



Predictors of severe anaphylaxis in Hymenoptera venom allergy

The importance of absence of urticaria and angioedema

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ABSTRACT

Background: Severe anaphylaxis (SA) in Hymenoptera venom allergy has been associated with a number of risk factors. However, the effect of several of those risk factors on the severity of anaphylaxis is poorly defined.

Objective: To evaluate risk factors for SA in Hymenoptera venom allergy.

Methods: We evaluated data from 500 patients who were referred to our department for the diagnosis of Hymenoptera venom allergy during a period of 11 years to identify risk factors for SA.

Results: Six significant risk factors for SA were identified ($P < .05$): short interval from sting to reaction, absence of urticaria or angioedema (U/A) during anaphylaxis, older age, male sex, elevation of baseline serum tryptase (BST) level, and diagnosis of systemic mastocytosis. Moreover, elevation in BST level was significantly associated with the absence of U/A and older age. No association could be established between SA and comorbidities, concurrent cardiovascular medication, or the severity of the systemic reaction during the initiation of venom immunotherapy.

Conclusion: Apart from BST and older age, male sex, short interval from sting to reaction, and absence of U/A are also risk factors for SA. The association between elevated BST level and SA was largely confined to those who had an absence of U/A after field sting, possibly because of the higher risk of concurrent systemic mastocytosis. Patients with an SA after a field sting do not have an elevated risk of systemic reactions during the initiation of venom immunotherapy compared with patients with mild anaphylaxis; therefore, additional preventive measures are not necessary.

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Introduction

Hymenoptera venom allergy affects approximately 3% of the adult population in Western countries^{1–4} and represents the most common cause of anaphylaxis in Germany, Austria, and Switzerland, accounting for 50% of reported cases.⁵ The incidence of insect sting-related mortality in Europe caused by anaphylaxis is estimated to be approximately 200 fatalities per year,⁶ but the incidence of near-fatal episodes might be considerably higher.⁷ Moreover, the documented mortality may be underestimated because of unrecognized insect stings in unexplained causes of death.⁸

European and North American practice guidelines recommend venom immunotherapy (VIT) in patients with a systemic allergic reaction to Hymenoptera stings exceeding generalized skin symptoms. The sensitization to the venom of the culprit insect must be

documented with skin prick or intradermal tests, specific serum IgE tests, and/or the basophil activation test.^{1,8} For individuals with systemic reactions limited to the skin, European guidelines (European Academy of Allergy and Clinical Immunology) recommend VIT for adults at high risk of reexposure and/or impairment of quality of life,⁸ whereas the US guidelines also consider risk factors for severe anaphylactic reactions (SARs).¹

In the past, numerous studies have tried to identify risk factors for SARs to contribute to an improved selection of patients for immunotherapy. According to those studies, systemic anaphylaxis in Hymenoptera venom allergy is clearly associated with an elevation of baseline serum tryptase (BST) level,^{9–12} older age,^{13–15} and male sex.^{12,15} In contrast, the effect of personal health issues (concomitant cardiovascular diseases^{10,16} and concurrent medication^{12,10}) on the severity of anaphylaxis is often controversial across different studies. Furthermore, anaphylaxis-associated findings (eg, skin symptoms and interval from sting to onset of reaction) have been proposed to be taken into account for individual risk assessment,¹⁰ but their association with the severity of the systemic reaction is poorly defined.

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The aim of this study was to investigate which factors significantly increase the risk of SARs (grade III and IV¹⁷) after field sting in patients with Hymenoptera venom allergy. In addition, it was investigated whether anaphylactic reactions during the initiation phase of VIT occur more frequently in patients with grade III and IV SARs after field sting.

Methods

Patients

A total of 500 consecutive patients (215 men and 285 women) with the diagnosis of insect venom allergy, who were referred to our department between 2007 and 2018 for VIT initiation according to the international guideline criteria,^{8,18} were included in this retrospective, single-center, observational cohort study. The patient enrollment and the analysis of retrospectively collected patient data were approved by the institutional review board of our center, and each patient consented to an anonymous data analysis.

Patient History

Patient histories were taken with a standardized questionnaire. Apart from insect sting history, demographic data (age and sex), medical history (cardiovascular and pulmonary diseases), and concurrent medication at the time of anaphylaxis were documented. In case of multiple insect stings, the field sting that resulted in the most severe reaction determined the index sting, to which all the data were referred. All symptoms that referred to the index sting were documented, and the severity of anaphylaxis was classified accordingly. All medical records were monitored by the director of the allergology department to ensure consistent quality of data.

Grading of Anaphylaxis

Severity of anaphylaxis was classified initially according to Ring and Messmer¹⁷ in 4 grades (Table 1). Because of the purposes of this study and the limited number of grade IV reactions in our patient collective, grade I and II reactions were defined as mild and grade III and IV reactions as severe (SARs).

