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Conflict of interest

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Risk stratification of systemic allergic reactions during Hymenoptera venom immunotherapy buildup phase

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Summary

Background: Comparability of previous studies assessing the incidence of systemic reactions during Hymenoptera venom immunotherapy (VIT) is impaired by methodical differences concerning the definition and classification of VIT-induced anaphylaxis. Our study aims to systematically evaluate the time course and clinical symptoms of VIT-related systemic reactions.

Patients and Methods: 12-year data on 818 buildup cycles including 8,504 single injections were retrieved from detailed inpatient treatment protocols. The severity of VIT-related anaphylaxis was graded according to a system proposed by the World Allergy Organization in 2010.

Results: Objective allergic reactions occurred in 28 (3.4 %) buildup cycles; treatment with antihistamines and/or corticosteroids was invariably effective. 23 exclusively cutaneous reactions occurred after a median time interval of 60 minutes (5–480 min.) following the last injection. 0.6 % of the buildup cycles were complicated by moderate to severe anaphylaxis, which occurred more rapidly than mere urticaria and predominantly during honeybee VIT. Patients with moderate to severe anaphylaxis more frequently reported severe index sting reactions and had higher baseline serum tryptase concentrations.

Conclusions: Objective allergic reactions during VIT are rare, and severe anaphylaxis is extremely rare. The use of a consistent classification system for VIT-induced systemic reactions is required to identify risk factors not only for their general incidence, but also for the exceptionally severe anaphylactic reactions.

Introduction

Approximately 3 % of the population of Western countries experience anaphylactic reactions following stings of honeybees or *Vespula* species [1, 2]. Hymenoptera venom immunotherapy (VIT) effectively protects venom allergic patients from potentially life threatening sting reactions [3]. Systemic allergic reactions may, however, complicate VIT itself [3]. Reports of the incidence of VIT-related systemic reactions vary within a broad range of 7–20% [4–10]. Most reactions occur during the buildup phase of

VIT [7, 9–12]. Since implementation of VIT in the late 1970s [13] several factors have been identified as being associated with a higher incidence of treatment-related anaphylaxis, e.g. honeybee VIT compared to *Vespula* VIT [4, 7–12, 14], an increase of the baseline serum tryptase concentration or mast cell diseases [4, 15, 16], and dose increase according to rush protocols involving a large number of injections within one day [8]. Severe and repeated systemic reactions during Hymenoptera VIT are considered to be indicative of insufficient protection and an increased risk of future sting-induced anaphylaxis [2].

Apart from needing general information on the risk factors and the incidence of VIT-related systemic reactions, physicians performing Hymenoptera VIT in daily practice need to become acquainted with the clinical details of VIT-induced anaphylaxis in order to provide appropriate treatment and to assess the consequences on the further course of VIT. Precise data are all the more important as the possibility of severe treatment-associated anaphylaxis is difficult to accept for both patients and physicians due to the relative electiveness of VIT (not all patients will experience a Hymenoptera field sting, and only a minority will develop a life-threatening reaction). Clinical details of VIT-associated reactions have not been the focus of recent prospective multicentre studies [4, 7]. Previous retrospective analyses [5, 6, 12, 17, 18] and prospective observational studies on smaller patients collectives [9, 11, 19] as well as an older questionnaire-based study [10] provide more detailed information, but are difficult to compare due to methodical differences in study design, patient collectives and treatment protocols. Most importantly, their comparability is impaired by the use of different definitions and inconsistent classification systems of VIT-related anaphylaxis.

The objective of our present study was to comprehensively assess all inpatient buildup cycles of VIT performed in our clinic since 2001. Emphasis is put on a detailed and standardized evaluation of the clinical symptoms, time course and severity of VIT-associated anaphylactic reactions. We define clinical parameters and risk factors of severe treatment-induced anaphylaxis and discuss requirements for its standardized documentation and classification.

