

REVIEW

The natural history and epidemiology of insect venom allergy: clinical implications

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Summary

Hymenoptera stings can cause severe systemic allergic reactions and occasionally fatal anaphylaxis, which contribute significantly to morbidity and deterioration in health-related quality of life. The latest epidemiological data confirm the importance of insect sting allergy as a cause of anaphylaxis. Despite the high prevalence of asymptomatic sensitization, the prevalence of sting-induced systemic reactions (SRs) is low. However, to date, no parameter has been identified that can predict who will have a future reaction and whether it will be a large local reaction or anaphylactic. The combination of several concomitant factors, which include environmental, genetics and individual factors, may account for the occurrence of a system reaction in individual patients. Several not completely known factors may be associated with the severity of systemic re-stings. As about 50% of subjects with fatal sting reactions had no documented history of a previous SR, greater insight of the natural history and risk factors is required, especially in asymptomatic sensitized subjects. For patients with SRs, prevention of future severe allergic reactions starts with referral to an emergency department, correct administration of epinephrine by medical staff, referral to an allergist and coaching for the self-administration of epinephrine. However, most insect sting victims failed to seek medical advice and hospital attendance does not always correlate with the severity of the allergic reaction. Moreover, only about one-third of patients received a prescription for self-injectable epinephrine and were officially referred to an allergist after being discharged, causing the non- or delayed prescription of specific immunotherapy. Significantly, this means that at least half of the sting fatalities in patients with a positive history could have been avoided through the timely administration of specific immunotherapy. These findings indicate the urgent need to educate the general population and doctors on the management of venom-allergic patients.

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Introduction

As is well known, hymenoptera stings can induce an allergic and occasionally fatal reaction [1, 2]. The culprit hymenoptera belong to the suborder *Aculeate*, which are made up of the *Apoidea* (*Apis mellifera*, *Bombus* spp.) and of *Vespidae* (*Vespinae* and *Polistinae* subfamilies) super-families. However, several of the European vespid species differ from those found in the United States, where popular names for vespids are different and may lead to confusion [3].

Also, in the United States, stinging hymenoptera include the Fire ant (*Solenopsis invicta*), which is also present in Australia, where its stings are of less consequence than the jack jumper ant (*Myrmecia pilosula*) from an epidemiological point of view.

Allergic sting reactions are responsible for significant morbidity and deterioration in health-related quality of life, as the emotional distress can lead to extreme avoidance behaviour [4].

Insect sting allergy encompasses most dilemmas in the immunology, pathophysiology, diagnosis and treatment of anaphylaxis. However, mysteries persist, mainly regarding the natural history of venom sensitization, and risk factors for an unfavourable outcome in both untreated and treated patients [5].

Clinical presentation

The clinical features of insect sting reactions and their pathogenesis are described elsewhere [1, 6].

The most frequent clinical patterns of hymenoptera venom allergy (HVA) are large local reactions (LLRs) and systemic reactions (SRs). The former is commonly defined as a swelling exceeding 10 cm in diameter lasting 24 h. In SRs, the skin, gastrointestinal, respiratory and cardiovascular systems may be involved.

Various classifications of the degree of severity of SRs have been proposed and those of H. Mueller and Ring are the most frequently referred to [1]. However, the former does not take into account the possible absence of cutaneous symptoms and that an isolated cardiovascular shock might be the only allergic sting-induced manifestation, while the latter focuses almost entirely on the cardiovascular collapse, considering it as more severe than respiratory compromise. A universal definition of anaphylaxis like the one recently proposed by the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network symposia (FAAN) [7, 8] would mean the uniform reporting of cases and a more accurate picture of the severity of insect sting reactions, after its validation by means of prospective multi-centre clinical trials.

Epidemiology

Insect sting prevalence

Scant data exist on the prevalence of hymenoptera stings in the general population. Depending on the climate, 56.6–94.5% of the general adult population remember receiving a hymenoptera sting at least once [9]. Still less data are available for children; in Israel 56.3% of 13–14 year olds have been stung once or more, as they probably spend longer hours outdoors on account of the good weather. Arab males, and children living in rural areas were at a greater risk of being stung [10]. In America, even more worrying data emerge in areas endemically infested by fire ants, where 55% of sting victims report being stung 3 weeks after moving there [11].

Venom sensitization

The prevalence of sensitization [indicated by a positive skin test and/or the detection of specific IgE (sIgE) in patients with no previous case history] is estimated at between 9.3% and 28.7% in adults [3]. In children, it has been studied to a lesser extent; in an unselected Italian child population the authors documented a prevalence of sensitization of 3.7% [12]. Asymptomatic sensitization is more common with repeated short-interval stings and is related to the degree of sting exposure (in 30–60% of beekeepers) as well as insect distribution and behaviour [9].

In atopic individuals, an increased risk for the presence of venom sIgE has been reported and a genetic predisposition that enhances the production and/or the persistence

of venom sIgE has been suggested [9]. Alternatively, carbohydrate determinants (CCDs) present in venoms and inhalant allergens could cause cross-reactivity [13, 14]. This finding probably has negligible clinical relevance but could interfere with the results of epidemiological studies when only *in vitro* methods are used. Some authors maintain that asymptomatic sensitization seems to be related to total IgE (tIgE) levels where its rate is significantly higher in subjects with high levels of tIgE (50–250 kU/L) than in those with low levels (<50 kU/L) [15]. As sIgE to rapeseed (a marker of CCDs) was found only in subjects with double sensitization to honeybee and wasp venom, at the same re-sting frequency between the two groups, the authors speculated that these asymptomatic sensitizations might originate from other sources [15]. However, inhibition tests were not performed.

Detection of sIgE to venoms in patients with no history of allergic sting reactions is often of no clinical relevance and may lead to a misdiagnosis. Therefore, the determination of sIgE is only mandatory in patients with a clear history of a SR [1].