Allergy Testing

Prick and intradermal skin tests with bee venom and wasp venom extract (ALK-Abello, Wedel, Germany) were performed according to international guidelines.^{1,2} Venom-specific IgE was determined using the ImmunoCAP (Phadia, Uppsala, Sweden) method and BST by using UniCAP Tryptase method (Phadia) according to the manufacturer's instructions.

Statistical Analysis

All statistical tests were performed by using SPSS, version 23.0, for MAC (SPSS Inc, Chicago, Illinois). Continuous variables were expressed as mean (SD). To assess the association of binary

variables with the severity of anaphylaxis, the Fisher exact test was used; for nonbinary variables, the Mann-Whitney *U* test was used. All tests were 2-tailed, and $P < .05$ was considered statistically significant. The multiple logistic regression models were estimated by using the R packages *arm* and *sjmisc*. All variables included in these models were dichotomized.

Results

Clinical Characteristics of the Cohort and VIT Initiation

A total of 500 patients were enrolled in this study; their demographic, clinical, and laboratory data are summarized in Table 2. Most patients were women (57%), and the mean age was 51.36 years (range, 18–86 years). The index field sting was mild in 373 patients (74.6%) and severe in 127 patients (25.4%).

Eight patients (1.6%) had systemic mastocytosis (SM) diagnosed by bone marrow biopsy, and 6 patients (75%) with SM had SARs. The BST level was determined in 490 patients (Table 2). Despite an existing indication ($BST \geq 20 \mu\text{g/L}$), 18 patients (3.6%) had not undergone a bone marrow biopsy for SM investigation by the time of this analysis. These patients were treated similar to patients with SM during hyposensitization (lifelong VIT, increased VIT maintenance dose, and prescription for 2 epinephrine autoinjectors). In 29 patients (6%), an increased BST in the range of 11.4 to 20 $\mu\text{g/L}$ was found. In these cases, regular BST follow-up but no bone marrow biopsy was performed. Patients with normal BST values ($<11.4 \mu\text{g/L}$) and absence of cutaneous mastocytosis were evaluated as individuals with no sign of SM.

Fifty-one patients (10.2%) underwent hyposensitization with bee venom and 449 (89.8%) with wasp venom. In total, only 25 patients (5%) had a systemic reaction during VIT initiation.

Bivariate Analyses

Six factors were significantly associated with the severity of anaphylaxis after Hymenoptera field sting: (1) a shorter interval from sting to reaction ($P = .004$), (2) absence of skin symptoms (urticaria or angioedema) during anaphylaxis ($P = .007$), (3) older age ($P < .001$), (4) male sex ($P = .007$), (5) higher BST level ($P = .004$), and (6) presence of SM ($P = .004$). The distribution of SARs after field sting with respect to baseline parameters is demonstrated in detail in Table 3.

No association was found between the severity of anaphylaxis and comorbidities, concomitant cardiovascular medication, sIgE concentration, and the threshold concentration of skin tests. The severity of systemic reactions during VIT initiation did not correlate with the severity of anaphylaxis after field sting.

A statistically significant association was observed between elevated BST level ($>11.4 \mu\text{g/L}$) and the absence of skin symptoms during anaphylaxis ($P < .001$). An increased BST was noted in 14 of 186 patients (18.3%) without skin symptoms compared with 18 of

Table 1
Grading the Severity of Anaphylaxis According to Ring and Messmer¹⁷

Location	Grade I (mild)	Grade II (mild)	Grade III (severe)	Grade IV (severe)
Skin	Itch, flushing, urticaria, angioedema	Itch, flushing, urticaria, angioedema (not obligatory)	Itch, flushing, urticaria, angioedema (not obligatory)	Itch, flushing, urticaria, angioedema (not obligatory)
Abdomen		Nausea, cramps	Vomiting, defecation	Vomiting, defecation
Respiratory tract		Rhinorrhea, hoarseness, dyspnea	Laryngeal edema, bronchospasm, cyanosis	Respiratory arrest
Cardiovascular		Tachycardia (heart rate increase $\geq 20/\text{min}$), hypotension (≥ 20 mm Hg decrease in SBP), arrhythmia	Shock	Circulatory arrest

Abbreviation: SBP, systolic blood pressure.

NOTE. Grading is always according to the worst manifestation present (no manifestation is obligatory).

