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Risk factors and indicators of severe systemic insect sting reactions

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Abstract

Hymenoptera venom allergy ranks among the top three causes of anaphylaxis worldwide, and approximately one-quarter of sting-induced reactions are classified as severe. Fatal sting reactions are exceedingly rare, but certain factors may entail a considerably higher risk. Delayed administration of epinephrine and upright posture are situational risk factors which may determine an unfavorable outcome of the acute anaphylactic episode and should be addressed during individual patient education. Systemic mastocytosis and senior age are major, unmodifiable long-term risk factors and thus reinforce the indication for venom immunotherapy. Vespid venom allergy and male sex likewise augment the risk of severe or even fatal reactions. Further studies are required to assess the impact of specific cardiovascular comorbidities. Available data regarding potential effects of beta-blockers and/or ACE inhibitors in coexisting venom allergy are inconclusive and do not justify recommendations to discontinue guideline-directed antihypertensive treatment. The absence of urticaria/angioedema during sting-induced anaphylaxis is indicative of a severe reaction, serum tryptase elevation, and mast cell clonality. Determination of basal serum tryptase levels is an established diagnostic tool for risk assessment in *Hymenoptera* venom-allergic patients. Measurement of platelet-activating factor acetylhydrolase activity represents a complementary approach but is not available for routine diagnostic use.

KEYWORDS

age, mastocytosis, medication, tryptase, venom

1 | BACKGROUND

Along with food and drug allergy, *Hymenoptera* venom allergy ranks among the top three causes of anaphylaxis worldwide.[1] Prevalence rates are estimated to reach up to 7.5% in the adult European population and up to 3.3% in the United States.[2,3] *Hymenoptera* insects of clinical significance in Europe include honeybees and vespids, that is, *Vespula* and *Polistes* species whereas the latter are predominantly relevant in the Mediterranean region.[4,5]

Sting-induced systemic reactions cover a broad clinical spectrum, ranging from urticaria/angioedema as the only manifestation to full-blown anaphylaxis with near-fatal and fatal outcomes. Approximately one-quarter (range 17.5%-42.0%) of these venom-induced reactions are classified as severe (Table 1).[6-13] The considerable range observed is likely to be due to the use of different anaphylaxis grading systems—the need for a standardized anaphylaxis scoring system is currently addressed by an international working group.[14]

The mean annual age-standardized rate for fatal sting-induced anaphylaxis as the worst imaginable outcome was recently set at 0.09 (95% confidence interval 0.07-0.10) per million in a study based on UK national databases including 93 sting-related deaths.[15]

TABLE 1 Studies specifically assessing risk factors and indicators of severe sting-induced anaphylaxis

Region	Cases (n)	Males(%)	Method	Causal insects	Anaphylaxis grading system	Severe reactions(%)	Risk factors/indicators identified	Authors, y
Austria	847	50.1	Retrospective single-center observational cohort study	*Vespula* spp Honeybees	Four-grade ordinal system based on classification according to Ring and Messmer[57]	31.0	Basal serum tryptase elevation Age >40 years Absence of urticaria/angioedema during anaphylaxis Short time span from sting to onset of symptoms	Arzt et al, 2016[6]
Italy	169	63.3	Case-control study	Not specified	Four-grade ordinal system according to Mueller[58]	21.9	Basal serum tryptase elevation Platelet-activating factor acetylhydrolase activity	Pravettoni et al, 2014[7]
Germany	657	54.9	Retrospective single-center observational cohort study	*Vespula* spp Honeybees European hornets Bumble bees	Three-grade ordinal system according to Muraro et al[56]	26.2	Basal serum tryptase elevation Increasing age Absence of cutaneous signs during anaphylaxis Short time span from sting to onset of symptoms	Stoevesandt et al, 2012[8]
Switzerland	758	57.5	Retrospective single-center observational cohort study	*Vespula* spp Honeybees European hornets Bumble bees	Four-grade ordinal system according to Mueller[58]	42.0	Basal serum tryptase elevation Increasing age	Blum et al, 2011[9]
Germany	274	55.8	Retrospective single-center observational cohort study	*Vespula* spp Honeybees	Four-grade ordinal system according to Mueller[58]	17.5	Basal serum tryptase elevation Increasing age	Guenova et al, 2010[10]
Germany, Italy, Austria, Poland, France, Switzerland	962	54.4	Retrospective multi-center observational cohort study	Vespids (including *Vespula*, *Vespa*, and *Polistes* spp) Honeybees	Four-grade ordinal system according to Ring and Messmer[57]	21.4	Basal serum tryptase elevation Increasing age Male sex Vespid venom allergy Medication with ACE inhibitor Preceding sting-induced anaphylaxis	Ruëff et al, 2009[11]
Austria	150	52.0	Retrospective single-center observational cohort study	*Vespula* spp Honeybees European hornets	Four-grade ordinal system based on classification according to Ring and Messmer[57]	36.0	Low levels of total IgE Increasing age	Sturm et al, 2007[12]
Poland	109	41.3	Retrospective single-center observational cohort study	Vespids Honeybees	Four-grade ordinal system according to Mueller[58]	22.9	Basal serum tryptase elevation Increasing age	Kucharewicz et al, 2007[13]