Patients and methods

Patients

VIT was initiated according to international treatment guidelines [1, 20, 21], provided that there was a conclusive history of a systemic anaphylactic reaction following a Hymenoptera sting, and sensitization to the corresponding venom was confirmed by intradermal and/or serologic tests. All VIT buildup cycles following an inpatient rush protocol between January 2001 and April 2013 were evaluated. In patients going through VIT buildup several times due to double allergy to honeybee and vespid venom or due to discontinuation of VIT for various reasons, each treatment cycle was evaluated separately. All patient-related diagnostic and therapeutic procedures took part during routine patient care following written informed consent.

Acquisition of data

Relevant patient-specific data (sex, age, concurrent diseases, medication, causative insect, degree of index sting-induced

anaphylaxis according to Ring [22]) and the results of routine allergy diagnostics (specific serum IgE, intradermal testing, baseline serum tryptase concentration) were taken from the patients files. Information on the course of VIT was derived from standardized treatment protocols documenting VIT-induced systemic reactions in relation to the cumulative and single venom doses administered and the time interval between venom injections and the onset of symptoms. These protocols contain standardized information on allergic symptoms affecting the skin, upper and lower respiratory tract, gastrointestinal tract, central nervous system and cardiovascular system as well as on the therapeutic intervention and the further course of VIT.

Allergy testing and initiation of VIT

Intradermal testing with honeybee and *Vespula* venom (ALK-Abelló, Wedel) was performed as recommended in international guidelines [23]. Venom specific IgE was measured using the ImmunoCAPTM system and baseline serum tryptase concentrations were determined using ImmunoCAP TryptaseTM (both Thermo Fisher Scientific, Schwerte).

VIT buildup with aqueous allergen extracts (ALK-lyophilisiert SQTM, ALK-Abelló) was performed under continuous medical supervision. An intravenous line was installed prior to initiation of VIT, pulse and blood pressure were closely monitored. Until 2007, the standard maintenance dose of 100 µg Hymenoptera venom toxin was achieved using a 5 day inpatient rush protocol comprising 14 single injections and a cumulative dose of 311.5 µg, which was then replaced by a 3 day protocol with 9 injections and a cumulative dose of 301.1 µg (Table 1). Once the maintenance dose was achieved, treatment was continued with a depot preparation containing aluminium hydroxide (ALK-depot SQTTM, ALK-Abelló). Premedication with H1- antihistamines was not routinely given.

Classification of treatment-associated reactions

Systemic reactions during the VIT buildup phase were considered “objective” if at least one of the following symptoms [24] was present: symptoms of the skin and mucous membranes (transient flush, urticaria, angioedema), of the upper or lower respiratory tract (laryngeal oedema, bronchospasm), cardiovascular dysregulation (arterial hypotension, circulatory collapse), or gastrointestinal symptoms (abdominal cramps, diarrhoea, vomiting). Any other symptoms comprising a generalized feeling of warmth, isolated pruritus, headache, general fatigue or panic were classified as “subjective”, as long as they were not accompanied or followed by objective symptoms. Severity of objective allergic reactions was categorized according to the classification established

Table 1 3 day and 5 day inpatient rush protocols for VIT buildup.

Rush protocol	3 days		5 days	
	Day	Dose (μg)	Day	Dose (μg)
	1	0.1	1	0.02
		1		0.08
		10		0.2
				0.4
	2	20	2	0.8
		30		2.0
		40		4.0
				6.0
	3	50	3	8.0
		50		20
				40
	4 0. 5 ¹	100 ²	4	50
				80
				100 ²
			5	
Cumulative dose (μg)		301.1	311.5	
Total number of injections		9	14	
¹outpatient administration, ²Depot preparation.				

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by Ring (grade I–IV, [22]) as well as according to a system proposed by the World Allergy Organization (WAO) in 2010 to grade immunotherapy-related anaphylactic reactions (grade 1–4 [24]) (Table 2).

Results

Patient cohort

Evaluation included 818 VIT buildup cycles with honeybee ($n = 160$, 19.6 %) and *Vespula* venom ($n = 658$, 80.4 %) being performed in our clinic between January 2001 and April 2013. 220 (26.9 %) buildup cycles initiated before 2007 followed the 5 day rush protocol, 592 (72.4 %) buildup cycles were performed according to the 3 day protocol, and 6 (0.7 %) buildup cycles were based on modified rush protocols. Altogether, 8,504 single injections were evaluated. The median time interval between the most severe anaphylactic reaction to a preceding Hymenoptera sting (referred to as the index sting) and the beginning of VIT was 7 months (0–372 months). The median age at the beginning of treatment was 46 years (7–84 years). Most of the patients were men

($n = 455$, 55.6 %). Further details on patient-specific data (grade of anaphylaxis to the index sting, concurrent diseases, and medication) are summarized in Table 3.