Table 2
Clinical and Laboratory Data

Variable	Finding (N = 500)
Age, mean (range), y	51 (18–86)
Male/female	215/285
Severity of anaphylaxis after field sting	
Grade I (mild)	122 (24.4)
Grade II (mild)	251 (50.2)
Grade III (severe)	124 (24.8)
Grade IV (severe)	3 (0.6)
Interval from sting to reaction, min	
Median (range)	10 (1–4320)
Interquartile range	5–20
Sensitization	
Bee venom	24 (4.8)
Wasp venom	210 (42)
Both	266 (53.2)
BST, $\mu\text{g/L}$	
<11.4	437
11.4–20	29
>20	25
Concomitant diseases	
Cardiovascular disease	184 (36.8)
Arterial hypertension	172 (34.4)
Coronary heart disease	5 (1)
Congestive cardiac failure	2 (0.4)
Atopic disease	93 (18.6)
Pulmonary disease (asthma and chronic obstructive pulmonary disease)	22 (4.4)
Concurrent cardiovascular medication	168 (33.6)
β -Blockers	38 (7.6)
Angiotensin receptor blocker	69 (13.8)
ACE inhibitors	48 (9.6)
Calcium channel blockers	89 (17.8)
VIT	
Bee venom	51 (10.2)
Wasp venom	449 (89.8)
Reaction during VIT initiation	
Local reaction	383 (76.6)
Large local reaction	92 (18.4)
Grade I	12 (2.4)
Grade II	10 (2)
Grade III	3 (0.6)

Abbreviations: ACE, angiotensin-converting enzyme; BST, baseline serum tryptase; VIT, venom immunotherapy.

NOTE. Data are presented as number (percentage) of patients unless otherwise indicated.

299 patients (6.0%) with skin symptoms during anaphylaxis (Table 4). An elevated BST level was also significantly associated with older age (>40 years; $P = .001$).

Logistic Regression Models

Of the 8 dichotomized variables included in the logistic regression model, 4 emerged as significant independent influence factors of SARs after Hymenoptera field sting: older age (>40 years), absence of skin symptoms, short interval from sting to reaction, and male sex (Table 5). As a possible confounder, the type of insect venom allergy was included in a sensitivity analysis of the model, which did not change these results (data not shown).

Because the elevated BST level was significantly associated with the severity of anaphylaxis in the bivariate analysis but not in the regression model, further regression analyses were performed to clarify its influence. When there were no other variables in the regression model, elevated BST level (>11.4 $\mu\text{g/L}$) was a risk factor of borderline significance for a SAR ($P = .053$). Adding age, interval from sting to reaction, or sex did not clearly modify this association. However, including the presence of skin symptoms in the regression model considerably changed the P value of the BST effect to .16, suggesting that the presence of skin symptoms acts as an effect modifier of the influence of BST on SARs. We therefore performed the regression analysis stratified

Table 3
Distribution of SARs After Field Sting and Associations

Variable	Patients with mild reactions, No. (%)	Patients with severe reactions, No. (%)	P value
Interval from sting to reaction, min			.007
≤ 5	113 (68.9)	51 (31.1)	
>5	260 (77.4)	76 (22.6)	
As metric variable)			.004
U/A			.007
No	128 (68.1)	60 (31.9)	
Yes	242 (79.1)	64 (20.9)	
Age, y			<.001
≤ 40	111 (90.2)	12 (9.8)	
>40	262 (69.5)	115 (30.5)	
As metric variable)			<.001
Sex			.007
Male	147 (68.4)	68 (31.6)	
Female	226 (79.3)	59 (20.7)	
BST > 11.4 $\mu\text{g/L}$			.013
In total			
No	333 (76.4)	103 (23.6)	
Yes	33 (60)	22 (40)	
In subset with U/A			>.99
No	222 (79.1)	59 (20.9)	
Yes	15 (83.3)	3 (16.7)	
In subset without U/A			.02
No	109 (71.7)	43 (28.3)	
Yes	17 (50)	17 (50)	
As metric variable			.004
SM			.004
No sign of mastocytosis	333 (76)	103 (24)	
SM diagnosed by BMB	2 (25)	6 (75)	
Cardiovascular diseases			.29
No	241 (76.3)	75 (23.7)	
Yes	132 (71.7)	52 (28.3)	
Pulmonary diseases			.80
No	357 (74.7)	121 (25.3)	
Yes	16 (72.7)	6 (27.3)	
Medication with β -blocker			.567
No	346 (74.9)	116 (25.1)	
Yes	27 (71.1)	11 (28.9)	
Medication with ACE inhibitors			.601
No	339 (75)	113 (25)	
Yes	34 (70.8)	14 (29.2)	
Anaphylactic reaction during VIT initiation			>.99
Grade I	10 (83.3)	2 (16.6)	
Grade II	6 (60)	4 (40)	
Grade III	2 (66.6)	1 (33.3)	

Abbreviations: ACE, angiotensin-converting enzyme; BMB, bone marrow biopsy; BST, baseline serum tryptase; SM, systemic mastocytosis; U/A, urticaria or angioedema; VIT, venom immunotherapy.

by the presence or absence of skin symptoms. Dichotomized BST was included as the only predictor of SARs in these models. BST turned out to be a significant influence factor in the subsample without skin symptoms ($P = .04$) but not in the subsample with skin symptoms ($P = .41$).