Remarkably consistent fatality rates were found in Australia (0.09 per million),[16] Canada (0.1 per million),[17] and the United States (0.09 per million[18] or 0.11-0.17 per million,[19] depending on the region and/or source of data; Table 2).[20] Mortality rates in individuals with a known insect venom allergy as calculated on the basis of a 3% population prevalence are obviously higher, but have still been estimated to be less than 1 per 100 000 per year in a recent review.[20] The authors go so far as to state that the estimated risk of fatal anaphylaxis for a venom-allergic patient adds little to his or her overall mortality risk.[20] Very severe or fatal reactions, however, may be considerably more frequent in certain subgroups. Moreover, an unspecified, though substantial proportion of fatal sting reactions is likely to remain undiagnosed due to the absence of witnesses and/or obvious signs of anaphylaxis (see Section 6.1).[2,3] To render the situation even more complex, up to 60% of fatal sting reactions occur in individuals who did not have a notion of being allergic to *Hymenoptera* venoms[17]—a group that does and will escape all efforts to identify patients at risk.

2 | OBJECTIVES

An accurate estimation of the risk of severe future sting reactions is a prerequisite for any recommendation regarding the initiation or discontinuation of venom immunotherapy[2,21] (Figure 1) and/or the prescription of epinephrine auto-injectors.[22] This article reviews the current knowledge about risk factors and indicators of severe or fatal anaphylactic sting reactions. It aims to enable the reader to perform an individual risk assessment during routine clinical practice based on information derived from the patient's history and/or diagnostic tests.

The authors herein present a differentiated discussion of established risk factors with an emphasis on novel aspects from the recent literature. Special emphasis is put on situational risk factors and cofactors of anaphylaxis, some of which have so far been underestimated in the context of *Hymenoptera* venom allergy. Finally, this review focuses on clinical observations in severe anaphylactic sting reactions, knowledge of which is essential in order to reliably identify high-risk situations.

3 | METHODS

3.1 | Search strategies

A search of the medical literature was performed using combinations of the terms acetylsalicylic acid, age, alcohol, anaphylaxis, angiotensin-converting enzyme inhibitor, antihypertensive, basophil activation test, beta-blocker, cardiovascular, epinephrine, exercise, fatal, honey bee, *Hymenoptera*, IgE, infection, Kounis syndrome, mastocytosis, medication, platelet activating factor acetylhydrolase, *Polistes*, posture, risk factor, severity, sting, tryptase, venom, vespid, and *Vespula*. The search included only English-language articles.

3.2 | Sources of data

Articles from 2008 to 2018 were included preferentially, older data if considered of particular interest. Data on risk factors for severe anaphylactic sting reactions were gathered from studies specifically assessing venom-allergic patients (Table 1) and studies evaluating various elicitors of anaphylaxis. Data on risk factors for

TABLE 2 Studies assessing risk factors for fatal anaphylaxis [a]

Region	Source of data	Total cases (n)	Deaths due to insects (n)	Causal insects	Risk factors/indicators identified	Authors, year
Australia	Australian Bureau of Statistics, National Coronial Information System	324	41	Honeybees Vespids Ants Ticks	Senior age Male sex Multiple comorbidities Upright posture Delayed administration of epinephrine	Mullins et al, 2016[16]
United Kingdom	Office for National Statistics	480	93	Not specified	Senior age	Turner et al, 2015[15]
Canada	Ontario Coroners' Database	92	30	Not specified	Senior age Male sex	Xu et al, (2014)[17]
United States	National Center for Health Statistics, Multiple Cause of Death Data	2548	374	Not specified	Senior age Male sex Caucasian origin Living in US southern states	Jerschow et al, 2014[19]
Australia	Australian Bureau of Statistics	112	20	Honeybees Vespids Ants	Middle and senior age Male sex	Liew et al, 2009[23]
United States	Florida Department of Health, Office of Vital Statistics	89	9	Honeybees Vespids Ants	Male sex	Simon et al, 2008[24]

[a]Only studies with a specific reference to risk factors for fatal venom-induced anaphylaxis were included.

