Risk Factors for Severe Sting Reactions and Side Effects During Venom Immunotherapy

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Learning objectives:

1. Identify risk factors for severe systemic sting reactions (SSRs) and systemic adverse events (sAEs) in venom immunotherapy.
2. Initiate the diagnostic work-up to identify high-risk patients.
3. Identify indicators of severe SSRs.

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Understanding the risk factors leading to severe systemic sting reactions (SSRs) is crucial for initiating venom immunotherapy (VIT) and for educating affected individuals and their families. Some of these risk factors are well established, some are no longer considered risk factors, and some remain controversial. Well-established risk factors for severe SSRs include clonal mast cell disease, high baseline serum tryptase, and advanced age. The absence of skin symptoms and the rapid onset of symptoms are indicators of severe SSRs. Recent publications indicate that antihypertensive treatment and stings in the head and neck area are not risk factors for severe SSRs. VIT is the only available treatment that can potentially prevent further anaphylactic reactions. Although rare and generally manageable, individuals undergoing VIT may experience systemic adverse events (sAEs). More sAEs are expected in patients undergoing bee VIT compared with vespid VIT. The role of elevated baseline serum tryptase as a risk factor for sAEs remains debated, but if it is a factor, the risk is increased by only about 1.5-fold. Rapid updosing protocols, depending on the specific regimen, can also be associated with more sAEs. Severe initial SSRs, antihypertensive medication, high skin test reactivity, and high specific IgE levels are not risk factors for sAEs. © 2024 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open

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Abbreviations used
ACEI- angiotensin-converting enzyme inhibitor
AE- adverse event
BST- baseline serum tryptase
CMD- clonal mast cell disease
HαT- hereditary alpha tryptasemia
OR- odds ratio
REMA- red Española de Mastocytosis (Spanish Network on Mastocytosis)
sAE- systemic adverse event
SSR- systemic sting reaction
VIT- venom immunotherapy

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INTRODUCTION

Hymenoptera venom-induced anaphylaxis is a severe and potentially fatal allergic reaction that occurs rapidly after the sting. In the United States, the prevalence of systemic sting reactions (SSRs) among adults can reach up to 3.3%, whereas European epidemiological studies report prevalence rates as high as 7.5%.[1] Prevalence data for severe systemic sting reactions should be interpreted with caution, because epidemiological studies often identify only a few patients with allergy within a large general population, complicating accurate statistical analysis. From these studies, we know that the proportion of SSRs that are severe ranges from 17% to 43%.[2-4]

Venom immunotherapy (VIT) is the only available treatment that can potentially prevent further anaphylactic reactions. It demonstrates remarkable efficacy, with high protection rates: 91% to 96% of patients treated with vespid venom and 75% to 85% of those treated with honeybee venom are protected against further SSRs.[5]

Several authors have attempted to identify risk factors for severe SSRs from Hymenoptera stings. This research aimed to identify individuals at higher risk and assist in selecting patients for VIT, as well as to determine which patients would benefit from adapted VIT, such as higher dosage or longer duration.

This review aimed to clarify the risk factors for severe SSRs and critically evaluate the more controversial risk factors. In addition, it will highlight risk factors for systemic adverse events (sAEs) to VIT.

RISK FACTORS FOR SEVERE SSRs

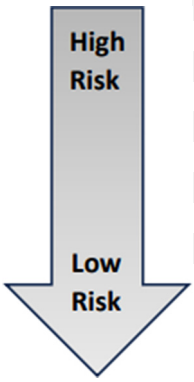
This discussion will focus on genuine risk factors that exacerbate the severity of anaphylactic reactions to Hymenoptera stings. In addition, we will outline indicators of severe SSRs (Table I). These indicators, based on observations, are conditions correlated with a higher likelihood of severe reactions, even if they do not directly cause them.

