 53% of patient with food allergy, it would have missed one-tenth of insect-sting allergy cases presenting to the ED [36].

### Natural history and risk factors influencing the outcome of an anaphylactic reaction

Compared with the higher prevalence of IgE sensitization found in the adult general population, systemic reactions occur in a small percentage. The mystery of why some sensitized patients react to a future sting and others do not still has to be elucidated, as well as why some sensitized patients develop LLR, whereas others experience severe systemic reactions. However, several factors associated with the occurrence and the severity of a systemic anaphylactic reaction are well known.

#### Age

In children, about 60% of systemic reactions are mild and generally restricted to the skin, whereas in adults, respiratory or cardiovascular symptoms occur in about 70%. Elderly patients more often develop particularly severe systemic reactions, and the fatality rate is higher than in children and young adults [1].

Children with cutaneous systemic reactions have a lower rate of recurrence over time than adults.

However, in a recent 10–20 year follow-up study, among untreated children who originally had a moderate or severe systemic reaction, as many as 32% had a systemic reaction to a sting compared with 5% among those treated with immunotherapy, meaning that children with more severe reactions remain at risk in the long run [37].

#### Severity of the preceding reaction

After a large local sting reaction, between 5 and 15% will develop a systemic reaction when next stung. It has been suggested that LLRs may play a 'protective' role in developing systemic reactions [8], a hypothesis that has not been verified in further prospective studies.

The risk of recurrence of systemic reactions is determined by previous reaction severity: the more serious the initial reaction, the greater the risk of recurrence. Linking the estimated risk of systemic reaction with severity, age and time elapsed from a previous reaction, adults with a recent history of severe anaphylaxis have a 40–60% chance of reacting to a future sting, and those with mild systemic reactions might have a 20% chance of subsequent systemic reactions [2].

#### Time interval between stings, number of stings

A short interval between a previous well tolerated sting and the next one increases the risk of a systemic reaction to a subsequent sting. With increasing interval between stings, the risk generally declines steadily, but remains in the range of 20–30% even after 10 years [1].

On the contrary, being stung very frequently (more than 200 annual stings) appears to induce tolerance, as in beekeepers [16].

#### Venom sensitization

In adult patients with asymptomatic venom sensitisation, the risk of a later anaphylactic sting reaction was 17 versus 0% in skin-test-negative individuals [38]. These data are alarming but provided by one single study on 65 patients and require further investigation. On the contrary, Fernandez *et al.* [10] suggested that this condition does not represent a clear risk for a future systemic reaction, at least in the case of vespids; the opposite could occur in the case of honeybee sensitization, as this sensitization persists over time.

#### Atopy

Currently, there is no evidence of a higher risk of severe reactions in atopic patients. A recent study showed that patients with Hymenoptera venom allergy and high levels (>250 kU/l) of total IgE predominantly developed mild-to-moderate reactions, as if they were protected from the most severe systemic reactions [39<sup>•</sup>]; however, as specified by the authors, this hypothesis should be confirmed by studies with sting challenge.

In contrast, atopy may increase the risk and severity of systemic reactions in beekeepers and their family members [16].

#### Insect

Bee venom-allergic patients are at a greater risk of a systemic reaction on their next sting than those with vespid venom allergy. The relative risk for life-threatening sting reactions in the Mediterranean area is about three times higher for hornet (*Vespa crabro*) stings than for honeybee or wasp stings [1]. In the USA, the frequency and the severity of a reaction to sting challenge seems to be higher with

*Vespula maculifrons* stings than with *Vespula germanica* stings, perhaps due to different stinging behavior [40].

Cardiovascular diseases and therapies

Preexisting cardiovascular diseases are risk factors for particularly severe and fatal sting reactions induced by anaphylaxis [41\*\*]. β-Blocker treatment does not seem to increase the overall risk of a systemic reaction, but may influence its severity. As cardiovascular diseases are much more frequent than anaphylaxis and these medications are very effective, these drugs cannot be substituted in patients with both diseases without a careful risk analysis [41\*\*].

Case reports document severe allergic reactions, including anaphylaxis in patients taking angiotensin-converting enzyme (ACE) inhibitors subsequent to being stung or receiving immunotherapy, suggesting that ACE-inhibitor therapy should be avoided when possible [42]. Similar reactions have not been described yet with angiotensin-receptor blockers, but are theoretically possible.