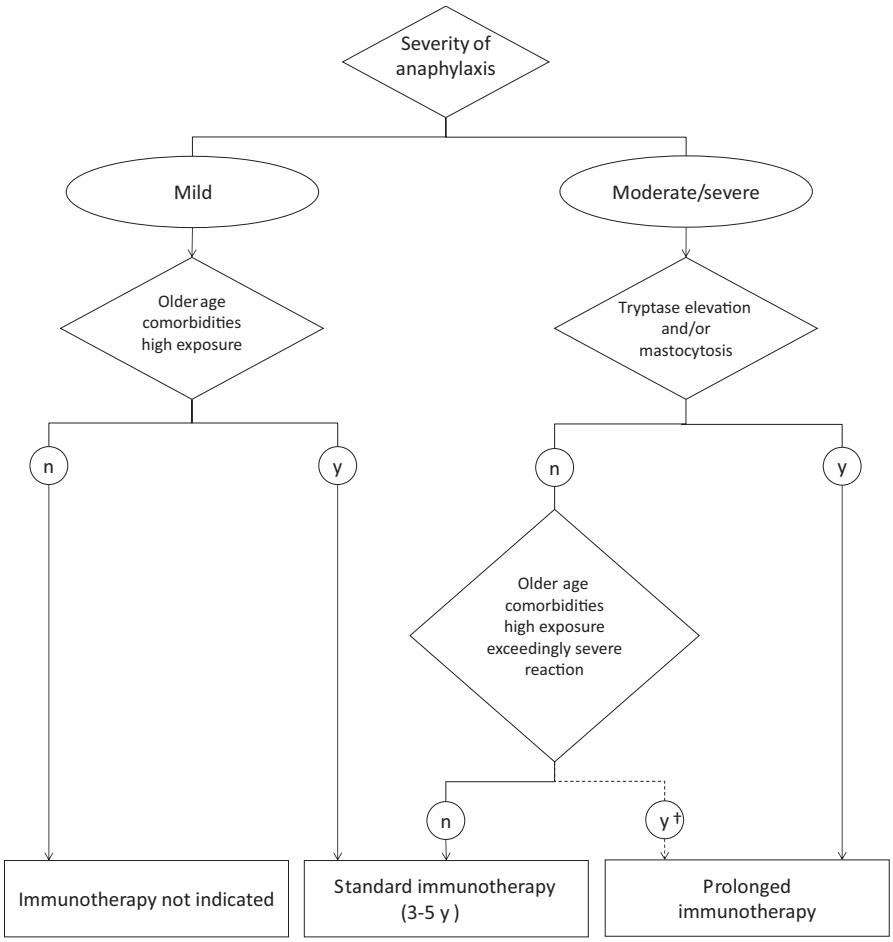

FIGURE 1 Algorithm for indicating immunotherapy in venom-allergic patients with respect to risk factors and degree of exposure. †individual decision/selected cases

fatal sting reactions were gathered from series of anaphylaxis fatalities (Table 2). Most of the latter were descriptive observations and did not include a statistical comparison with control groups. Studies focusing on severe sting reactions invariably originated from Europe and were confined to observations from honeybee and vespid stings.[6-13] The fatality case series predominantly originated from Australia[16,23] and Northern America[17,19,24] and consequently considered a broader spectrum of culprit insects including ticks and ants, but did not allow for any conclusions on species-specific risk factors.

Studies assessing specific subgroups of venom-allergic patients (eg, with mastocytosis) as well as studies examining risk factors for severe/fatal anaphylaxis *in general* were considered if providing novel or particularly relevant aspects.

3.3 | Definition of terms

We use the term "risk factor" to refer to parameters which may actually augment the severity of anaphylaxis. This includes so-called "co-factors," which may lower the allergen dose required for triggering an anaphylactic reaction by either increasing allergen bioavailability or decreasing the threshold for mast cell activation.[25] "Indicator" is used to refer to variables suggestive of a greater risk of severe reactions while not causally increasing it; this includes observations from previous sting reactions and a limited number of diagnostic tests. An overview of potential indicators and risk factors is given in Table 3 and Figure 2.

4 | SITUATIONAL RISK FACTORS

Situational risk factors for severe venom-induced anaphylaxis are mostly exogenous and may thus, at least in theory, be modified. Available data, however, are remarkably scarce and are mostly derived from studies assessing all-cause anaphylaxis.