High baseline serum tryptase

Baseline serum tryptase (BST) is recognized as a biomarker of total mast cell number. As shown in numerous studies over the last years, an elevated baseline tryptase level reflecting a high mast cell burden is a very well-established risk factor for severe SSRs.[6-8] Individuals with a high baseline tryptase concentration, defined as BST levels greater than 11.4 mg/L, show a 2.4- to 2.7-fold increased risk for severe allergic reactions to field stings.[6,8,9] This is a well-known risk factor that has been reconfirmed in several large studies.[10,11] Because of this association, BST levels have been suggested as a parameter for stratifying the risk of SSRs among Hymenoptera venom-allergic patients. Farioli et al[12] proposed the following classification: low-risk patients have tryptase levels below 4 mg/L, intermediate-risk patients have levels ranging from 4 to 7.5 mg/L, and high-risk patients have tryptase levels above 7.5 mg/L.

Recent data indicate that elevated tryptase levels predominantly arise from the presence of KIT p.D816 mutation and alpha tryptasemia.[13] Notably, 196 of 285 patients (69%) with the KIT p.D816 mutation in the peripheral blood had normal tryptase levels, and when excluding patients with KIT p.D816 mutation from the analysis, the concentration of tryptase was comparable in patients with mild and severe reactions.[14] These

TABLE I. Risk factors and indicators for severe SSRs



Risk factors	No risk factors
High BST	Antihypertensive medication
CMD/KIT p.D816V mutation	Cardiovascular disorders
Senior age	Pulmonary disorders
Preceding SSRs	Stings in the head and neck area
(*Male sex*)	High specific IgE and skin test reactivity at lower venom doses
(*Vespid venom allergy*)	
Indicators for severe SSRs	
Absence of urticaria/angioedema	
Short time interval until onset of symptoms	

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findings suggest that, in addition to measuring tryptase levels, patients should be tested for the KIT p.D816V mutation in the peripheral blood using a highly sensitive allele-specific PCR test to accurately diagnose clonal mast cell disorders. Moreover, in cases of strong suspicion of clonal mast cell disease (CMD), it is important to complete the diagnosis with an accurate diagnostic workup according to World Health Organization guidelines.[15]

Summary. Patients with elevated BST have a 2.4- to 2.7-fold risk for severe SSRs. However, more precise information can be obtained by testing patients for the KIT p.D816V mutation and conducting tryptase genotyping to detect hereditary alpha tryptasemia (HαT). In case of unclear results, a more detailed hematological workup can be conducted to ensure accuracy.

CMD and KIT p.D816V mutation

CMD is a well-established risk factor for severe SSRs, especially including hypotensive shock.[16-18] Male individuals affected by indolent systemic mastocytosis without skin involvement (bone marrow mastocytosis), multilineage KIT mutations, and with comparatively low serum tryptase levels are at the highest risk for severe SSRs.[19,20] Up to 69% of patients with CMD can have normal BST levels below11.4 μg/L.[14,16]

To simplify the diagnostic workup, the Spanish Network on Mastocytosis (red Española de Mastocytosis (Spanish Network on Mastocytosis [REMA]) has designed a simple clinical score to predict CMD. The REMA score considers the sex of the patient, the reported clinical symptoms (syncopal episodes, absence of urticaria and angioedema), and the tryptase basal value to decide who needs a bone marrow biopsy to exclude the presence of CMD. The initial validation of this score revealed both a high sensitivity (91%) and a high specificity (75%).[17] However, data on the application of the REMA score in a large venom-allergic population were lacking, and a recently published multicenter study found that the REMA score achieved a sensitivity of only 70%.[14]

Summary. Patients with KIT p.D816V mutation in the peripheral blood have an approximately 2-fold higher risk for severe SSRs. The application of the REMA score and testing for the KIT p.D816V mutation are crucial in patients with severe SSRs, because BST levels may be within the normal range, leading to potential oversight.