Course of VIT

673 (82.3 %) of 818 documented buildup cycles were tolerated without complications (Figure 1). In 35 (4.3 %) buildup cycles large local reactions required oral treatment with H1-antihistamines. 71 (8.7 %) patients complained of subjective symptoms during VIT buildup. 31 patients with subjective reactions (43.7 % of this group, 3.8 % of the total patient cohort) were treated with oral or intravenous H1-antihistamines. In almost all cases VIT-buildup could be continued. VIT buildup was temporarily discontinued in a female patient who received systemic corticosteroids while giving a very dramatic account of her subjective symptoms (a later restart of VIT was well tolerated). Objective allergic symptoms were observed in 28 (3.4 %) buildup cycles and will be discussed in detail below. 11 (1.3 %) buildup cycles were complicated by independent diseases (e.g. infections, insufficiently controlled arterial hypertension, or migraine

Table 2 Grading of objective allergic reactions during Hymenoptera VIT (modified according to Cox L., 2010 [24]).

Grade 1	Grade 2	Grade 3	Grade 4
Presence of symptoms of one organ system including	Symptoms of more than one organ <i>or</i> presence of at least one of the following symptoms	Presence of at least one of the following symptoms	Presence of at least one of the following symptoms
Skin Urticaria, flush or angioedema	Lower respiratory tract Asthma / bronchial obstruction with adequate response to inhalative therapy	Lower respiratory tract Asthma / bronchial obstruction with insufficient response to inhalative therapy	Respiratory tract Respiratory insufficiency due to asthma or laryngeal edema
Upper respiratory tract Rhinitis with nasal congestion or rhinorrhea	Gastrointestinal Vomiting, diarrhea, abdominal cramps	Upper respiratory tract Laryngeal edema	Cardiovascular system Arterial hypotension with or without loss of consciousness
Conjunctivae Conjunctival erythema or tearing	Other Uterine cramps		

Definite classification is performed after the therapy-associated allergic reaction is over, considering the following aspects:
 1. Grade of severity, 2. First symptom of the adverse reaction, 3. Time interval (in minutes) between preceding injection and beginning of the reaction. The WAO additionally suggests to state if and when epinephrine was or was not administered. As administration of epinephrine was not required during our observation period, this information was not routinely included in the final reports.

attacks), in some cases requiring temporary interruption of treatment.

Objective reactions

Objective reactions with at least one unambiguous symptom affecting the skin or mucous membranes, respiratory system, gastrointestinal tract or cardiovascular system were observed in 28 (3.4 %) of the 818 buildup cycles (see patients and methods). The median age of these patients was 42 years (7–75 years); men and women were equally affected. 13 patients reacted to honeybee VIT, 15 patients reacted to *Vespula* VIT. Objective reactions were observed more frequently during VIT buildup following the 5 day rush protocol and mainly occurred after injection of moderate to high doses (median 45 µg, range 8–100 µg). Details on objective reactions including information on venom doses, time intervals between the preceding injection and the onset of symptoms, clinical symptoms of skin- and other organs, severity grade, emergency treatment and the further course of VIT are summarized in Table 4 (Table 4). 23 exclusively cutaneous objective reactions were classified as “mild” (grade I or 1 respectively) in both classification systems. Three reactions were graded as “moderate” due to gastrointestinal symptoms and/or bronchial obstruction (grade II or 2 respectively). Two patients developed tachycardia and transient arterial