Large local reactions

The prevalence of LLRs in the general population ranges from 2.4% to 26.4%, up to 38% in beekeepers [3]. In children, the prevalence reported in one study is 19% [12] and 11.5% in another [10]. In Table 1 studies on the prevalence of LLRs over the last decade in adults and children are shown [10, 12, 16–21]. Skin tests and/or sIgE are positive in up to 80% of patients with LLRs (Table 1). Although this wide variation cannot be fully explained, differences in defining the LLR and the degree of exposure could be involved [9].

Systemic reactions and anaphylaxis

Population-based studies of sting-induced systemic reactions. The prevalence of hymenoptera sting SRs in the general population has been the subject of various population-based studies. In America, the prevalence of SRs among adults ranges from 0.5% to 3.3% [2]. European epidemiological studies report a prevalence of SRs between 0.3% and 7.5% [3]. Table 1 shows studies on the prevalence of SRs over the last decade, among which anaphylaxis was reported in 0.3–42.8% of cases [10, 12, 16–21].

From very few studies in children, the prevalence rates of SRs are lower, ranging from 0.15% to 0.8%. However, in a recent study from Israel, a self-administered questionnaire was completed by 10 021 schoolchildren. Of those who had been stung, 11.6% (6.5% of the whole study group) reported having mild (cutaneous) SRs and 4.4% (2.5% of the whole study group) reported having a moderate to severe SR [10]. These figures are similar to

Table 1. Prevalence of hymenoptera venom allergy obtained by questionnaire. Epidemiological studies for the last decade (original)

References	Country	Study population	No. of subjects	Large local reactions (%)	Skin test and/or serum IgE positivities in large local reactors (%)	Systemic reactions (%)	Skin test and/or serum IgE positivities in systemic reactors (%)
Novembre et al. [12]	Italy	School children	1175	19	7 (PT) (all reactors)	0.34	7 (PT) (all reactors)
Fernandez et al. [16]	Spain	Rural area population	1600	26.4	28.5 (serum IgE)	2.3 (42.8)*	57.6 (serum IgE)
Incorvaia et al. [17]	Italy	Factory workers	462	10.6	Not done	2.8	Not done
		Foresters	112	9.8		4.5	
Navarro et al. [18]	Spain	Working population (Ford factory)	1064	5.3	80 IDT 78.6 serum IgE	2.3 (0.6)*	100 (IDT and serum IgE)
Nittner-Marszalska et al. [19]	Poland	General population	169	11.8	42.8 (IDT/or serum IgE)	8.9 (0.6)*	53.3 (IDT/or serum IgE)
Fernandez et al. [20]	Spain	Rural area population	145	15.5	70 (serum IgE)	2.8 (25)*	50 (serum IgE)
Graif et al. [10]	Israel	High school children	10 021	11.5	Not done	6.5 [†] 2.5 [‡]	Not done
Onbasi et al. [21]	Turkey	General population	709	11.5	Not done	5.4 (1.2) [‡]	Not done

*Systemic IV grade reaction (Mueller classification) (%).

[†]Moderate to severe systemic reaction.

[‡]Severe systemic reaction (%).

PT, prick testing; IDT, intradermal testing.

those reported in older populations; however, as the authors suggest, this might be an overestimate due to the methodology and/or the lack of sound evidence provided by detailed history and diagnostic tests [10].

Skin testing and/or sIgE were positive in 50–100% of adults with SRs (Table 1); the one Italian study [12] that yielded 7% skin test positivity reflects a paediatric population and only skin prick testing was performed.

Variability in the prevalence of SRs is induced by various influencing factors, which include failure to reach consensus on a universal definition of anaphylaxis and consequently more than one disease classification [22], insect distribution patterns world-wide, sting exposure, age distribution of the studied populations and data collection technique [3]. With sting exposure, the prevalence of SRs among beekeepers is high and falls between 14% and 32% [23]. A self-administered questionnaire completed by 494 Turkish beekeepers revealed a 6.5% and 2% prevalence of systemic and anaphylactic reactions, respectively [24]. Similar findings emerged from Germany, where 46 out of 1039 beekeepers (4.4%) reported SRs [25]. According to these authors, this low prevalence of SR might be due to the protective role of a high frequency of bee stings [24] or due to older age [25]. As bumblebees are docile, anaphylaxis is rare, except in occupationally exposed people. Nevertheless, epidemiological data are lacking [26].

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 for anaphylaxis due to any cause. Analysis of the latest population-based studies of anaphylaxis, whatever the trigger, conducted over 1–6 years, revealed that insect sting-induced anaphylaxis was responsible for 7.3–59% of the total number of cases reported and was more frequent in adults than in children [3].

In a very recent population-based retrospective study of the incidence and causes of anaphylaxis conducted in Rochester, MN, over a 10-year period from 1990 to 2000, applying a definition of anaphylaxis comparable to the one created by the NIAID and FAAN [8], insect stings account for 18.5% of anaphylaxis (39 out of 211 cases) [27]. Insect stings continue to be the second major inciting allergen for anaphylaxis, responsible for 11.7% of anaphylaxis between 1990 and 1993, 23.6% between 1994 and 1997 and 17.7% between 1998 and 2000 [27].

Over the last decade, in ED studies of anaphylaxis due to any cause [28–38], the prevalence of insect sting anaphylaxis is 1.5–34% (Table 2). The lowest figure was reported in a study performed in a hospital in the centre of Milan [30], where the likelihood of being stung was, however, slight. Brown's study, on the other hand, confirms the close relationship between reactions and exposure to the *Myrmecia* ant, as it documents a higher percentage of insect stings as the cause of anaphylaxis in Australia [32].