4.1 | Delayed administration of epinephrine

Delayed administration of epinephrine is considered to dictate an unfavorable outcome of anaphylactic reactions regardless of the elicitor.[17,26] Recent observations from an Australian cohort of 324 anaphylaxis fatalities including 41 deaths from insect stings strongly suggest that this also applies in the context of venom allergy.[16] The prescription of epinephrine auto-injectors is clearly recommended for untreated venom-allergic patients with a history of sting reactions involving more than one organ system and may also be considered in those with reactions confined to the skin and/or mucous membranes.[2,22] The rates of epinephrine self-injection or lay-injection

TABLE 3 Potential indicators of severe anaphylactic sting reactions

Diagnostic tests	Available data/evidence
Basal serum tryptase elevation	Several observational studies and case series assessing indicators of severe sting-induced anaphylaxis[6-11,13]
Platelet-activating factor acetylhydrolase activity	One case-control study specifically assessing severe systemic sting reactions[7] and several studies assessing the severity of all-cause anaphylaxis[50,90]
Predominant sensitization to Api m 4	One study[93]
Angiotensinogen gene polymorphism	One study[94]
Observations from index field sting	
Severity of previous sting reactions	Several observational studies[79,80]
Absence of urticaria/angioedema	Several observational studies[6,8,37,81]
Time of onset/dynamics	Several observational studies[6,8,51]

during anaphylactic reactions, however, did not change over the past ten years whereas a slight increase was observed regarding epinephrine injections administered by healthcare professionals.[27]

4.2 | Upright posture

Upright posture during anaphylaxis has been identified as a risk factor for sudden death which has been attributed to ischemic heart damage.[28] This is supported by observations from the above-mentioned Australian case series describing fatal outcomes in venom-allergic patients who were driven to hospital in a sitting position.[16] As a matter of course, international anaphylaxis treatment guidelines strongly recommend a supine position of hypotensive patients.[1] The reason and importance of this advice, however, may be unknown to patients and/or their caregivers and should therefore be in the focus of patient education.

4.3 | Miscellaneous

Physical exercise during or prior to the onset of anaphylaxis has long been recognized a risk factor for severe food-induced reactions[25] and was specifically demonstrated to lower the threshold and increase the severity of wheat-dependent, exercise-induced anaphylaxis.[29] Recent data from the European Anaphylaxis Registry including 7316 cases of all-cause anaphylaxis indicate that vigorous rather than mild or moderate exercise increases the risk of a severe reaction independent of the triggering factor.[30] There are yet no published data specifically confirming the impact of exercise on venom-induced reactions. Clinical observations, however, likewise suggest a tendency toward more severe anaphylactic sting reactions during physical activity, especially if exercise is continued after the sting (own unpublished data). Concurrent intake of alcohol or acetylsalicylic acid has likewise been identified as cofactors in food-dependent exercise-induced anaphylaxis[25,31] whereas there are insufficient data regarding their relevance in reactions to stings or other triggers.[30] Potential effects of concurrent infection, psychological stress, and/or perimenstrual status have not been assessed with regard to anaphylactic sting reactions.

Stings in the head region have been accused to account for more severe or even fatal anaphylaxis. Recent studies, however, did not confirm the localization of the sting to be a risk factor.[6,8] Increased fatality rates in patients with multiple stings were attributed to direct venom toxicity rather than anaphylactic reactions.[32]

5 | LONG-TERM RISK FACTORS

Available data on long-term risk factors for severe sting-induced anaphylaxis are based on a comparatively large number of retrospective studies assessing the severity of sting reactions with regard to clinical baseline parameters.[6-13]

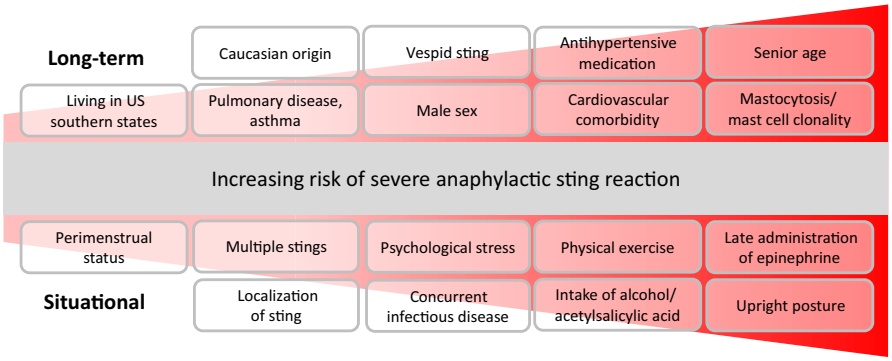

FIGURE 2 Potential long-term and situational risk factors for severe systemic sting reactions