hypotension, leading to classification as a “severe” reaction (grade III and 4 respectively). All documented reactions were successfully treated using systemic H1-antihistamines and/or corticosteroids and, if required, short-acting inhalative beta2-agonists. In 4 cases VIT buildup was interrupted due to the necessity of treatment with systemic corticosteroids. Systemic administration of epinephrine was not required during the study inclusion period. The maintenance dose of 100 µg was successfully achieved within the same hospital stay subsequent to 67.9 % of the overall number of objective reactions and to 78.3 % of reactions confined to the skin. In 4 cases (14.3 %) a reduced dose was reached during inpatient treatment to be subsequently increased up to the target dose of 100 µg following an outpatient protocol. In another 4 cases (14.3 %) VIT buildup was temporarily discontinued to be restarted following an inpatient rush protocol on a later occasion. In only one case VIT was permanently discontinued due to subjective concerns following a mild/cutaneous reaction during inpatient dose increase.

Comparison between mild and moderate to severe reactions

Table 5 compares the characteristics of patients with systemic reactions confined to the skin (WAO grade 1, n = 23) to those with moderate to severe systemic anaphylaxis (grade

Table 3 Patient cohort.

	n	(%)
Total number* of buildup cycles, 01/2001–04/2013	818	
Patient specific data		
Age in years at VIT-initiation, median (range)	46 (7–84)	
Sex, female/male	363/455	
Grade of index sting-induced anaphylaxis according to Ring [22]		
Grade I	117	(14.3)
Grade II	485	(59.3)
Grade III to IV	216	(26.4)
Concurrent cardiovascular disease	207	(25.3)
Cardiovascular medication during VIT		
Beta-blocker	23	(2.8)
ACE inhibitor	91	(11.1)
Elevation of baseline serum tryptase		
> 11.4 µg/l	66	(8.1)
> 20.0 µg/l	27	(3.3)
VIT-related data		
Hymenoptera venom		
Bee venom	160	(19.6)
<i>Vespula</i> venom	658	(80.4)
Treatment protocol		
3 days	592	(72.4)
5 days	220	(26.9)
Modified	6	(0.7)
Months between index sting and initiation of VIT, median (range)	7 (0–372)	
*In patients who underwent VIT buildup more than once due to double allergy to honey bee and <i>Vespula</i> venom (n = 16) or following discontinuation of treatment due to various reasons (n = 19), each buildup cycle was evaluated separately.		

2–4, n = 5). It may only describe clinical tendencies. Quantitative statistical statements may not be made due to the low rate of objective VIT-related reactions and to the exceedingly small number of severe systemic reactions.

No differences were noted in age or gender distribution. Compared to patients with VIT-induced grade 1 reactions, patients with moderate to severe reactions more frequently had a history of severe index sting-induced anaphylaxis. The latter had a higher median concentration of the baseline serum tryptase (11.11 vs. 3.85 µg/l) – in both patients with grade 4 anaphylactic reactions tryptase levels were clearly above the 95th percentile of 11.4 µg/l (patient 8: 41.4 µg/l; patient 10: 19.0 µg/l). Moderate to severe anaphylaxis was

more common during honeybee VIT while exclusively cutaneous reactions occurred more often during *Vespula* VIT. Still, the group of patients suffering VIT-related grade 1 cutaneous reactions contained a higher proportion of individuals receiving honeybee VIT (39.1 %) than the total study group of 818 patients (19.6 %). The median time interval between the preceding injection and the onset of allergic symptoms was significantly shorter in moderate to severe anaphylaxis compared to grade 1 reactions (10 versus 60 min.). Urticaria as an isolated symptom frequently developed several hours (maximum 8 h) after the last injection. According to their definition, all grade 1 reactions remained limited to the skin (urticaria: 78.3 %; flush: 21.7 %). In contrast,