Many factors may underlie the disparate estimates of the occurrence of insect sting-induced anaphylaxis, and

Table 2. Insect sting anaphylaxis: data extrapolated from the latest emergency departments (ED) visits for anaphylaxis due to any cause of anaphylaxis [original]

References	Country	Type of study	Period of study (years)	Study population	No. of cases of anaphylaxis	Insect sting (%)	No. of fatalities
Cianferoni et al. [28]	Italy	R	11	Children	107	29	0
Brown et al. [29]	Australia	R	1	Adults	142	17.5	1*
Pastorello et al. [30]	Italy	R	2	Adults	140	1.5	0
Bellou et al. [31]	France	R	1	Adults	12	25	0
Brown [32]	Australia	R	9	Children and adults	1149	30	Not known
Smit et al. [33]	Hong Kong	R	6	Children and adults	282	7.1	0
Braganza et al. [34]	Australia	R	3	Children	57	5.3	0
Jirapongsananuruk et al. [35]	Thailand (hospital admissions)	R	5	Children and adults	101	11	1
Simon and Mulla [36]	Texas (hospital admissions)	R	1	Children and adults	464	34.1	4 [†]
De Silva et al. [37]	Australia	R	5	Children	123	3	1

*Mortality due to a bee sting.

[†]Two fatalities due to ant bites.

R, retrospective.

Table 3. Hymenoptera stings and biphasic anaphylactic reactions [original]

References	Country	Study population	Type of study	No. of biphasic reaction (%)	No. of fatalities
Brazil and MacNamara [41]	USA	Adults	ED study	6 (18)*	0
Lee and Greenes [42]	Boston	Children	Hospital admissions	6 (6) [†]	0
Smit et al. [33]	Hong Kong	Children and adults	ED study	15 (5.3) [‡]	0
Ellis and Day [44]	Canada	Children and Adults	ED study	20 (19.4) [§]	0
Yang et al. [43]	Korea	Children and Adults	ED + inpatients + outpatients	3 (2.2)	0
De Swert et al. [45]	Belgium	Children	PB study	2 (3) [‡]	0

PB study: population-based study of anaphylaxis due to any cause.

ED study: emergency department study of anaphylaxis due to any cause.

*Three cases due to an insect sting.

[†]Two cases due to bee stings.[‡]One case due to an insect sting.[§]Five cases due to an insect sting.

include the lack of standard diagnostic guidelines, the diverse population profiles, different International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes and other system codes, geography or allergen exposure [22]. Moreover, in ED studies, the aetiology of anaphylaxis is based on ED assessments rather than allergy evaluations with confirmatory diagnostic tests.

Emergency department admissions after insect stings. The largest multi-centre study of individuals presenting to the ED for insect sting allergic reactions was performed in 15 North American EDs [39], using the ICD-9-CM code. Of the total number of admissions, 358 (58%) were local reactions, diagnosed as rashes, hives or swelling confined to or contiguous with the sting site. Using Brown's classification, 259 (42%) were SRs, of which 70 (27%) were mild, 143 (55%) moderate and 46 (18%) severe [39]. According to the same authors, although the ICD-9-CM

codes identified 87% of insect sting-allergic patients vs. 53% of food allergy patients, in the ED setting, a tenth of insect sting-allergy cases would have gone undetected [40].

Biphasic anaphylactic reactions

A biphasic anaphylactic reaction (BAR) is defined as a recurrence of anaphylactic symptoms after an initial remission. BAR occurs in 1–20% of cases of anaphylaxis [33, 41–46] but seems to be uncommon with insect stings as it is generally associated with the most severe reactions [47]. Indeed, among 46 cases of BARs, hymenoptera stings were responsible for about 20% (Table 3). Fatalities can occur, but it is very rare in insect sting BAR. Although rare, the possible occurrence of a BAR raises the question of how long to keep patients under observation following anaphylaxis. A review of the data published to date reveals that no right and at the same time practical post-

anaphylaxis observation period exists, but rather that a period of 8 h might suffice to ensure that most severe recurrences would manifest while the patient was still under observation [46]. To the best of our knowledge, protracted in-field insect sting anaphylaxis is rare, with only two out of three severe anaphylactic episodes occurring among the 14 SRs to sting challenge during an old controlled clinical trial of venom immunotherapy [47]. Delayed onset of anaphylaxis has been reported but only anecdotally.

Mortality

Low but not negligible, the incidence of insect sting mortality due to early anaphylaxis ranges from 0.03 to 0.48 fatalities per 1 000 000 inhabitants per year [3] (Table 4). At least 40–100 fatal sting reactions occur annually in America [48]. In Italy, according to ISTAT figures, 13 cases of fatal insect sting-induced anaphylaxis were reported between 1980 and 1990. ISTAT data available from 1994 up to 2003 report 94 cases of insect sting deaths, according to the ICD-9-CM code 989.5 (insect sting allergy). Greater awareness of the phenomenon in Italy may explain the higher number of sting deaths officially recorded in the last decade. However, this is probably an underestimate since 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 [49], compared with ISTAT's five cases for the whole country.

Underestimates are common world-wide, with many sting fatalities going unrecognized and misinterpreted as unexplained [3, 22, 50]. The latest studies on fatal anaphylaxis from different countries indicate that the percentage of fatal stings is around 20% in Britain [50], New Zealand [51], Florida [52] and Australia [53] (Table 5).

In Pumphrey's study, 47 cases of fatal anaphylaxis were due to insect stings (29 wasp, four bee and 14 unidentified) [50]. Death commonly resulted from shock 10–15 min after the sting and in a quarter of cases from angioedema of the upper airways. Although fatalities occurred mostly in those above 40 years old, children are

Table 5. Insect sting fatal anaphylaxis: data extrapolated from the latest studies on deaths due to any cause of anaphylaxis [original]

References	Country	Study period	No. of fatal anaphylaxis	No. of insect sting fatal anaphylaxis (%)
Pumphrey [50]	UK	1992–2001	202*	47 (23)
Low and Stables [51]	New Zealand	1985–2005	18†	4 (22)
Simon and Mulla [52]	Florida	1996–2005	89	9 (20)‡
Liew et al. [53]	Australia	1997–2005	112	20 (18)

*Derived from a dedicated anaphylaxis deaths registry.

†Derived from a single hospital's forensic department database.