Hereditary alpha tryptasemia

HαT is an autosomal-dominant genetic trait that leads to increased levels of baseline serum tryptase due to an augmented copy number of α-tryptase—encoding tryptase alpha/beta 1 that encodes for alpha-tryptase.[21] HαT is the most common cause of elevated BST.[13] If present, BST is typically greater than 6.2 or 8.0 μg/L, depending on the study population.[22,23]

According to some analyses, a subset of patients with HαT also carry the KIT p.D816V mutation. These patients face a higher risk of experiencing severe anaphylaxis, with an increased relative risk of 2.0 ($P < .05$).[24] However, another study found that HαT alone was not a significant risk factor.[13] It is known that HαT and systemic mastocytosis can coexist, leading to an additive effect; in a study, 31% of patients with venom allergy who tested positive for HαT were also found to be positive for cKIT.[11] Individuals with HαT and concomitant KIT p.D816V mutation appear to have the highest risk for severe SSRs, with a higher prevalence of loss of consciousness following a sting.[14,25] However, another study did not corroborate these findings.[26]

Summary. Patients with HαT, particularly in combination with systemic mastocytosis, may be at a higher risk for severe SSRs. The risk of severe SSRs in patients with HαT is slightly increased but in case of additional KIT p.D816V mutation, it increases by 3.8 times overall. Further research is needed to clarify the role of HαT as an independent risk factor.

Senior age

Higher age is a major well-examined risk factor for SSRs, as confirmed by data from several studies.[6,8,11,27] Patients aged 40 years and older are more commonly affected by severe SSRs when compared with younger individuals (36.9% vs 22.6%).[8] In the United Kingdom, 93 deaths caused by sting-induced anaphylaxis were identified between 1992 and 2012. The mean age of fatal cases was 59 years (95% CI, 56-63 years), with fatalities being rare before the age of 50 years.[28] Possible explanations for this phenomenon remain speculative and encompass the coexistence of cardiovascular diseases that lead to an impaired endogenous counterregulation in such reactions. Furthermore, higher BST levels since a continuous increase in BST concentration with age have been described.[29,30] The prevalence of CMD may also increase with age.[14]

Summary. Patients aged 40 years and older have an approximately 2-fold higher risk for severe SSRs.

Preceding SSRs

Patients who experienced severe SSRs in the past are more likely to develop further serious SSRs in the future, which will most likely show a similar reaction pattern to following stings.[31,32]

Summary. Patients with a history of severe SSRs are more likely to experience future severe SSRs and should preferably be treated with VIT.

Male sex

The role of male sex as a risk factor for severe SSRs is quite controversial. Two large case series have indicated a higher risk for severe SSRs in men.[6,18] However, one study did not provide an odds ratio (OR),[6] and the other reported only a minimally increased risk (OR, 1.2; 95% CI, 1.1-1.3).[18] In addition, several studies have not found an elevated risk associated with male sex.[8,30,33]

Summary. The slightly increased risk of more severe SSRs in males is a subject of debate and can generally be disregarded in clinical practice.

Vespid venom allergy

There is a tendency for patients allergic to vespid venom to experience more severe sting reactions compared with those allergic to bee venom.[6,18] However, other studies do not support this finding.[8,27,33]

Summary. The slightly increased risk of more severe SSRs in patients with vespid venom allergy is a subject of debate and can generally be disregarded in clinical practice.

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INDICATORS OF SEVERE SSRs

Absence of urticaria/angioedema

The absence of urticaria and angioedema in sting-induced anaphylaxis is known to be an indicator of severe anaphylactic reactions including loss of consciousness and cardiopulmonary symptoms.[8,11,33] This condition is often associated with CMD. To exclude CMD, initially the REMA score should be assessed and patients should be tested for elevated BST and the KIT p.D816V mutation in the peripheral blood. If results are unclear, patients should undergo comprehensive hematological workup.

Summary. The absence of skin symptoms is an indicator of severe SSRs.

Time of onset/dynamics

The time interval between a Hymenoptera sting and the onset of symptoms is a well-known indicator of reaction severity, with a shorter interval generally leading to more severe anaphylaxis.[8,33,34] Patients who experienced symptoms within 5 minutes after a sting generally exhibited more severe anaphylactic reactions as compared with those whose symptoms developed after a longer time interval.[33] Severe reactions typically occurred within 5 to 8 minutes, whereas mild to moderate symptoms generally appeared after 15 to 18 minutes.[8,34]

Summary. Patients with a rapid onset of symptoms usually have more severe SSRs.