Table 4
Number (Percentage) of Patients With and Without U/A by BST Levels

U/A	BST		P value
	Normal	Elevated	
No	152 (81.7)	34 (18.3)	<.001
Yes	281 (94)	18 (6)	

Abbreviations: BST, baseline serum tryptase; U/A, urticaria or angioedema.

Risk of Anaphylaxis During VIT Initiation

The risk of an anaphylactic event during VIT was not different for those with a history of systemic anaphylaxis to a field sting (5.5%) and those with a history of mild reaction (4.8%; relative risk, 1.146; 95% CI, 0.488–2.671; Table 6). Performing this analysis stratified by BST level (<11.4 or ≥ 11.4 $\mu\text{g/L}$) did not change the result substantially.

Discussion

Patients with an anaphylactic reaction after Hymenoptera field sting are at increased risk for subsequent reactions that will most likely follow a similar clinical pattern to the previous one.^{14,19} As a result and given the often controversial findings in the literature,^{12,10,16} a definitive identification of the risk factors for systemic anaphylaxis after field sting is of great significance. Our study was designed to identify those risk factors of SARs to Hymenoptera field stings and compare these results with the findings that have already been described in the literature.

The virtual absence of grade IV reactions documented in our cohort is consistent with data from a previous multicenter study that used the same classification system.¹² In accordance with this study, a SAR was defined as a grade III or IV reaction, resulting in a similar SAR incidence of 25.4%. The comparability of our data with those of other studies that used different grading systems is limited.^{9–11}

Short Interval From Sting to Reaction

A strong association was found between SARs after field sting and a short interval from sting to reaction. Older studies have assumed that a short TI (less than 30 minutes) correlates with the severity of anaphylaxis.^{20,21} This hypothesis was initially presented in an early retrospective study describing a decrease in the incidence of moderate and severe systemic sting reactions over time.²² It has also been reported that lethal anaphylactic reactions had a median time of only 15 minutes from insect sting to cardiac arrest.²³ As part of a sting challenge, short interval from sting to reaction was also associated with SARs.¹³ Another large study demonstrated that an interval from sting to reaction of less than 5

Table 5
Logistic Regression Analysis of Risk Factors for Severe Anaphylactic Reactions After Field Sting

Variable	Coefficient	P value
Presence of at least 1 cardiovascular disease	0.0005	.99
BST > 11.4 $\mu\text{g/L}$	0.0695	.32
Age > 40 y	0.1856	<.001
Interval from sting to reaction > 5 min	−0.1048	.01
Presence of skin symptoms (U/A)	−0.1146	.007
Female sex	−0.1371	<.001
Medication with β -blocker	0.0100	.91
Medication with ACE inhibitors	−0.0965	.22

Abbreviations: ACE, angiotensin-converting enzyme; BST, baseline serum tryptase; U/A, urticaria or angioedema.

Table 6

Distribution of Anaphylactic Reactions During VIT Initiation After Severity of Anaphylaxis After Field Sting

Severity	Reaction during VIT initiation, No. (%)		Total, No. (%)
	Local reaction	Anaphylaxis	
Mild	355 (95.2)	18 (4.8)	373 (100)
Severe	120 (94.5)	7 (5.5)	127 (100)
Total	475 (95)	25 (5)	500 (100)

Abbreviation: VIT, venom immunotherapy.

minutes is a significant risk factor for SARs.¹⁰ Our results are therefore in accordance with previous studies.

Older Age

Older age is an established risk factor for systemic anaphylaxis not only in Hymenoptera venom allergy^{12,9,13–15,24} but also in other causes of life-threatening anaphylaxis. A plausible explanation would be that older patients often have coexisting severe cardiopulmonary diseases (eg, coronary heart disease and cardiomyopathies) that may affect the endogenous counterregulation in anaphylaxis. In accordance with this hypothesis, a study on 29 fatalities from Hymenoptera stings found a peak between the ages of 60 and 70 years, and autopsy in 12 of those patients revealed 11 with cardiac disease, 10 with coronary heart disease, and 7 with cardiomyopathy.¹⁴ In addition, BST levels increase^{9,11,25,26} and mast cell degranulation pathways change continuously with increasing age,²⁷ which may be at least partially related to the increasing severity of the anaphylactic reaction.

In accordance with these reports, patients older than 40 years had significantly more SARs (30.5%) in our patient population compared with younger patients (9.8%; $P = .007$). In addition, we found a highly significant increase in BST levels in older patients (>40 years). However, age older than 40 years was also a highly significant risk factor for systemic anaphylaxis in the logistic regression model. In accordance with previous studies, this finding suggests that the effect of age occurred independently of BST,^{12,9} medication with β -blockers or angiotensin-converting enzyme (ACE) inhibitors,¹² and the other included variables (Table 5).