‡Among 44 cases in which the trigger was specified, nine (20%) were due to insect stings.

also at risk. Fifteen percent of fatal stings occurred at work, 32% in the garden, 34% at home and even 5% in bed [50]. In Florida among 44 cases in which the trigger was specified, nine (20%) were insect sting induced (two wasp, two bee, four ant and one unidentified) [52]. Men were more likely than women to have died from hymenoptera anaphylaxis than from other types of anaphylaxis [52]. In Australia out of 112 fatal anaphylaxis 20 deaths were insect sting induced: 13 bee, wasp and hornet, six by other arthropods, including jack-jumper ants and one due to a non-venomous arthropod. Most of them occurred in male adults. From the scant details, it is known that three casualties had ischaemic heart disease or dysarrhythmia, and one was asthmatic [53].

Natural history and risk factors

In contrast with the higher prevalence of IgE sensitization in adults with no previous case history of an allergic reaction, SRs occur in a small percentage. Why some sensitized patients react to a future sting and others do not is still unknown, as well as why some sensitized subjects develop LLR while others experience severe SRs. On the other hand, the risk for adults, who experienced a first anaphylactic reaction, of re-reacting to a further sting is between 40% and 60%; in the remainder, symptoms may be less severe or even completely absent [5]. A distinction has to be drawn between risk factors that are associated with a higher risk of stings and those that influence the outcome and severity of a reaction. This review will focus on the latter factors, many of which are well known [3] (Table 6).

Factors influencing the occurrence of an allergic reaction

Genetic factors. Little data are available on the genetic factors that may be involved in the production and

Table 4. Fatalities following hymenoptera sting [original]

Country	Fatalities/ 1 000 000 inhab/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

Table 6. Factors determining the severity of hymenoptera stings [original]

History of prior severe sting reaction (with respiratory or cardiovascular symptoms)
Older age
Insect type (honeybee, European hornet)
Pre-existing disease: cardiovascular disease, asthma
Drugs: particularly β -blockers (also eye drops), angiotensin-converting enzyme inhibitors*
Sting site (e.g., head) [†]
Mast cell diseases, elevated baseline serum tryptase concentration

*Controlled studies are needed.

[†]Not confirmed by all studies.

persistence of IgE antibodies in subjects stung by hymenoptera. A possible protective role of black race was suggested some years ago and more recently it has been hypothesized that the higher rate of allergic sting reactions in Israeli children may be related to genetic factors [10]. Protection linked to particular alleles (HLA-DR4 and DQw3), whose presence is connected to the inability to synthesize IgE against two important bee venom allergens, has been shown [54]. Particularly, alterations in the renin-angiotensin system [55] as well as elevated serum levels of calcitonin gene-related peptide [56] have been described but never confirmed.

Atopy. An atopic constitution is found with similar frequency in HVA patients and in the general population [6]. However, in an American study, asymptomatic sensitization to aeroallergens was associated with asymptomatic sensitization to venoms, although a history of allergy symptoms was not associated with a history of SRs to stings [57]. Patients who have had anaphylaxis from other sources are at no greater risk than that of the general population of reacting similarly to insect stings or bites [58]. In contrast, atopic beekeepers, either through inhalation or multiple stings, may be sensitized more easily their non-atopic counterparts and are at a significantly increased risk of developing SR when re-stung [23].

Venom sensitization. Venom asymptomatic sensitization is as common as that to aeroallergens and food allergens [59]. As the synthesis of sIgE subsequent to a sting is usually transitory [60] and the frequency of stings is usually low, the majority of subjects lose their sensitivity. However, in adults with asymptomatic venom sensitization that persisted over time, the risk of subsequent sting-induced anaphylaxis was 17% vs. 0% in skin-test-negative individuals, regardless of whether they were stung after 1–4 or 5–9 years from the time of initial testing [60]. It is curious that this risk seems to be higher than that of patients with a history of LLRs. These data are alarming but emerge from one single study on 65 patients and require further investigation.

In contrast, Fernandez suggested that this condition does not represent a clear risk for a future SR, at least in the case of vespids; the opposite could occur in the case of honeybee sensitization, as this persists over time [20]. Nevertheless, the risk associated with the condition of asymptomatic sensitization can, at least in part, explain the absence of a previous positive case history in 40% of fatalities [6, 60].

Time interval between stings. The time interval between stings could be one of the key factors in changing the natural history of the disease from asymptomatic sensitization to HVA. Indeed, the risk of SR increases by 58% compared with controls if the first sting-induced reaction has been preceded by a well-tolerated sting within the two previous months [1]. With an increasing sting interval the risk generally declines steadily, but remains in a 20–30% range even after 10 years [1].

Number of stings. A large number of simultaneous stings (> 50) may sensitize and then be followed by single-sting anaphylaxis [9]. Moreover, patients who have had multiple stings at one time may have experienced true anaphylaxis and not a toxic response [6, 58]. On the other hand, being stung very frequently (> 200 annual stings) appears to induce tolerance, as in beekeepers [23].

Factors influencing the severity of an allergic reaction

Age. In children, about 60% of SRs are mild and generally cutaneous, whereas in about 70% of adults symptoms are respiratory or cardiovascular. Elderly patients more often develop particularly severe SRs, and the fatality rate is higher than in children and young adults [1]. Children with cutaneous SRs have a lower rate of recurrence over time than adults, while those with moderate to severe SR continue to have a high risk of reactions even 15–20 years later [61].

Severity of the preceding reaction. In general, after a LLR, between 5% and 15% will develop an SR when re-stung. In one study, 7% of children with LLRs had SRs to a re-sting [61]. In a recent study in Israeli schoolchildren, the authors reported that 33.9% of those with LLRs also had SR. However, the reactions were not reported chronologically, meaning an estimate of the reaction severity to re-stings cannot be made [10].

The risk of recurrence of SRs is determined by previous reaction severity: the more serious the initial reaction, the greater the risk of recurrence. Linking the estimated risk of SR with severity, age and sting interval, adults with a recent history of severe anaphylaxis have a 40–60% chance of reacting to a re-sting, and those with mild SRs might have a 20% chance of subsequent SRs [5].