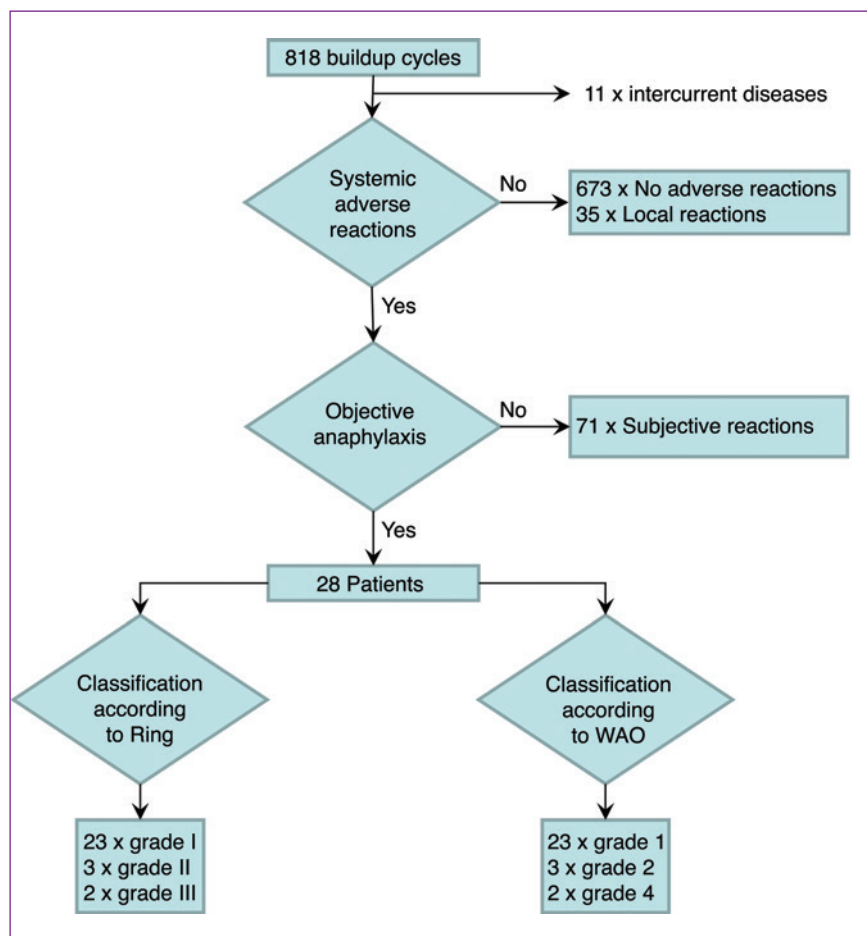


Figure 1 Overview on the course of 818 cycles of VIT buildup phase.

only 2 patients (40 %) with moderate to severe anaphylaxis had generalized urticaria. Two other patients developed a flush reaction and one patient did not have any cutaneous symptoms.

Discussion

We present a detailed analysis of 818 inpatient VIT buildup cycles performed in our clinic. Compared to recent multicentre studies assessing the incidence and general risk factors of VIT-related adverse reactions [4, 7] and to two large questionnaire-based historical studies [10, 12] our study has the advantage of a single study centre providing homogenous treatment conditions. Highly standardized documentation of VIT-related systemic reactions warrants consistent quality and comparability of data throughout the entire observation period of 12 years. The transferability of our results to the context of other facilities, conventional buildup protocols or to the maintenance phase of VIT, however, remains to be validated.

Objective reactions during Hymenoptera VIT are rare

Our data confirm the high safety of our rush protocols. The 3.4 % rate of objective VIT-related anaphylactic reactions is seemingly lower than that of previous studies using different anaphylaxis classification systems and/or including subjective symptoms into evaluation [4, 7–10]. If subjective symptoms were included, our reaction rate (12.1 %) was within the range of previous studies. Various symptoms such as feeling of warmth, isolated pruritus, panic, or general fatigue were classified as “subjective”, as long as they were not accompanied or followed by objective anaphylactic symptoms. While the above mentioned subjective complaints do commonly derive from anxiety, they may also precede an objective anaphylactic reaction in the sense of an aura [24]. In our patient cohort, 31 of 71 patients (43.7 %) suffering from subjective symptoms were systemically treated with H1-antihistamines. This early intervention may theoretically lead to an underdiagnosis of objective reactions as some of the treated patients might have developed early stage anaphylaxis / urticaria in

Table 4 Objective reactions during Hymenoptera VIT buildup.