5.1 | Mastocytosis

There is overwhelming evidence of a strong association of mast cell clonality with both a higher incidence[33-35] and an increased severity[30,34,35] of sting-induced anaphylactic reactions, the predominant clinical presentation being hypotensive shock.[36,37] The risk of severe venom-induced anaphylaxis was demonstrated to be highest in a distinct subgroup of patients with indolent systemic mastocytosis which has been characterized by a marked male predominance, the absence of cutaneous manifestations of mastocytosis, absence of multi-lineage *KIT* mutations, and comparatively low basal serum tryptase levels (see Section 7.1).[38] Despite the association with severe, but nonfatal anaphylaxis, evidence of mastocytosis as a risk factor for fatal sting reactions remains restricted to the level of case reports.[39-41] The lack of studies confirming an association with sting-related fatalities, however, is not proof of the contrary, but presumably results from methodological difficulties, namely missing information about the presence or absence of mastocytosis in a significant proportion of cases. It may be speculated that press reports of unexpected sting-induced fatalities, some of which document hypotensive shock and/or cardiac arrest as the cause of death, commonly relate to individuals with undiagnosed mastocytosis.

Clonal mast cell disorders are a potential risk factor for relapsing sting reactions during or after venom immunotherapy,[35,42] which are again likely to be severe.[43] The prescription of an epinephrine auto-injector is thus considered mandatory before, during, and after stopping venom immunotherapy in this patient group,[22] and equipment with two auto-injectors may be considered.[5] Most,[2,3] though not all[44] international treatment guidelines recommend prolonged immunotherapy for mastocytosis patients. Concurrent mastocytosis may potentially increase the risk of side effects during venom immunotherapy,[35,41,45,46] but there is a general consent that treatment is still reasonably safe and effective.[35,46-48] Testing of mastocytosis patients for insect venom sensitivity is recommended by some authors even in the absence of a history of sting-induced anaphylaxis,[3,39] but available data on the natural course and potential impact of hitherto asymptomatic venom-specific sensitization in underlying mastocytosis are very limited. With regard to the risk of under-diagnosing *Hymenoptera* venom allergy in concurrent mastocytosis, decreasing the threshold of IgE positivity below the standard of 0.35 kU/L and measuring specific IgE to recombinant venom marker allergens were proposed in order to improve diagnostic sensitivity.[39,49]

5.2 | Senior age

Older age is a very potent risk factor for severe anaphylactic reactions in general[50]—recent data from the European Anaphylaxis Registry actually suggest that it has an even stronger impact on the incidence of severe and near-fatal anaphylaxis than mastocytosis,[30] though this may depend on the eliciting allergen. Whereas an age-dependent predisposition to fatal food-induced anaphylaxis has been described for the second and third decades of life,[15,20] severe and fatal outcomes of venom-induced reactions are clearly more common in the elderly.[6,8-12,15-17,19,23,30,51] A continuous and strictly linear association between increasing age and the frequency of severe sting reactions was detected in the 2009 European multicenter study,[11] and other groups confirmed an increase in severe reactions from 40 years onwards.[6] Severe sting-induced anaphylaxis is accordingly uncommon in children.[52] The increasing prevalence of cardiovascular comorbidities in senior age may in part explain the growing vulnerability to severe sting reactions (see Section 5.3). Moreover, an age-dependent increase in basal serum tryptase concentrations was described.[9,10,13,34] As a consequence of these findings, the use of higher venom doses for immunotherapy and prolonged treatment of elderly people with increased tryptase levels is recommended by some authors.[10]

5.3 | Cardiovascular comorbidities

Concurrent cardiovascular disease has long been connected to an unfavorable outcome of all-cause anaphylactic reactions,[53,54] and a retrospective analysis of 38 695 patients seen in US emergency departments for anaphylaxis recently confirmed an association of cardiac disease with increased odds of severe reactions requiring hospital admission, treatment on an intensive care unit, or intubation.[55] Moreover, anaphylaxis frequently involves cardiovascular symptoms, and the presence of hypotensive shock generally results in classification as a "severe" reaction.[14,56-58] The coincidence of anaphylaxis with cardiac ischemia or even myocardial infarction has been referred to as Kounis syndrome[59] and is based on a sound pathophysiological background. The human heart contains high concentrations of mast cells which express high-affinity immunoglobulin E receptors and are located in close proximity to myocytes and coronary vessels.[60] Mast cell numbers are increased in concurrent cardiomyopathy or ischemic heart disease, and locally released mediators including histamine, leukotrienes, prostaglandin D2, and platelet-activating factor (see Section 7.2) have been demonstrated to cause coronary vasoconstriction and trigger tachycardia or cardiac arrhythmia.[60]