Male Sex

Male sex has already been reported as an independent risk factor for SARs after Hymenoptera field sting.^{12,15} This association contradicts findings in other type I allergies, in which sex hormones increase the risk of anaphylactic reactions in female patients.²⁸ However, a recent multicenter study found that male sex is an independent risk factor for systemic anaphylactic reactions to food, drugs, insect venom, and other triggers.¹⁵ In accordance with the literature,^{12,15} male sex was found to be a highly significant risk factor for SARs in our cohort.

Concurrent Cardiovascular Disease and Cardiovascular Medication

Several studies report that a positive history of cardiovascular disease is a risk factor for SARs.^{14,16,21,29} This association was not confirmed in our patient population ($P = .29$). This lack of association may be because the patients in our cohort were relatively young (median age, 51 years) and the cardiovascular diagnosis was predominantly hypertension ($n = 172$), whereas severe cardiovascular diseases, such as coronary heart disease ($n = 5$) or heart failure ($n = 2$), were rare. Our results are consistent with findings from other comparable studies,^{12,10} which could support the hypothesis that only certain severe cardiovascular diseases (eg, coronary heart disease and cardiomyopathies) could be predictors of systemic anaphylaxis. This hypothesis is endorsed by the observation that the number and concentration of cardiac mast cells in

patients with those diseases are elevated,²⁹ which could increase the risk of systemic anaphylaxis. Future studies are needed to answer this question definitely.

Regarding the concurrent cardiovascular medication, β -blockers and ACE inhibitors could increase the severity of anaphylaxis and impair the response to treatment by inducing mediator release and inhibiting the endogenously released and injected epinephrine.^{18,30} In a large, multicenter, observational study, medication with ACE inhibitors was the only independent pharmacologic predictor of systemic anaphylaxis after field sting.¹² However, we found no significant effect of cardiovascular comedication on the severity of anaphylaxis, which is in line with another study.¹⁰ These findings also support the hypothesis that general cardiovascular comorbidities, such as arterial hypertension, might not be associated with SARs, which is also reflected in the missing association between hypertensive comedication and SARs.

Absence of Skin Symptoms

Skin symptoms (urticaria, angioedema, and flushing) are common during anaphylactic reactions, and their presence evokes suspicion of allergy. All anaphylaxis grading systems include the presence of skin symptoms, and, generally, the anaphylactic reactions with symptoms that are limited to the skin are classified with the lowest grade of severity of anaphylaxis.^{17,31} The absence of skin symptoms has been linked to anaphylactic hypotensive shock,^{14,20,21} especially in patients with SM,^{32–34} presumably because of the counteracting release of endogenous epinephrine leading to peripheral vasoconstriction.^{20,33} In a recent study, it was reported that in the case of anaphylaxis with hypotension after Hymenoptera field sting, the absence of skin symptoms may represent a significant BST-independent factor for the identification of a clonal mast cell disease. The authors suggested that those patients should undergo bone marrow biopsy despite normal BST values.³⁵

In accordance with these studies, our study found that SARs occurred significantly more often in patients without skin symptoms (31.9%) compared with patients with skin symptoms (20.9%; $P = .007$). We also found BST to be elevated more often in patients without skin symptoms (18.3% vs 6%, $P < .001$).

Elevated BST Levels

A strong association of BST with the severity of anaphylaxis after Hymenoptera field sting has been observed for many years and subsequently confirmed in large studies.^{11,12,25,32,36–38} A significant proportion of patients (5%–19%) who experienced anaphylaxis after field sting have elevated BST levels ($>11.4 \mu\text{g/L}$).^{34,39} Even slight increases in the normal range of BST ($<11.4 \mu\text{g/L}$) are associated with SARs after Hymenoptera field sting, regardless of other prognostic variables.^{12,20}

In the bivariate analysis, our study confirmed the significant association of BST level elevation with the severity of anaphylaxis. However, elevated BST level ($>11.4 \mu\text{g/L}$) was not an independent predictor of SARs in the regression model. This result appears to contradict a multicenter study report¹² that identified BST as an independent risk factor. However, the deviation of our results was probably caused by adding the presence of skin symptoms to our regression model. This factor was a confounder and an effect modifier in our cohort and was not considered by Ruëff et al.¹²

Presence of SM

SM is a clonal mast cell disease that can lead to fatal anaphylactic reactions through massive release of mast cell mediators. SM is a rare disease in general, but its prevalence in patients with Hymenoptera venom allergy is significantly higher than that in the

general population (1%–7.9% in patients with Hymenoptera venom allergy vs 0.01% in the general population).^{35,38,40}

SM is an established risk factor for SARs.^{35,41,42} We found significantly more SARs in the subgroup of patients with a diagnosis of SM (6 of 8 [75%]) compared with the subgroup of patients with no evidence of SM (103 of 436 [24%]; $P = .004$), which is proportionally in accordance with another recent study (69.9% vs 22%).⁴³