Atopy. Currently, there is no evidence of a higher risk of severe reactions in atopic patients. A recent study showed that patients with HVA and high levels (> 250 kU/L) of tIgE predominantly developed mild to moderate reactions, as if they were protected from the most severe SRs [62]; however, this hypothesis needs to be confirmed by sting challenge studies. In contrast, atopy may increase the severity of SRs in beekeepers and their family members [23].

Gender. In the vast majority of investigations of HVA, men are more often affected than women [6]. However, some controversial data exist on the prevalence of HVA [63]. For example, the prevalence of SRs and LLRs was similar in both genders in eastern Spain [20]. Also, gender made no difference in the severity of SRs to bee sting in a Turkish study [64]. On the other hand, in the latest studies on fatal anaphylaxis from different countries fatalities occurred mostly in males [50–53].

Sting site. The fact that reactions from stings in the head, neck or throat are more severe than stings in the extremities, either in fatal or non-fatal cases [6], is not confirmed by all studies [58].

Insects. Bee venom-allergic patients are at a greater risk of a SR on re-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 America, 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 because of different stinging behaviours [65]. Besides patients suffering from mast cell diseases, anaphylaxis is usually confined to a specific insect species for the individual [58].

Cardiovascular diseases and therapies. Pre-existing cardiovascular diseases are risk factors for particularly severe and fatal anaphylactic sting reactions [66]. β -blockers do not seem to increase the overall risk of an SR, but may influence its severity. Because cardiovascular diseases are much more frequent than anaphylaxis and β -blockers are very effective, this medication cannot be substituted in cases of comorbidity without a careful risk analysis [66].

There are some reports that angiotensin-converting enzyme inhibitors (ACEI) might also increase risk, suggesting that this therapy should be avoided when possible [67]. However, a more recent study shows no association between ACEI use and increased frequency of SRs to venom immunotherapy [68].

Elevated serum tryptase, mastocytosis. Particularly severe cardiovascular, even fatal sting reactions may occur in patients with mast cell diseases; even in HVA patients

without diagnosed mastocytosis, elevated baseline serum tryptase levels were found to be associated with very severe anaphylactic reactions to stings [69]. In one Spanish study, out of 210 subjects with mastocytosis 22% developed anaphylaxis. In nine cases the trigger was identified as an insect, in seven of which sIgE antibodies were detected [70], making an IgE-anaphylaxis diagnosis possible. Although anaphylaxis in mastocytosis patients may also be due to toxic mediator release from mast cells, some authors [69] question these pseudo-allergic sting reactions, suggesting that the poor sensitivity of the diagnostic tests may distort findings.

A further study shows that the cumulative incidence of anaphylaxis in mastocytosis patients was lower in children than in adults, where reactions were more frequent in patients with systemic rather than cutaneous mastocytosis and mainly due to hymenoptera stings [71]. In contrast, few data exist regarding the prevalence of mast cell diseases in populations with HVA. A recent study indicates that 65% of patients with an elevated serum basal tryptase level (> 11.4 ng/mL) and a history of sting SR have an underlying clonal mast cell disorder that is either systemic mastocytosis or monoclonal mast cell activation syndrome [72], suggesting the necessity for a bone marrow biopsy.

Other potential risk factors

Besides elevated basal serum tryptase levels, it seems likely that there are a number of defects in mediator degradation pathways or intracellular signalling pathways that may be associated with more severe or fatal anaphylactic reactions. A recent study showed that serum PAF levels were directly correlated and serum PAF acetylhydrolase activity was inversely correlated with the severity of anaphylaxis [73]. Forty-one patients were studied, in 22 of whom the allergic reaction was triggered by food, in 12 by drugs and insect stings in two patients, while five episodes were idiopathic. Moreover, PAF acetylhydrolase activity was significantly lower in patients with fatal anaphylactic reactions to peanuts than in controls. The authors concluded that failure of PAF acetylhydrolase to inactivate PAF may contribute to the severity of anaphylaxis [73].

Unlike what has so far been stressed regarding an elevated basal serum tryptase level identified for the time being as a risk factor only for insect sting allergy, the defect in PAF acetylhydrolase activity could represent a risk factor for anaphylaxis whatever its underlying trigger (food, drugs and insects). The study by Vadas et al. [73] has catalysed an interesting debate on the subject. Other authors have noted that the rising levels of oxidative stress with worsening acute anaphylaxis could explain the inverse correlation between PAF and serum PAF acetylhydrolase activity [74] as well as low PAF

acetylhydrolase activity in patients with fatal anaphylaxis might be caused by severe hypoxia, followed by systemic necrosis [75]. Further studies are needed to confirm the role of low PAF acetylhydrolase in anaphylaxis.

Risk factors for biphasic anaphylactic and fatal sting reactions

Several risk factors for biphasic and protracted reactions emerge from the literature that probably apply to 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 β -blockers [46]. Possible factors for fatal stings include a positive history of hymenoptera allergy (but not always), male sex, age over 40 years, probably because of comorbidity with cardiovascular diseases, perhaps the sting site (head or neck), bee and European hornet stings, mast cell diseases and the delayed administration or non-use of epinephrine [1, 22].

Prevention of insect sting anaphylaxis

In the range of 40–85% [1] of fatal sting reaction, victims had no history of previous anaphylaxis. Therefore, greater insight into the natural history and risk factors is vital, especially in asymptomatic sensitized subjects. For patients with SRs, prevention of future severe allergic reactions goes through the referral to an ED and the correct use of epinephrine by the doctors in order to prevent progression of the allergic reaction, the referral to an allergist for preventive measures, for diagnosis and in some cases prescribing specific immunotherapy, and the proper techniques for self-administration of epinephrine [3, 39, 48]. However, most insect sting victims failed to seek medical advice and hospital attendance does not always correlate with the severity of the allergic reaction.