PREVIOUSLY SUSPECTED RISK FACTORS FOR SEVERE SSRs

Antihypertensive medication

For decades, there has been an ongoing debate about whether antihypertensive treatment with β-blockers and/or angiotensin-converting enzyme inhibitors (ACEIs) is a risk factor for more SSRs and whether it increases the incidence of sAEs during VIT. The available data are controversial and consistently come from case reports, case series, or studies with insufficient power to properly evaluate the effect of antihypertensive drugs. Therefore, some studies did not identify a significant risk for severe SSRs with the use of antihypertensive drugs,[8,33,35] whereas other studies did indicate a potential risk.[18,36] A prospective multicenter trial involving 1425 patients, including 388 who were taking antihypertensive drugs, provided robust evidence that the use of β-blockers or ACEIs did not aggravate SSRs.[27]

Summary. It is now well established that β-blockers and ACEIs are not risk factors for severe SSRs.

Cardiovascular disorders

Concurrent cardiovascular disease has long been associated with poor outcomes in all types of anaphylactic reactions.[37,38] Most of the patients who died from an insect sting in Switzerland had preexisting cardiovascular diseases.[39] However, both a large retrospective study[33] and a large prospective study[27] examining the incidence of severe but nonfatal venom-induced anaphylaxis have not identified cardiovascular comorbidities as a risk factor.

Preexisting pulmonary conditions

Patients with preexisting pulmonary diseases including asthma have been considered a subgroup at risk for hypoxemic reactions and delayed deterioration of anaphylaxis in general and especially in food-induced reactions.[7] In Hymenoptera venom allergy, many studies assessing risk factors for severe SSRs did not consider pulmonary conditions[6,8,27]; one study found no association with severe SSRs.[33]

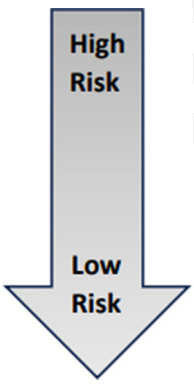
Stings in the head and neck region

Stings to the head and neck region were long believed to lead to the most severe including fatal reactions and are still regarded by some authors to account for more severe SSRs compared with stings to other sites of the body such as the extremities.[40,41] Although clinically impressive, primarily due to extensive swelling, sting reactions to the head and neck area do not pose an increased risk for serious SSRs. This has been demonstrated in recent publications involving a large number of patients.[8,33]

High levels of specific IgE and skin test reactivity at lower venom doses

The general opinion sometimes suggests that high specific IgE levels or skin test reactivity at lower venom doses poses a risk for severe sting reactions. However, clear data show that skin test reactivity and specific IgE levels cannot predict the outcome of a future sting.[8,34,42] Among laboratory tests, only high basophil sensitivity, measured by basophil activation test (BAT), was an independent risk factor influencing the severity of honeybee sting reaction.[11]

TABLE II. Risk factors for AEs during VIT



Risk factors	No risk factors
Bee VIT	CMD
	Severe initial sting reactions
No/slightly increased risk/controversial	High specific IgE and skin test reactivity
High BST	Antihypertensive medication
Rapid updosing protocols	

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Importantly, currently available routine tests are unable to distinguish between asymptomatic sensitization, large local reactions, and systemic reactions.[43]

RISK FACTORS FOR sAEs DURING VIT

Over the past decades, many efforts have been made to identify risk factors for sAEs (Table II). This allows for the detection of individuals at a high risk before the initiation of VIT, ensuring that they receive special attention and care.

Bee venom allergy

Consistent reports in the literature indicate that treatment with bee venom is a risk factor for sAEs.[44-46] Patients treated with bee venom showed a 3.4- to 3.6-fold higher risk of developing sAEs compared with those receiving wasp VIT. [27,47]

Summary. sAEs during VIT should be anticipated in patients undergoing bee VIT.