Our data provide indirect evidence that elevated BST levels and the absence of skin symptoms do not directly influence the severity of anaphylaxis. Instead, an undiagnosed SM may be the underlying cause of SARs. Elevated BST levels are associated with SM,⁴⁴ and recent studies have found that the absence of skin symptoms is a risk factor for the presence of mast cell disease.³⁴

The diagnosis of SM is challenging.⁴⁵ Currently, the most widely used laboratory test for suspected SM is the determination of BST.^{46,47} Values above $20.0 \mu\text{g/L}$ are considered by the World Health Organization as a minor criterion.⁴⁴ However, hypertryptasemia is not specific for the presence of SM,^{48,49} and clonal mast cell disease cannot be excluded in patients with severe anaphylaxis (SA) after field sting and normal BST levels.⁵⁰ In the case of severe Hymenoptera field sting anaphylaxis with elevated BST level, bone marrow biopsy is recommended to rule out the presence of SM.³⁸ The case is more complex when, despite the severity and number of reactions, BST levels are normal ($<11.4 \mu\text{g/L}$) and there are no signs of cutaneous mastocytosis. A recent study found that systemic anaphylaxis with hypotension and absence of skin symptoms may be a significant factor in the identification of clonal mast cell disease regardless of BST levels.³⁵

In our cohort, bone marrow biopsy was routinely recommended in patients with BST levels above $20 \mu\text{g/L}$ ($n = 25$) according to the SM guideline.⁴⁷ According to the studies mentioned above,^{35,50} it is possible that among some patients with BST levels up to $20 \mu\text{g/L}$, the diagnosis of clonal mast cell disease is missed. To reduce the number of undiagnosed SM cases, future studies should improve the sensitivity and specificity of the diagnostic methods and expand the indication for SM diagnostics. Recently, sensitive KIT D816V mutation analysis of blood was proposed as a better tool to guide bone marrow investigation in suspected SM.⁵¹

Because of the low number of confirmed SM cases, we were unable to test directly whether SM is the underlying factor that mediates the associations of elevated BST levels or absence of skin symptoms with SARs. However, the following observations endorse this hypothesis. First, an elevated BST level was significantly associated with the absence of skin symptoms. Second, an elevated BST level ($>11.4 \mu\text{g/L}$) was significantly associated with SARs in the bivariate analysis but not in the multivariate regression model. The additional regression analyses suggested that skin symptoms, but not the other predictors, were a mediator for the association between BST and SARs. This finding indicates that elevated BST level is not a cause of SARs. Third, skin symptoms were also an effect modifier. Elevated BST level was associated with SARs in the subgroup of patients without skin symptoms but not in other patients.

Such observations can be expected if it is true that (1) a combination of elevated BST level and absence of skin symptoms after field sting is indicative of SM, as stated by the Red Española de Mastocytosis (REMA) score,⁵² and (2) that SM is a strong risk factor for SARs.^{35,41,42} Our findings therefore provide indirect support for the validity of the REMA score, which is used in several centers for risk assessment of SM.⁵³ The molecular context of the complex associations between these variables should be further clarified in future studies.

Relative Risk of Severe Reactions During VIT Initiation

In accordance with other studies,⁵⁴ our study found no increased risk of anaphylaxis during VIT initiation in patients with

SARs after Hymenoptera field sting compared with patients with mild reactions (relative risk, 1.146; 95% CI, 0.488–2.671). As a result, additional preventive measures and a higher degree of surveillance during VIT initiation are not required for patients who had a SAR after field sting.

Conclusions

Although this study has the known disadvantages of a retrospective analysis, including recall bias and variability of the field stings, our work confirms established risk factors for SA after field sting (male sex and older age and elevated BST level and SM in bivariate analysis) and provides strong evidence that previously suggested predictors are also significant risk factors (short interval from sting to onset of anaphylaxis and absence of skin symptoms). Cardiovascular concomitant diseases in general were not associated with the severity of anaphylaxis, suggesting that only severe cardiovascular diseases (eg, coronary heart diseases and congestive cardiac failure) might be predictors of SARs. In addition, our study data did not provide evidence of an aggravation of sting-induced anaphylaxis by concurrent β -blockade or ACE inhibition. Our findings indirectly confirm that the absence of skin symptoms in anaphylaxis after Hymenoptera field sting and an elevated BST level indicate the presence of SM, as stated by the REMA score. Finally, patients with SA after field sting in our cohort did not have an elevated risk of systemic reactions during VIT initiation.