A multi-centre American study of ED visits for insect sting allergies [39] reported that 58% of patients (aged > 16 years old) who attended an ED had local reactions, and 31% had multisystem organ involvement or hypotension. In Israel, despite good access to medical care, > 10% of children with LLR attended a hospital compared with only 14.5% of those with severe SR [10]. As LLRs usually last for several days and may be bothersome, it is possible that parents perceive them as being more hazardous than other reactions.

Moreover, compliance with international guidelines for the treatment of anaphylaxis, even in the specific case of insect sting anaphylaxis, appears to be very low. Also, recently, in the previous cited study of ED visits for insect sting allergies, only 13% of patients with insect sting anaphylaxis received epinephrine in the ED, only 27% of

SR patients received a prescription for self-injectable epinephrine and only 20% were officially referred to an allergist, while among patients with anaphylaxis, 39% had a known history of insect sting allergy [39]. The authors also underline that the participating EDs in this study are academic medical centres, many of which support emergency medicine residency programmes. Thus, the results of this study may not reflect management patterns among non-academic or rural EDs [39].

A prompt and accurate diagnosis identifies those patients at greatest risk for an adverse outcome who will benefit from specific immunotherapy. Because of the proven efficacy of VIT [76], at least 50% of deaths in patients with a positive case history could have been avoided through specific immunotherapy.

Good news seems to have emerged from Australia, where, in contrast to the stable time trends in age-specific admission rates for contact with hymenoptera, an 88% decrease in age-standardized rate for insect sting-induced fatal anaphylaxis was estimated over the 9-year study period [53]. According to the authors, possible explanations include the widespread use of insect venom immunotherapy and the recent increased availability of epinephrine autoinjectors [53].

Conclusions

Despite the high prevalence of asymptomatic sensitization, the prevalence of sting-induced anaphylaxis is low. However, to date, no parameter has been identified that can predict who will have a future reaction and whether it will be LLR or anaphylactic. The combination of several concomitant factors, which include environmental (the frequency of stings and the type of insect), genetics (the persistence of sIgE antibodies and probably other factors) and individual (age; morbidities like asthma, mastocytosis or ischaemic heart disease; concurrent medication; strenuous exercise; and others) factors, may account for the occurrence of an SR in individual patients. Several not completely known factors may be associated with the severity of a systemic re-sting. Although underestimated insect sting mortality is low compared with other causes. Better knowledge of the epidemiology, natural history and risk factors is crucial for improving venom-allergic patient care.

Prevention of insect sting allergic reactions can be achieved through improvements in emergency management, implementing techniques for prompt diagnosis and treatment of acute allergic reactions and anaphylaxis. Wider awareness of the existence and efficacy of specific immunotherapy as well as better training of patients on allergen avoidance strategies and how to auto-inject epinephrine are also essential to this goal. Thus, there is considerable room for further improvement in venom-allergic patient care.