Patient data		Reaction¹		Symptoms of anaphylaxis²					Therapy		Outcome³	
Nr.	Age, sex	Dose (µg)	Interval (min)	Skin	Cardiovascular system	Respiratory tract	Gastrointestinal system	Other	Ring	WAO		
Honeybee VIT												
1	7, ♀	50	15	U	–	BO	Nausea	–	II	2;asthma:15	Corticosteroids iv H₁-AH iv β₂-Symp	2
2	17, ♂	8	60	U	–	–	–	–	I	1;U:60	H₁-AH oral	1
3	21, ♀	100	60	U	–	–	–	–	I	1;U:60	H₁-AH oral	1
4	42, ♀	20	10	–	–	BO	Cramps	Uterine cramps	II	2;asthma:10	H₁-AH oral β₂-Symp.	1
5	42, ♂	30	30	F	–	–	–	Palmar pruritus	I	1;pruritus:30	H₁-AH oral	1
6	43, ♀	50	80	U	–	–	–	–	I	1;U:80	H₁/H₂-AH iv	1
7	43, ♀	40	20	U	–	–	–	–	I	1;U:20	H₁-AH iv	1
8	45, ♂	40	5	F	RR↓	BO	Vomiting	–	III	4;flush:5	Corticosteroids iv H₁/H₂-AH iv	3
9	46, ♀	40	60	U	–	–	–	–	I	1;U:60	H₁-AH oral	1
10	47, ♂	60	10	F	RR↓	BO	–	–	III	4;hypotension:10	Corticosteroids iv H₁-AH iv β₂-Symp	3
11	50, ♂	50	30	F	–	–	–	–	I	1;flush:30	H₁-AH oral	1
12	61, ♀	40	45	F	–	–	–	–	I	1; flush:45	H₁-AH iv	1
13	61, ♀	80	5	U	–	–	–	Pruritus	I	1;pruritus:5	H₁-AH iv	2
Vespula VIT												
14	7, ♂	50	120	U	–	–	–	–	I	1;U:120	H₁-AH iv	2
15	7, ♂	40	60	U	–	–	–	–	I	1;U:60	H₁-AH oral	1
16	20, ♂	80	150	U	–	–	–	–	I	1;U:150	H₁-AH oral	1
17	31, ♂	20	30	U	–	–	–	–	I	1;U:30	H₁-AH iv	3

Table 4 Continued.

Patient data		Reaction¹		Symptoms of anaphylaxis²					Grading		Therapy	Outcome³
Nr.	Age, sex	Dose (µg)	Interval (min)	Skin	Cardiovascular system	Respiratory tract	Gastrointestinal system	Other	Ring	WAO		
18	31, ♂	30	45	F	—	—	—	—	I	1;flush:45	H₁-AH iv	2
19	31, ♀	80	480	U	—	—	—	—	I	1;U:480	H₁-AH iv	1
20	36, ♀	40	240	U	—	—	—	—	I	1;U:240	H₁-AH iv	1
21	39, ♀	80	420	U	—	—	—	—	I	1;U:420	H₁-AH oral	1
22	41, ♀	40	360	U	—	—	—	—	I	1;U:360	H₁-AH oral	1
23	42, ♀	40	180	U	—	—	Vomiting	Arthralgia	II	2;U:180	Corticosteroids iv H₁/H₂-AH iv	3
24	43, ♂	50	450	U	—	—	—	—	I	1;U:450	None	1
25	45, ♂	40	15	U	—	—	—	—	I	1;U:15	H₁-AH iv	1
26	54, ♂	80	20	F	—	—	—	—	I	1;flush:20	H₁-AH oral	1
27	61, ♀	80	10	U	—	—	—	tinnitus	I	1;tinnitus:10	H₁-AH iv	1
28	75, ♂	60	60	U	—	—	—	—	I	1;U:60	H₁-AH iv	4

¹Last single dose administered and time interval until beginning of the adverse reaction.²First symptoms are highlighted in bold italics.³Outcome: 1 = Maintenance dose of 100 µg achieved; 2 = Lower dose achieved (to be increased to 100 µg following an outpatient dose increase protocol); 3 = Temporary discontinuation of treatment; 4 = Permanent discontinuation of treatment.Abbr.: AH, antihistamines; β₂-Symp, inhalative beta agonist; BO, bronchial obstruction; F, flush; RR↓, arterial hypotension; U, urticaria.