References

- Golden DBK, Demain J, Freeman T, et al. Stinging insect hypersensitivity: a practice parameter update 2016. *Ann Allergy Asthma Immunol*. 2017;118(1):28–54.
- Biló BM, Rueff F, Mosbech H, Bonifazi F, Oude-Elberink JNG; EAACI Interest Group on Insect Venom Hypersensitivity. Diagnosis of Hymenoptera venom allergy. *Allergy*. 2005;60(11):1339–1349.
- Golden DBK. Insect sting allergy and venom immunotherapy: a model and a mystery. *J Allergy Clin Immunol*. 2005;115(3):439–447; quiz 448.
- Biló BM, Bonifazi F. Epidemiology of insect-venom anaphylaxis. *Curr Opin Allergy Clin Immunol*. 2008;8(4):330–337.
- Worm M, Eckermann O, Dölle S, et al. Triggers and treatment of anaphylaxis: an analysis of 4,000 cases from Germany, Austria and Switzerland. *Dtsch Arztebl Int*. 2014;111(21):367–375.
- Müller UR. Insect venoms. *Chem Immunol Allergy*. 2010;95:141–156.
- Graft DF. Insect sting allergy. *Med Clin North Am*. 2006;90(1):211–232.
- Sturm GJ, Varga E-M, Roberts G, et al. EAACI guidelines on allergen immunotherapy: Hymenoptera venom allergy. *Allergy*. 2018;73(4):744–764.
- Blum S, Gunzinger A, Müller UR, Helbling A. Influence of total and specific IgE, serum tryptase, and age on severity of allergic reactions to Hymenoptera stings. *Allergy*. 2011;66(2):222–228.
- Stoevesandt J, Hain J, Kerstan A, Trautmann A. Over- and underestimated parameters in severe Hymenoptera venom-induced anaphylaxis: cardiovascular medication and absence of urticaria/angioedema. *J Allergy Clin Immunol*. 2012;130(3):698–704.e1.
- Kucharewicz I, Bodzenta-Lukaszyk A, Szymanski W, Mroczko B, Szmikowski M. Basal serum tryptase level correlates with severity of Hymenoptera sting and age. *J Investig Allergol Clin Immunol*. 2007;17(2):65–69.
- Rüeff F, Przybilla B, Biló MB, et al. Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum tryptase—a study of the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom Hypersensitivity. *J Allergy Clin Immunol*. 2009;124(5):1047–1054.
- van der Linden PW, Hack CE, Struyvenberg A, van der Zwan JK. Insect-sting challenge in 324 subjects with a previous anaphylactic reaction: current criteria for insect-venom hypersensitivity do not predict the occurrence and the severity of anaphylaxis. *J Allergy Clin Immunol*. 1994;94(2 Pt 1):151–159.
- Sasvary T, Müller U. Fatalities from insect stings in Switzerland 1978 to 1987 [in German]. *Schweiz Med Wochenschr*. 1994;124(43):1887–1894.
- Worm M, Francuzik W, Renaudin J-M, et al. Factors increasing the risk for a severe reaction in anaphylaxis: an analysis of data from the European Anaphylaxis Registry. *Allergy*. 2018;73(6):1322–1330.
- Mueller UR. Cardiovascular disease and anaphylaxis. *Curr Opin Allergy Clin Immunol*. 2007;7(4):337–341.
- Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet*. 1977;1(8009):466–469.
- Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. 2011;127(1 suppl):S1–S55.
- Reisman RE. Natural history of insect sting allergy: relationship of severity of symptoms of initial sting anaphylaxis to re-sting reactions. *J Allergy Clin Immunol*. 1992;90(3 Pt 1):335–339.
- 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(8):884–889.
- Greenberger PA, Rotskoff BD, Lifschultz B. Fatal anaphylaxis: postmortem findings and associated comorbid diseases. *Ann Allergy Asthma Immunol*. 2007;98(3):252–257.
- Lockey RF, Turkeltaub PC, Baird-Warren IA, et al. The Hymenoptera Venom Study I, 1979–1982: demographics and history-sting data. *J Allergy Clin Immunol*. 1988;82(3 Pt 1):370–381.
- Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy*. 2000;30(8):1144–1150.
- Brown SGA. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol*. 2004;114(2):371–376.
- Guenova E, Volz T, Eichner M, et al. Basal serum tryptase as risk assessment for severe Hymenoptera sting reactions in elderly. *Allergy*. 2010;65(7):919–923.
- Schliemann S, Seyfarth F, Hipler U-C, Elsner P. Impact of age and heterophilic interference on the basal serum tryptase, a risk indication for anaphylaxis, in 1,092 dermatology patients. *Acta Derm Venereol*. 2012;92(5):484–489.
- Nguyen M, Pace AJ, Koller BH. Age-induced reprogramming of mast cell degranulation. *J Immunol*. 2005;175(9):5701–5707.
- Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. *Allergy*. 2008;63(11):1418–1427.