References

- 1 Bilò BM, Rueff F, Mosbech H, Bonifazi F, Oude Elberink JNG, the EAACI Interest Group on Insect Venom Hypersensitivity. Diagnosis of Hymenoptera venom allergy. *Allergy* 2005; **60**:1339–49.
- 2 Moffitt JE, Golden DB, Reisman RE *et al.* Stinging insect hypersensitivity: a practice parameter update. *J Allergy Clin Immunol* 2004; **114**:869–86.
- 3 Bilò BM, Bonifazi F. Epidemiology of insect-venom anaphylaxis. *Curr Opin Allergy Clin Immunol* 2008; **8**:330–7.
- 4 Oude Elberink JN, de Monchy JG, Golden DB *et al.* Development and validation of a health-related quality-of-life questionnaire in patients with yellow jacket allergy. *J Allergy Clin Immunol* 2002; **109**:162–70.
- 5 Golden DB. Insect sting allergy and venom immunotherapy: a model and a mystery. *J Allergy Clin Immunol* 2005; **115**:439–47.
- 6 Mueller UR. *Insect sting allergy. Clinical picture, diagnosis and treatment.* Stuttgart: Gustav Fischer Verlag, 1990.
- 7 Sampson HA, Muñoz-Furlong A, Bock SA *et al.* Symposium on the definition and management of anaphylaxis: summary report. *J Allergy Clin Immunol* 2005; **115**:584–91.
- 8 Sampson HA, Muñoz-Furlong A, Campbell RL *et al.* Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006; **117**:391–7.
- 9 Antonicelli L, Bilò MB, Bonifazi F. Epidemiology of Hymenoptera allergy. *Curr Opin Allergy Clin Immunol* 2002; **2**:341–6.
- 10 Graif Y, Romano-Zelekha O, Livne I, Green MS, Shohat T. Allergic reactions to insect stings: results from a national survey of 10 000 junior high school children in Israel. *J Allergy Clin Immunol* 2006; **117**:1435–9.
- 11 Kemp SF, deShazo RD, Moffitt JE, Williams DF, Buhner WA. II Expanding habitat of the imported fire ant (*Solenopsis invicta*): a public health concern. *J Allergy Clin Immunol* 2000; **105**:683–91.
- 12 Novembre E, Cianferoni A, Bernardini R *et al.* Epidemiology of insect venom sensitivity in children and its correlation to clinical and atopic features. *Clin Exp Allergy* 1998; **28**:834–8.
- 13 van Ree R. Carbohydrate epitopes and their relevance for the diagnosis and treatment of allergic diseases. *Int Arch Allergy Immunol* 2002; **129**:189–97.
- 14 Hemmer W, Focke M, Kolarich D, Dalik I, Götz M, Jarisch R. Identification by immunoblot of venom glycoproteins displaying immunoglobulin E-binding N-glycans as cross-reactive allergens in honeybee and yellow jacket venom. *Clin Exp Allergy* 2004; **34**:460–9.
- 15 Sturm GJ, Schuster C, Kranzelbinder B, Wiednig M, Groselj-Strele A, Aberer W. Asymptomatic sensitization to hymenoptera venom is related to total immunoglobulin E levels. *Int Arch Allergy Immunol* 2009; **148**:261–4.
- 16 Fernandez J, Blanca M, Soriano V *et al.* Epidemiological study of the prevalence of allergic reactions to Hymenoptera in a rural population in the Mediterranean area. *Clin Exp Allergy* 1999; **29**:1069–74.
- 17 Incorvaia C, Senna G, Mauro M *et al.* Prevalence of allergic reactions to Hymenoptera stings in northern Italy. *Eur Ann Allergy Clin Immunol* 2004; **36**:372–4.
- 18 Navarro LA, Peláez A, de la Torre F *et al.* Epidemiological factors on hymenoptera venom allergy in a Spanish adult population. *J Investig Allergol Clin Immunol* 2004; **14**:134–41.
- 19 Nittner-Marszalska M, Liebhart J, Liebhart E *et al.* Prevalence of Hymenoptera venom allergy and its immunological markers current in adults in Poland. *Med Sci Monit* 2004; **10**:324–9.
- 20 Fernandez J, Soriano V, Mayorga L, Mayor M. Natural history of Hymenoptera venom allergy in Eastern Spain. *Clin Exp Allergy* 2005; **35**:179–85.
- 21 Onbaşı K, Onbaşı O, Eminbeyli L, Kaynak C. Prevalence and alternative therapy methods for bee and wasp allergy in Van. *Allergy* 2008; **63**:246–7.
- 22 Clark S, Camargo CA Jr. Epidemiology of anaphylaxis. *Immunol Allergy Clin North Am* 2007; **27**:145–63.
- 23 Müller UR. Bee venom allergy in beekeepers and their family members. *Curr Opin Allergy Clin Immunol* 2005; **5**:343–7.
- 24 Celikel S, Karakaya G, Yurtsever N *et al.* Bee and bee products allergy in Turkish beekeepers: determination of risk factors for systemic reactions. *Allergol Immunopathol (Madrid)* 2006; **34**:180–4.
- 25 Münstedt K, Hellner M, Winter D, von Georgi R. Allergy to bee venom in beekeepers in Germany. *J Investig Allergol Clin Immunol* 2008; **18**:100–5.
- 26 de Groot H. Allergy to bumblebees. *Curr Opin Allergy Clin Immunol* 2006; **6**:294–7.
- 27 Decker WW, Campbell RL, Manivannan V *et al.* The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project. *J Allergy Clin Immunol* 2008; **122**:1161–5.
- 28 Cianferoni A, Novembre E, Mugnaini L *et al.* Clinical features of acute anaphylaxis in patients admitted to a university hospital: an 11-year retrospective review (1985–1996). *Ann Allergy Asthma Immunol* 2001; **87**:27–32.
- 29 Brown AF, McKinnon D, Chu K. Emergency department anaphylaxis: a review of 142 patients in a single year. *J Allergy Clin Immunol* 2001; **108**:861–6.
- 30 Pastorello EA, Rivolta F, Bianchi M *et al.* Incidence of anaphylaxis in the emergency department of a general hospital in Milan. *J Chromatogr B Biomed Sci Appl* 2001; **756**:11–7.
- 31 Bellou A, Manel J, Samman-Kaakaji H *et al.* Spectrum of acute allergic diseases in an emergency department: an evaluation of one years' experience. *Emerg Med* 2003; **15**:341–7.
- 32 Brown SG. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 2004; **114**:371–6.
- 33 Smit DV, Cameron PA, Rainer TH. Anaphylaxis presentations to an emergency department in Hong Kong: incidence and predictors of biphasic reactions. *J Emerg Med* 2005; **28**:381–8.
- 34 Braganza SC, Acworth JP, McKinnon DR *et al.* Paediatric emergency department anaphylaxis: different patterns from adults. *Arch Dis Child* 2006; **91**:159–63.
- 35 Jirapongsananuruk O, Bunsawansong W, Piyaphanee N *et al.* Features of patients with anaphylaxis admitted to a university hospital. *Ann Allergy Asthma Immunol* 2007; **98**:157–62.
- 36 Simon MR, Mulla ZD. Hospitalizations for anaphylaxis in Florida: analysis of month of discharge. *Int Arch Allergy Immunol* 2007; **146**:89–90.
- 37 de Silva IL, Mehr SS, Tey D, Tang ML. Paediatric anaphylaxis: a 5 year retrospective review. *Allergy* 2008; **63**:1071–6.
- 38 Helbling A, Hurni T, Mueller UR, Pichler WJ. Incidence of anaphylaxis with circulatory symptoms: a study over a 3-year period comprising 940 000 inhabitants of the Swiss Canton Bern. *Clin Exp Allergy* 2004; **34**:285–90.