Table 5 Comparison of patients with mild (WAO grade 1, Ring grade I) and moderate to severe (WAO grade 2–4, Ring grade II–III) anaphylactic reactions during Hymenoptera VIT buildup.

WAO [24] Ring [22]	Grade 1 Grade I		Grade 2–4 Grade II–III		Total	
Patient specific data						
Age in years, median (range)	42	(7–75)	42	(7–47)	42	(7–75)
Sex, female/male	11/12		3/2		14/14	
Grade of anaphylaxis to index sting according to Ring						
Grade I (%)	4	(17.4)	0	(0.0)	4	(14.3)
Grade II (%)	15	(65.2)	2	(40.0)	17	(60.7)
Grade III (%)	4	(17.4)	3	(60.0)	7	(25.0)
Diagnostic parameters						
Specific IgE in IU/ml, median (range)	4,85	(0.14–53.2)	71.0	(1.79–100.0)	5.77	(0.14–100.0)
Baseline serum tryptase in µg/l, median (range)	3,85	(1.0–12.8)	11.11	(2.23–41.4)	3.85	(1.0–41.4)
Intradermal threshold concentration in µg/ml, median	0.01		0.01		0.01	
VIT-related data						
Hymenoptera venom						
Honeybee venom (%)	9	(39.1)	4	(80.0)	13	(46.4)
<i>Vespula</i> venom (%)	14	(60.9)	1	(20.0)	15	(53.6)
Treatment protocol						
3 days (%)	9	(39.1)	3	(60.0)	12	(42.9)
5 days (%)	14	(60.9)	1	(20.0)	15	(53.6)
Modified (%)	0	(0)	1	(20.0)	1	(3.6)
Data on VIT-related systemic reactions						
Preceding venom dose in µg, median (range)	50	(8–100)	40	(20–60)	45	(8–100)
Minutes after last injection, median (range)	60	(5–480)	10	(5–180)	52,5	(5–480)
Cutaneous symptoms						
Urticaria (%)	18	(78.3)	2	(40.0)	20	(71.4)
Flush (%)	5	(21.7)	2	(40.0)	7	(25.0)
None (%)	0	(0)	1	(20.0)	1	(3.6)

the further course. High grade systemic anaphylaxis, however, may not be prevented by H1-antihistamines alone [19, 25]. We therefore conclude that severe anaphylactic reactions have been reliably detected despite our limitation to objective symptoms.

Delayed manifestation of VIT-induced urticaria

Isolated urticaria was the most frequent VIT-induced anaphylactic symptom in our patient cohort. As a consequence,

the majority of objective VIT-related reactions did not fulfil the definition of “anaphylaxis” in the strict sense if extracutaneous organ involvement is required as a diagnostic criterion [26]. Grading systems for immunotherapy-related anaphylaxis, however, usually consider single organ symptoms including isolated cutaneous signs in order to accurately detect early stage anaphylaxis [10, 24, 27–29]. Isolated urticaria frequently developed with a time delay of up to 8 hours following the last injection. This observation is an argument in favour of inpatient dose increase of Hymenoptera VIT in

order to continuously ensure adequate supervision and treatment of patients with delayed cutaneous reactions. We conclude that isolated cutaneous symptoms were generally mild, responded well to treatment with H1-antihistamines, and did not require discontinuation of VIT buildup. Isolated urticaria may therefore be considered as an *acceptable* side effect patients should be informed about prior to initiation of VIT. It may be prevented or attenuated by premedication with H1-antihistamines [19]. Delayed occurrence of allergic symptoms requires further consideration of their pathogenesis. In addition to IgE-mediated mechanisms, allergen-specific IgG may play a pathogenetic role. Clinical differentiation from serum sickness-like reactions may prove difficult.