- Triggiani M, Patella V, Staiano RI, Granata F, Marone G. Allergy and the cardiovascular system. *Clin Exp Immunol*. 2008;153(suppl 1):7–11.
- Müller UR, Haerli G. Use of beta-blockers during immunotherapy for Hymenoptera venom allergy. *J Allergy Clin Immunol*. 2005;115(3):606–610.
- Muraro A, Roberts G, Clark A, et al. The management of anaphylaxis in childhood: position paper of the European Academy of Allergology and Clinical Immunology. *Allergy*. 2007;62(8):857–871.
- Brockow K, Jöfer 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(2):226–232.
- Potier A, Lavigne C, Chappard D, et al. Cutaneous manifestations in Hymenoptera and Diptera anaphylaxis: relationship with basal serum tryptase. *Clin Exp Allergy*. 2009;39(5):717–725.
- Brockow K, Akin C. Hymenoptera-induced anaphylaxis: is it a mast cell driven hematological disorder? *Curr Opin Allergy Clin Immunol*. 2017;17(5):356–362.
- Zanotti R, Lombardo C, Passalacqua G, et al. Clonal mast cell disorders in patients with severe Hymenoptera venom allergy and normal serum tryptase levels. *J Allergy Clin Immunol*. 2015;136(1):135–139.
- Oude Elberink JNG, van der Heide S, Guyatt GH, Dubois AEJ. Immunotherapy improves health-related quality of life of adult patients with dermal reactions following yellow jacket stings. *Clin Exp Allergy*. 2009;39(6):883–889.
- Haerli G, Brönnimann M, Hunziker T, Müller U. Elevated basal serum tryptase and Hymenoptera venom allergy: relation to severity of sting reactions and to safety and efficacy of venom immunotherapy. *Clin Exp Allergy*. 2003;33(9):1216–1220.
- Bonadonna P, Zanotti R, Müller U. Mastocytosis and insect venom allergy. *Curr Opin Allergy Clin Immunol*. 2010;10(4):347–353.
- Alfaya Arias T, Soriano Gómis V, Soto Mera T, et al. Key issues in Hymenoptera venom allergy: an update. *J Investig Allergol Clin Immunol*. 2017;27(1):19–31.
- Brockow K. Epidemiology, prognosis, and risk factors in mastocytosis. *Immunol Allergy Clin North Am*. 2014;34(2):283–295.
- Greenhawt M, Akin C. Mastocytosis and allergy. *Curr Opin Allergy Clin Immunol*. 2007;7(5):387–392.
- Bonadonna P, Zanotti R, Pagani M, et al. How much specific is the association between Hymenoptera venom allergy and mastocytosis? *Allergy*. 2009;64(9):1379–1382.
- Vos BJPR, van Anrooij B, van Doormaal JJ, Dubois AEJ, Oude Elberink JNG. Fatal anaphylaxis to yellow jacket stings in mastocytosis: options for identification and treatment of at-risk patients. *J Allergy Clin Immunol Pract*. 2017;5(5):1264–1271.
- Bains SN, Hsieh FH. Current approaches to the diagnosis and treatment of systemic mastocytosis. *Ann Allergy Asthma Immunol*. 2010;104(1):1–10; quiz 10–12, 41.
- Biedermann T, Rüeff F, Sander CA, Przybilla B. Mastocytosis associated with severe wasp sting anaphylaxis detected by elevated serum mast cell tryptase levels. *Br J Dermatol*. 1999;141(6):1110–1112.
- Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. *Blood*. 2017;129(11):1420–1427.
- Hartmann K, Biedermann T, Brockow K, et al. Mastozytose: Leitlinie der Deutschen Gesellschaft für Allergologie und Klinische Immunologie (DGAKI) und der Deutschen Dermatologischen Gesellschaft (DDG). *Allergo J*. 2009;18(3):196–207.
- Lyons JJ, Yu X, Hughes JD, et al. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. *Nat Genet*. 2016;48(12):1564–1569.
- Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. *Immunol Allergy Clin North Am*. 2006;26(3):451–463.
- Metcalfe DD, Schwartz LB. Assessing anaphylactic risk? Consider mast cell clonality. *J Allergy Clin Immunol*. 2009;123(3):687–688.

51. Kristensen T, Vestergaard H, Bindslev-Jensen C, Møller MB, Broesby-Olsen S, Mastocytosis Centre, Odense University Hospital (MastOUH). Sensitive KIT D816V mutation analysis of blood as a diagnostic test in mastocytosis. *Am J Hematol*. 2014;89(5):493–498.
52. Álvarez-Twose I, de Olano DG, Sánchez-Muñoz L, et al. Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms. *J Allergy Clin Immunol*. 2010;125(6):1269–1278.e2.
53. 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(10):1547–1555.
54. Ruëff F, Przybilla B, Biló MB, et al. Predictors of side effects during the buildup phase of venom immunotherapy for Hymenoptera venom allergy: the importance of baseline serum tryptase. *J Allergy Clin Immunol*. 2010;126(1):105–111.e5.