- 39 Clark S, Long AA, Gaeta TJ, Camargo CA Jr. Multicenter study of emergency department visits for insect sting allergies. *J Allergy Clin Immunol* 2005; **116**:643–9.
- 40 Clark S, Gaeta TJ, Kamarthi GS, Camargo CA. ICD-9-CM coding of emergency department visits for food and insect sting allergy. *Ann Epidemiol* 2006; **16**:696–700.
- 41 Brazil E, MacNamara AFJ. “Not so immediate” hypersensitivity – the danger of biphasic anaphylactic reactions. *Accid Emerg Med* 1998; **15**:252–3.
- 42 Lee JM, Greenes DS. Biphasic anaphylactic reactions in pediatrics. *Pediatrics* 2000; **106**:762–6.
- 43 Yang MS, Lee SH, Kim TW *et al.* Epidemiologic and clinical features of anaphylaxis in Korea. *Ann Allergy Asthma Immunol* 2008; **100**:31–6.
- 44 Ellis AK, Day JH. Incidence and characteristics of biphasic anaphylaxis: a prospective evaluation of 103 patients. *Ann Allergy Asthma Immunol* 2007; **98**:64–9.
- 45 De Swert LF, Bullens D, Raes M, Dermaux AM. Anaphylaxis in referred pediatric patients: demographic and clinical features, triggers, and therapeutic approach. *Eur J Pediatr* 2008; **167**:1251–61.
- 46 Tole JW, Lieberman P. Biphasic anaphylaxis: review of incidence, clinical predictors, and observation recommendations. *Immunol Allergy Clin North Am* 2007; **27**:309–26.
- 47 Golden DB. Patterns of anaphylaxis: acute and late phase features of allergic reactions. In: Bock G, Goode J, eds. *Anaphylaxis. Novartis Found Symp* 257. Chichester, UK: John Wiley and Sons, 2004; 101–10.
- 48 Clark S, Camargo CA Jr. Emergency treatment and prevention of insect-sting anaphylaxis. *Curr Opin Allergy Clin Immunol* 2006; **6**:279–83.
- 49 Antonicelli L, Bilò MB, Napoli G, Garritani MS, Bonifazi F. Prevalence and treatment of insect sting reactions in emergency departments. *Allergy* 2001; **56**:37.
- 50 Pumphrey RS. Fatal anaphylaxis in the UK, 1992–2001. In: Bock G, Goode J, eds. *Anaphylaxis. Novartis Found Symp* 257. Chichester, UK: John Wiley and Sons, 2004; 116–28.
- 51 Low I, Stables S. Anaphylactic deaths in Auckland, New Zealand: a review of coronial autopsies from 1985 to 2005. *Pathology* 2006; **38**:328–32.
- 52 Simon MR, Mulla ZD. A population-based epidemiologic analysis of deaths from anaphylaxis in Florida. *Allergy* 2008; **63**:1077–83.
- 53 Liew WK, Williamson E, Tang ML. Anaphylaxis fatalities and admissions in Australia. *J Allergy Clin Immunol* 2009; **123**:434–42.
- 54 Lympny P, Kemeny DM, Welsh KI, Lee TH. An HLA-associated nonresponsiveness to mellitin: a component of bee venom. *J Allergy Clin Immunol* 1990; **86**:160–70.
- 55 Hermann K, Ring J. The renin-angiotensin system in patients with repeated anaphylactic reactions during hymenoptera venom hyposensitization and sting challenge. *Int Arch Allergy Immunol* 1997; **112**:251–6.
- 56 Volcheck GW, Butterfield JH, Yunginger JW, Klee GG. Elevated serum levels of calcitonin gene-related peptide in Hymenoptera sting-induced anaphylaxis. *J Allergy Clin Immunol* 1998; **102**:149–51.
- 57 Golden DB, Marsh DG, Kagey-Sobotka A *et al.* Epidemiology of insect venom sensitivity. *JAMA* 1989; **262**:240–4.
- 58 Solley GO. Stinging and biting insect allergy: an Australian experience. *Ann Allergy Asthma Immunol* 2004; **93**:532–7.
- 59 Arbes SJ Jr, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 2005; **116**:377–83.
- 60 Golden DB, Marsh DG, Freidhoff LR *et al.* Natural history of Hymenoptera venom sensitivity in adults. *J Allergy Clin Immunol* 1997; **100**:760–6.
- 61 Golden DB, Kagey-Sobotka A, Norman PS *et al.* Outcomes of allergy to insect stings in children, with and without venom immunotherapy. *N Engl J Med* 2004; **351**:668–74.
- 62 Sturm GJ, Heinemann A, Schuster C *et al.* Influence of total IgE levels on the severity of sting reactions in Hymenoptera venom allergy. *Allergy* 2007; **62**:884–9.
- 63 Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. *Allergy* 2008; **63**:1418–27.
- 64 Kalyoncu AF, Demir AU, Ozcan U, Ozkuyumcu C, Sahin AA, Barış YI. Bee and wasp venom allergy in Turkey. *Ann Allergy Asthma Immunol* 1997; **78**:408–12.
- 65 Golden DB, Breisch NL, Hamilton RG *et al.* Clinical and entomological factors influence the outcome of sting challenge studies. *J Allergy Clin Immunol* 2006; **117**:670–5.
- 66 Mueller UR. Cardiovascular disease and anaphylaxis. *Curr Opin Allergy Clin Immunol* 2007; **7**:337–41.
- 67 Bilò MB, Bonifazi F. Advances in Hymenoptera venom immunotherapy. *Curr Opin Allergy Clin Immunol* 2007; **7**:567–73.
- 68 White KM, England RW. Safety of angiotensin converting enzyme inhibitors while receiving venom immunotherapy. *Ann Allergy Asthma Immunol* 2008; **101**:426–30.
- 69 Rueff F, Placzek M, Przybilla B. Mastocytosis and Hymenoptera venom allergy. *Curr Opin Allergy Clin Immunol* 2006; **6**:284–8.
- 70 González de Olano D, de la Hoz Caballer B, Núñez López R *et al.* Prevalence of allergy and anaphylactic symptoms in 210 adult and pediatric patients with mastocytosis in Spain: a study of the Spanish network on mastocytosis (REMA). *Clin Exp Allergy* 2007; **37**:1547–55.
- 71 Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy* 2008; **63**:226–32.
- 72 Bonadonna P, Perbellini O, Passalacqua G *et al.* Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased serum tryptase levels. *J Allergy Clin Immunol* 2009; **123**:680–6.
- 73 Vadas P, Gold M, Perelman B, Liss GM *et al.* Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. *N Engl J Med* 2008; **3**:28–35.
- 74 Bansal AS, Chee R, Sumar N. Platelet-activating factor, PAF acetylhydrolase, and anaphylaxis. *N Engl J Med* 2008; **3**:1515–6, author reply.
- 75 Okamoto H, Kamatani N. Platelet-activating factor, PAF acetylhydrolase, and anaphylaxis. *N Engl J Med* 2008; **3**:1516, author reply.
- 76 Bonifazi F, Jutel M, Bilò BM, Birnbaum J, Muller U, the EAACI Interest Group on Insect Venom Hypersensitivity *et al.* Prevention and treatment of hymenoptera venom allergy: guidelines for clinical practice. *Allergy* 2005; **60**:1459–70.