Available data on cardiovascular comorbidities as a risk factor for severe venom-induced anaphylaxis are surprisingly scarce and somewhat inconsistent. On the one hand, cardiovascular shock leading to circulatory arrest was described as the main cause of fatal outcomes in an early study of venom-induced deaths,[61] and other case series suggested an increased risk of fatal sting reactions in patients with cardiac comorbidities.[16,62] Several case reports give evidence of sting-related Kounis syndrome.[63,64] On the other hand, large retrospective studies assessing the incidence of severe but nonfatal venom-induced anaphylaxis failed to recognize cardiovascular comorbidities as a risk factor.[8,11] This should be reassessed in future studies considering specific cardiovascular conditions as the impact of mere arterial hypotension might differ from that of coexisting coronary heart disease, cardiomyopathy, or cardiac arrhythmia.

5.4 | Antihypertensive medication

Safety concerns regarding the use of antihypertensives in venom-allergic patients date back to the 1980s when beta-blockers were accused to aggravate sting-induced anaphylactic reactions in a number

of case reports.[65,66] There has since then been an ongoing discussion which is certainly fueled by the fact that, in contrast to other long-term risk factors, cardiovascular medication is modifiable which makes it an interesting and potentially important target. Detrimental effects of beta-blockers on the course of anaphylaxis were attributed to the inhibition of both endogenously released and therapeutically administered epinephrine and to an enhanced release of mast cell mediators.[67,68] The focus of interest recently moved to ACE inhibitors which were accused to aggravate anaphylactic reactions due to the impaired breakdown of bradykinin or through direct interaction with mast cells.[68] Experimental data from mouse models and in vitro models supporting an additive detrimental effect of combinations of beta-blockers and ACE inhibitors were published in 2015,[68] and a number of recent observational studies and case series accordingly seem to provide clinical evidence of an aggravation of all-cause anaphylaxis by antihypertensive medication. Lee and colleagues found an increased risk of multiple organ involvement and need for hospitalization in emergency department patients with anaphylaxis taking beta-blockers, ACE inhibitors, or diuretics.[69] Data from the European Anaphylaxis Registry suggest an increased frequency of severe reactions during concurrent intake of ACE inhibitors or beta-blockers[30] and an even higher risk if both drugs are combined.[68]

The main and obvious limitation of these clinical studies, however, is that coexisting cardiovascular disease as a potential confounder was not included in the multivariate statistical models with reference to its obvious correlation with the use of antihypertensive drugs and in order to avoid problems of collinearity.[30,69] While this may be legitimate from a statistical point of view, it leaves open the question of what is the true risk factor, antihypertensive medication or rather the underlying cardiovascular comorbidity.

The situation is even more complex in the context of *Hymenoptera* venom allergy. Recent retrospective studies and case series quite consistently come to the conclusion that concurrent beta-blockade does not have an impact on the outcome of field sting-induced anaphylaxis.[8,11] The 2016 study by Arzt and colleagues demonstrates that a tendency toward a higher frequency of severe sting reactions in patients taking ACE inhibitors or beta-blockers is no longer statistically significant if an adjustment for age is made.[6] A higher incidence of severe anaphylactic sting reactions in patients taking ACE inhibitors was nonetheless observed by some groups,[11] but remained unconfirmed by others.[8] There is growing evidence that the concurrent intake of antihypertensive medication during venom immunotherapy does not increase the incidence of treatment-induced anaphylactic adverse reactions,[45,67,70-72] whereas information about a potential impact on the severity of these adverse effects is lacking, and data regarding an influence of ACE inhibitors on the efficacy of treatment remain controversial.[42,70,73]

Large-scale international studies may enable a more evidence-based risk assessment in patients taking antihypertensive medication before, during, and after venom immunotherapy in the near future. For the time being, a thorough individual risk analysis should precede any recommendation to discontinue these drugs in venom-allergic patients who are exceedingly unlikely to die from sting-induced anaphylaxis,[20] while there may be compelling arguments in favor of a guideline-directed cardiovascular treatment.