No/slightly increased risk for AE

Elevated BST levels. There is growing evidence that patients with elevated BST levels have no or only a slightly elevated risk for sAEs. An European Academy of Allergy and Clinical Immunology multicenter study found a slightly elevated risk in vespid venom-allergic patients with elevated tryptase levels (OR, 1.56; 95% CI, 1.15-2.10).[47] A more recent multicenter study yielded similar results (OR, 1.54; 95% CI, 0.83-2.90), though the increased risk was not statistically significant.[27] This aligns with another study involving honeybee venom-allergic patients, which did not observe an increased risk.[48]

Summary. The overall risk for sAEs in patients with elevated BST levels is absent or low. However, some individuals may experience (repeated) sAE during the build-up phase of VIT.

No risk factor for AE

Clonal mast cell disorders. CMDs such as mastocytosis are not associated with an increased risk for adverse events during VIT. A study on patients with mastocytosis concluded that VIT is both safe and efficacious.[47] However, if there was a severe initial SSR or sAE during VIT in patients with CMD, VIT administration should be prolonged or even lifelong.[49]

Severe initial sting reaction. Severe initial SSRs, such as loss of consciousness or cardiac arrest, often cause hesitation among physicians regarding the initiation of VIT. This hesitation is likely due to concerns about a potentially higher risk of sAEs in these individuals.

However, the literature clearly indicates that these patients are not at a higher risk for AEs during VIT.[11,46,47,50,51]

Summary. Because patients with severe initial SSRs are not at increased risk for sAEs, there should be no delay in initiating VIT.

High specific IgE and skin test reactivity. Specific IgE levels and skin test results neither influence the frequency nor severity of sAEs during VIT.[27,50,51] Among laboratory tests, only high basophil sensitivity, measured by BAT, was an independent risk factor for frequency and severity of sAEs during honeybee VIT.[11]

Rapid updosing protocol. Rapid dose increase during the build-up phase was a weaker, but nonetheless established risk factor for sAEs.[46,47] However, modern protocols do not necessarily result in more sAEs,[52] and the rate of sAEs may even be lower.[53]

Antihypertensive medication. There has never been strong evidence that antihypertensive medication increases the rate of sAEs.[47,54,55] On the contrary, there was even a trend toward fewer sAEs.[51] A prospective multicenter study now provides robust evidence that beta-blockers and ACEIs do not increase the frequency of sAEs during VIT. In fact, the incidence of AEs was even lower in patients taking antihypertensive treatment compared with those without such treatment (5.6% vs 7.4%, respectively; OR, 0.74; 95% CI, 0.43-1.22).[27]

CONCLUSION

We now have a more detailed understanding of risk factors for severe SSRs and sAEs during VIT. Elevated BST levels, CMD, and higher age are well-established risk factors for severe SSRs. Over the past decade, we also have learned that some factors, such as antihypertensive treatment and stings in the head and neck region, are not risk factors for severe SSRs. The primary important risk factor for sAEs is treatment with bee venom. Patients undergoing rapid updosing protocols may have a higher risk for sAEs, and there may be an elevated risk in some patients with elevated BST levels. However, relevant predictors of sAEs are scarce.

A significant issue is the lack of quality in study designs, with many studies being underpowered for accurate statistical analysis. Most studies do not have a primary aim but rather examine multiple risk factors without proper calculation of patient numbers, resulting in low evidence levels and reliance on case series.

Knowledge gaps

- The risk for severe SSRs in patients with HαT without the KIT p.D816 mutation should be explored.
- Recent data indicate that elevated tryptase levels predominantly result from the presence of the KIT p.D816 mutation and HαT. This needs to be confirmed by further studies.
- The potentially increased risk of future severe SSRs in patients with a history of severe SSRs should be evaluated.
- The role of cardiovascular diseases as risk factors for severe SSRs should be clarified. Because cardiovascular disease is a broad term encompassing many conditions such as hypertension, coronary artery disease, heart failure, and heart valve diseases, each specific condition should be individually evaluated for its potential risk.
- It needs to be determined whether VIT should be extended for more than 5 years or even lifelong to all patients with CMD and a history of SSRs, or only to those with both CMD and a history of severe SSRs.

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