Elevated serum tryptase, mastocytosis

Particularly severe cardiovascular, even fatal sting reactions may occur in patients with mast cell diseases [43]. A recent study shows that the cumulative incidence of anaphylaxis in patients with mastocytosis was less in children than in adults, in which reactions were more frequent in patients with systemic rather than cutaneous mastocytosis and mainly due to Hymenoptera stings [44\*\*].

In venom-allergic patients without diagnosed mastocytosis, elevated baseline serum tryptase levels were found to be associated with very severe anaphylactic reactions to stings. Preliminary data from a multicenter European prospective study on about 1000 patients with Hymenoptera venom allergy confirm these findings (manuscript in preparation).

In patients with mastocytosis, anaphylactic reactions may also be due to toxic mediator release from mast cells,

although some authors [43] question these pseudoallergic sting reactions, suggesting that in these patients, the negativity of the diagnostic tests may be due to their low sensitivity.

Biphasic anaphylactic reaction

Biphasic anaphylactic reaction (BAR) occurs in 1–20% of cases of anaphylaxis [24,25\*,31,45\*\*,46,47,48\*] (Table 5), but seems to be uncommon with insect stings in which it is generally associated with the most severe reactions [49]. Indeed, among 46 cases of BARs, Hymenoptera stings were responsible for about 20% (Table 5).

In a prospective population-based study in children, among 64 cases of anaphylaxis, De Swert *et al.* [25\*] found two BARs (3%), one of which was caused by a bee sting.

A total of 103 ED patients were prospectively identified, among which 20 (19.4%) experienced confirmed BAR; five BARs were due to Hymenoptera stings [48\*].

Fatalities can occur, but it is very rare in insect-sting BAR. We have described [47] a case of fatal BAR after multiple vespid stings in a 70-year-old atopic man with a history of previous large local reactions, suffering from ischemic cardiomyopathy. The case’s analysis led us to raise the question whether early administration of epinephrine or a longer observation period would have benefited the patient [47]. Looking at all the data published to date, it is not possible to establish the right and, at the same time, practical period of observation after an anaphylactic reaction, but it seems that an 8-h observation period might be sufficient to ensure that most severe recurrences would manifest while the patient was still under medical observation [45\*\*].

To our knowledge, protracted anaphylaxis due to in-field insect sting is a rare phenomenon; two cases occurred out of three severe anaphylaxis among the 14 systemic

Table 5 Hymenoptera stings and biphasic anaphylactic reactions

| References                    | Country   | Study population    | Type of study                  | Biphasic reaction, n (%) | Number of fatalities |
|-------------------------------|-----------|---------------------|--------------------------------|--------------------------|----------------------|
| Lee and Greenes [46]          | Boston    | Children            | Hospital admissions            | 6 (6) <sup>a</sup>       | 0                    |
| Cortellini <i>et al.</i> [47] | Italy     | Elderly man         | Case report                    | 1                        | 1 <sup>b</sup>       |
| Smit <i>et al.</i> [31]       | Hong Kong | Children and adults | ED study                       | 15 (5.3) <sup>c</sup>    | 0                    |
| Ellis and Day [48*]           | Canada    | Children and adults | ED study                       | 20 (19.4) <sup>d</sup>   | 0                    |
| Yang <i>et al.</i> [24]       | Korea     | Children and adults | ED, inpatients and outpatients | 3 (2.2)                  | 0                    |
| De Swert <i>et al.</i> [25*]  | Belgium   | Children            | PB study                       | 2 (3) <sup>c</sup>       | 0                    |

BAR, biphasic anaphylactic reaction; ED study, emergency department study of anaphylaxis due to any cause; PB study, population-based studies of anaphylaxis due to any cause.

<sup>a</sup>Two cases due to bee stings.

<sup>b</sup>Fatality due to BAR caused by Hymenoptera stings.

<sup>c</sup>One case due to a insect sting.

<sup>d</sup>Five cases due to an insect sting.

**Table 6 Fatalities following Hymenoptera sting**

| Country     | Fatalities per 1 000 000 inhabitants/year |
|-------------|-------------------------------------------|
| USA         | 0.16                                      |
| Australia   | 0.10                                      |
| Denmark     | 0.25                                      |
| France      | 0.48                                      |
| Germany     | 0.18                                      |
| Italy       | 0.03                                      |
| England     | 0.09                                      |
| Switzerland | 0.45                                      |

reactions to sting challenge that occurred in an old controlled clinical trial of venom immunotherapy [49].