5.5 | Male sex

A male predominance is almost invariably observed in cohorts of venom-allergic patients,[7-12] and male sex was identified as a predictor of more severe reactions in some,[11] but not all studies.[6,8,13] Moreover, there is an increased risk of sting-related death in men compared with women.[16,17,19,23,24] In accordance with these findings, male sex was recently identified as a risk factor for severe anaphylactic reactions independent of the elicitor.[30] These observations stand in some contrast to previous concepts assuming an augmenting effect of female sex hormones on the incidence and/or the severity of anaphylactic reactions.[74] The effect of male sex as a risk factor in venom-allergic patients, however, was mainly attributed to a higher degree of exposure to stinging insects.[11,19] Detailed instructions on how to avoid *Hymenoptera* stings might thus be an adequate strategy to prevent severe reactions in venom-allergic males, especially if the patient's history is suggestive of high exposure to the culprit insect due to occupational or recreational outdoor activities.

5.6 | Culprit insect

Several authors described a tendency toward more severe sting reactions in patients allergic to vespid venom compared to those allergic to bee venom.[11,30] This observation is noteworthy as, in seeming contrast, bee venom allergy is clearly associated with an increased risk of both side effects[45,70,75] and failure[42] of venom immunotherapy. Though the particular risk of bee sting-induced anaphylactic reactions observed in beekeepers and their family members obviously is a result of repetitive exposure, the incidence of sting-induced anaphylaxis has been shown to decrease during long-standing beekeeping activities and in heavily exposed beekeepers[76] who may develop allergen-specific tolerance.[77,78] There is no evidence of a higher severity of systemic sting reactions in beekeepers compared to normally exposed controls.[77] The risk of severe anaphylaxis in venom-allergic beekeepers, however, is considered to be highest following the first stings of the beekeeping season in springtime.[76,77]

5.7 | Miscellaneous

Pre-existing pulmonary disease including asthma was identified as a risk factor for hypoxemic reactions and delayed deterioration of anaphylaxis in general,[50] and to specifically impair the outcome of food-induced anaphylaxis.[15,16,20] Some authors accordingly observed an increased incidence of respiratory symptoms during sting-induced anaphylactic reactions in a subgroup of atopic patients which was likely to contain a significant proportion of individuals with concurrent asthma.[9] Other studies assessing risk factors for severe insect venom-induced anaphylaxis, however, did not consider pulmonary conditions[6,11,12] or did not confirm an association with the frequency of severe sting reactions.[8]

The observation of an increased incidence of fatal anaphylactic sting reactions in US citizens of Caucasian origin compared to Hispanics or African Americans has been suggested to reflect different occupational and/or recreational activities.[19] Living in the US southern states (compared to the northern states) was likewise associated with an increased risk of sting-related death which has been attributed to a greater or longer exposure to unspecified venomous insects.[19]

6 | OBSERVATIONS FROM PREVIOUS STING REACTIONS

Current international treatment guidelines do not routinely recommend venom immunotherapy for patients with a history of only cutaneous systemic sting reactions.[2,3,44] This approach is based on studies on the natural course of venom allergy in untreated patients which found that the severity of re-sting-induced anaphylaxis generally corresponds to that of the initial reaction.[79,80] In seeming contrast, Ruëff and colleagues found preceding mild sting reactions to be a predictor of future more severe anaphylaxis.[11] This does not necessarily contradict previous concepts as Ruëff's observations are based on a comparison of venom-allergic patients to individuals who never had an anaphylactic sting reaction. Moreover, patients suffering only mild symptoms on the occasion of a re-sting are less likely to seek allergological advice than those with a severe relapse which may result in a risk of bias.

6.1 | Absence of urticaria/angioedema

The frequent absence of urticaria/angioedema during severe, venom-induced anaphylaxis has been attributed to either counter-regulatory release of endogenous epinephrine or preferential activation of cardiac mast cells.[6,8] The complete lack of cutaneous symptoms, or flushing rather than urticaria/angioedema,[81] is associated with increased tryptase levels[6,8,81] and was recently suggested to be an even stronger predictor of mast cell clonality than tryptase elevation itself in venom-allergic patients with severe, hypotensive sting reactions.[37] The REMA score as proposed by the Red Española de Mastocitosis (Spanish Network on Mastocytosis) for screening patients for the necessity of bone marrow biopsy accordingly includes the absence of urticaria/angioedema during anaphylaxis as a predictor of bone marrow mast cell clonality along with male sex, hypotensive shock, and tryptase elevation >25 ng/mL.[36]

6.2 | Short time interval from sting to onset of anaphylaxis

Stoevesandt and colleagues found a time interval of less than 5 minutes between an insect sting and the first onset of symptoms to be predictive of severe anaphylaxis,[8] and Arzt et al recently confirmed the mean time to precede a severe reaction to be only 6.5 minutes.[6] A short time span was likewise shown to be indicative of severity in the setting of intentional sting challenges,[51] and the median time from insect sting to cardiac arrest was as short as 15 minutes in a study of anaphylaxis fatalities.[61] The time elapsing between an insect sting and the onset of anaphylaxis is thus an important indicator of severity and ought to be addressed in any case history of venom-allergic patients.