VIT-induced anaphylaxis may be severe in exceptional cases

Systemic VIT-induced anaphylaxis with extracutaneous organ involvement is considerably less frequent than mild cutaneous reactions. In our study group, 5 patients (0.6 % of the total cohort) had moderate to severe systemic anaphylaxis, and only two patients (0.2 %) transiently developed cardiovascular involvement with arterial hypotension. The low rate of potentially life threatening anaphylactic side effects has likewise been observed in previous studies specifically assessing the incidence of severe VIT-related anaphylaxis [6–10, 17]. To date, only two casuistic reports of treatment-related fatalities have been documented: The first occurred in the 1970s in a patient receiving immunotherapy with a combination of Hymenoptera whole body extracts and inhalative allergens [30]. A *Vespula* VIT-related fatal reaction was subsequently reported in a woman with ventricular arrhythmia following pre-treatment discontinuation of her beta blocker [31].

Due to the small number of moderate to severe anaphylactic reactions, our study is not powered to permit valid statistical conclusions on clinical features and potential risk factors of systemic VIT-related anaphylaxis compared to isolated cutaneous reactions. Clinical characteristics of both groups are descriptively evaluated in Table 5. We will hereinafter discuss our own findings in the context of the medical literature. Comparability with previous studies, however, is impaired due to differences concerning the definition of anaphylaxis (some authors include subjective symptoms) and use of different grading systems.

1. *Compared to patients with isolated urticaria, patients with moderate to severe VIT-induced anaphylaxis more frequently had a history of severe index-sting related anaphylactic reactions.* Previous studies did not confirm a significant association between the severity of index sting-related anaphylaxis and the incidence and/or the severity of VIT-induced reactions [4, 6, 7, 9, 10, 12].

2. *Patients with moderate to severe VIT-induced anaphylaxis had a higher median baseline serum tryptase concentration than patients with isolated cutaneous reactions.* An elevation of the baseline serum tryptase level is significantly associated with an increased risk of severe and life-threatening anaphylaxis to Hymenoptera stings [32–35]. Previous studies likewise suggest an association with the incidence and the severity of VIT-induced anaphylactic reactions [4, 15, 16].
3. *Moderate to severe anaphylactic reactions were most frequent during honeybee VIT.* Regardless of their severity, treatment-induced anaphylactic reactions are more frequent during honeybee VIT compared to *Vespula* VIT [4, 6–9, 11, 12, 14]. Older studies additionally suggest a risk of more severe anaphylaxis during honeybee VIT [6, 9, 12].
4. *The median time interval between the preceding injection and the onset of allergic symptoms was shorter if the VIT-induced anaphylactic reaction was severe.* A short latency time before the onset of symptoms is considered to be indicative of severe and life-threatening reactions during immunotherapy with inhalative allergens [24, 27, 29, 36]. This has likewise been observed in the context of Hymenoptera field stings [35, 37] and intentional sting challenges [38]).
5. *Patients with moderate to severe VIT-induced anaphylaxis were more likely to experience mere flushing or no cutaneous symptoms at all than to develop generalized urticaria.* The absence of urticaria has been identified as a characteristic of severe sting-induced anaphylaxis with predominating cardiovascular symptoms [35, 37, 39]. Amin et al. described an absence of cutaneous involvement in 30 % of life-threatening and in 81 % of fatal anaphylactic reactions during immunotherapy with inhalative allergens [36].

The use of a uniform classification system for VIT-induced anaphylaxis is required

Current anaphylaxis grading systems including the system according to Ring [22] are of limited value for classification of immunotherapy-induced anaphylaxis as obvious exposure to a known allergen generally permits early treatment in this particular situation. Over the last decades, a number of grading systems for anaphylactic reactions to immunotherapy have been proposed; but none have been globally accepted [10, 28, 29]. The WAO subcutaneous immunotherapy systemic reaction grading system proposed in 2010 has hitherto been mainly used to classify anaphylactic reactions to immunotherapy with inhalative allergens [24, 27] (Table 2). We consider it suitable for classification of VIT-related objective reactions. In addition to the final grading, the WAO system

provides information on the time course of treatment-related allergic reactions, hereby facilitating the differentiation between anaphylaxis in the strict sense and any delayed allergic reactions. In our experience, standardized documentation of whether or not and when epinephrine was administered as proposed by the WAO is not necessary in the context of VIT because most reactions do not require catecholamine treatment. The use of a uniform classification system for VIT-induced systemic reactions is a prerequisite to define risk factors not only for their general incidence, but for the exceptionally severe anaphylactic reactions in a multicentre approach.

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