Several risk factors for biphasic and protracted reactions emerge from all the published reports and they can probably be applied to the field of insect-sting anaphylaxis: more rapid onset of anaphylaxis, delayed use of epinephrine, an inadequate amount of epinephrine given for the first response, the requirement of large doses of epinephrine, cardiovascular and respiratory diseases and concurrent therapy with  $\beta$ -blockers [45<sup>••</sup>].

### Mortality

The incidence of insect-sting mortality due to early anaphylaxis is low, but not negligible, ranging from 0.03 to 0.48 fatalities per 1 000 000 inhabitants per year [1,4] (Table 6).

At least 40–100 fatal sting reactions occur each year in the USA [50].

In Italy, according to official figures released by the Italian Institute of Statistics (ISTAT), 13 cases of fatal insect-sting-induced anaphylaxis were reported between 1980 and 1990. Data available from 1994 up to 2002 (ISTAT unpublished data) report 85 cases of insect-sting deaths, according to the ICD-9-CM code 989.5 (insect-sting allergy). Deeper awareness of the existence of the problem in Italy may account for the higher number of sting deaths officially recorded in the last decade. However, these data are probably underestimated, as we documented two Hymenoptera-sting-related deaths in September 1999 alone in a prospective study involving 32 EDs mainly located in north and central Italy [51], whereas in the same year, ISTAT statistics reported five cases in the whole of Italy. This underestimation is a worldwide phenomenon; many sting fatalities may be unrecognized and misinterpreted as unexplained [1,12<sup>••</sup>,52].

Pumphrey [52] from 1992 to 2001 identified 214 anaphylaxis deaths, among which 47 (22%) were due to insect stings (29 wasp, four bee and 14 unidentified). Death commonly occurred from shock 10–15 min after the sting and in a quarter of cases due to upper airways occlusion by angioedema. Although fatalities occurred mostly in those

older than 40 years, children can also be affected. Fatal stings occurred in a wide range of situations including 15% at work, 32% in the garden, 34% at home and even 5% in bed [52].

The risk factors for fatal stings include a positive history of Hymenoptera allergy (but non always), male sex, age over 40 years, probably because of comorbidity with cardiovascular diseases, the sting site (head or neck), bee and European hornet stings, mast cell diseases, and the delayed administration or nonuse of epinephrine [1,12<sup>••</sup>].

### Prevention of insect-sting anaphylaxis

Around 40–85% [1] of the patients with sting fatal reactions had no documented history of previous anaphylactic reactions. Therefore, drastically improving our knowledge of the natural history and risk factors, especially in asymptomatic-sensitized patients is vital.

For patients with anaphylactic reactions, prevention of future systemic reactions goes through the correct use of epinephrine by the doctors, the referral to an allergist for diagnosis, and the proper techniques for self-administration of epinephrine [4,35,50].

However, compliance with international guidelines for the treatment of anaphylaxis, also in the specific case of insect-sting anaphylaxis, appears to be very low. Indeed, epidemiological studies conducted in the 2000s continues to reveal the poor management of venom-allergic patients and the startling lack of awareness of venom immunotherapy efficacy.

Also recently, in a multicenter American study of ED visits for insect-sting allergies, only 13% of patients with anaphylactic reaction due to insect sting received epinephrine whereas in the ED, only 27% of systemic reaction patients received a prescription for self-injectable epinephrine, only 20% had documentation of referral to an allergist, while among patients with anaphylaxis, 39% of them had a known history of insect-sting allergy [35].

The wide persistence of this 'cultural' risk factor should have been virtually eradicated many years ago. Because of its efficacy [53], at least half of deaths in patients with a positive case history could have been avoided through specific immunotherapy.

### Conclusion

Despite a high prevalence of asymptomatic sensitization, the prevalence of anaphylactic reaction to stings is low. However, up to now no parameter has been identified that

can predict who will have a future anaphylactic reaction. A combination of several concomitant factors, such as environmental (the frequency of stings), genetic (the persistence of specific IgE antibodies and probably other factors) and individual (age; morbidities like asthma, mastocytosis or ischemic heart disease; concurrent medication; strenuous exercise; and certainly others) factors may explain the occurrence of an anaphylactic reaction in each patient. Several factors not completely known may be associated with the severity of a systemic resting reaction. Biphasic anaphylactic reactions seem to be uncommon, although generally associated with the most severe reactions. The insect mortality rate is low compared with other causes, but is certainly underestimated.

Better knowledge of the natural history and risk factors, better management and education of patients and better knowledge of the existence and efficacy of specific immunotherapy should improve venom-allergic patient care.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 364–365).

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