7 | DIAGNOSTIC TESTS

Of a number of diagnostic tests, only the measurement of basal serum tryptase values is both suited to predict an individual risk of severe sting reactions and available for broad routine diagnostic use.

7.1 | Basal serum tryptase concentration

Most studies evaluating risk factors for severe sting-induced anaphylaxis consider basal serum tryptase levels as an indicator of an increased mast cell burden instead of or in addition to definite mastocytosis cases.[6-11,13] As tryptase measurement is broadly available and easier to realize than a full hematologic work-up including mutational analyses (which can today be done from peripheral blood[82-84] though the sensitivity is still below that of analyses based on bone marrow biopsies), this approach is surely legitimate for routine diagnostic screening. Ruëff et al found a nonlinear, continuous association between basal serum tryptase concentrations and the risk of severe sting reactions and consequently recommended to take into account the whole range of tryptase concentrations rather than defined cutoff levels for individualized risk assessment.[11] This is in accordance with the observation that tryptase levels of less than 11.4 ng/mL do not exclude mast cell clonality,[37] but does not seem to apply for very high tryptase concentrations. Rather on the contrary, the risk of *Hymenoptera* venom-induced anaphylaxis declines in mastocytosis patients with a very high mast cell burden,[85] and the frequency of all-cause anaphylaxis was demonstrated to decrease when tryptase levels exceed 40 ng/mL.[86] This has been attributed to dysfunction of dedifferentiated mast cells[87] and is in accordance with the observation that *Hymenoptera* venom allergy preferentially affects a subset of patients with indolent systemic mastocytosis[38] (see Section 5.1) and does not typically occur in aggressive systemic mastocytosis or mastocytosis with an associated hematologic non-mast cell disease.[87,88] An asymptomatic increase in tryptase levels on the first day of venom immunotherapy was found to be predictive of future treatment-related anaphylactic side effects.[89]

7.2 | Miscellaneous

Determination of the activity of platelet-activating factor acetylhydrolase, the enzyme responsible for catabolizing platelet-activating factor, has not yet been implemented into routine diagnostic practice, but represents a complementary diagnostic tool for risk assessment—low activity levels were shown to be associated with a risk of both severe IgE-mediated anaphylactic reactions in general,[50,90] and severe sting-induced anaphylaxis.[7] Platelet-activating factor acetylhydrolase activity is inversely correlated with levels of

platelet-activating factor, a proinflammatory phospholipid synthesized and secreted by mast cells.[90]

The observation of low total IgE levels in patients with severe anaphylactic sting reactions[12] is in accordance with the finding of a lower total and venom-specific IgE in venom-allergic mastocytosis patients compared to controls without concurrent mastocytosis.[39,49] Total or specific IgE levels including specific IgE to recombinant venom marker allergens, however, were not confirmed as independent indicators of severe sting-induced anaphylaxis.[9,91,92] Predominant Api m 4-specific sensitization was proposed to be an indicator of more severe sting reactions by one group.[93] Skin test negativity despite a convincing history of a systemic sting reaction is considered a common finding in coexisting mastocytosis,[49] but has not been characterized as an independent predictor of severe sting-induced anaphylaxis. There is limited evidence of angiotensinogen gene polymorphisms being indicative of an increased risk of severe sting reactions.[94]

8 | CONCLUSIONS AND CLINICAL IMPLICATIONS

- Indolent systemic mastocytosis and older age are major unmodifiable risk factors for severe sting-induced anaphylaxis and thus reinforce the indication for venom immunotherapy and prescription of an epinephrine auto-injector.
- Concurrent antihypertensive medication is modifiable and thus a potential target for risk reduction measures. Its relevance as a risk factor in *Hymenoptera* venom allergy, however, is still controversial, and a thorough analysis of the pros and cons ought to precede any decision to replace a guideline-directed antihypertensive treatment.
- A greater exposure to *Hymenoptera* stings resulting from occupational and recreational activities possibly accounts for a higher rate of severe reactions in male patients who may benefit from targeted information on how to avoid stings.
- The correct and timely use of epinephrine auto-injectors as well as recommendations to discontinue physical exercise and take a supine position during the acute anaphylactic episode need to be addressed in individual patient education.
- The absence of urticaria (with or without angioedema) during sting-induced anaphylaxis is strongly indicative of a severe reaction, tryptase elevation, and mast cell clonality.

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CONFLICT OF INTEREST

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