

- analysis of a cohort of 1058 patients. *J Intern Med.* 2015;277(5):585-593.
5. Zingale LC, Beltrami L, Zanichelli A, et al. Angioedema without urticaria: a large clinical survey. *CMAJ.* 2006;175(9):1065-1070.
 6. Du-Thanh A, Raison-Peyron N, Drouet C, Guillot B. Efficacy of tranexamic acid in sporadic idiopathic bradykinin angioedema. *Allergy.* 2010;65(6):793-795.
 7. Cicardi M, Bergamaschini L, Zingale LC, Gioffré D, Agostoni A. Idiopathic nonhistaminergic angioedema. *Am J Med.* 1999;106(6):650-654.

8. Bucher MC, Petkovic T, Helbling A, Steiner UC. Idiopathic non-histaminergic acquired angioedema: a case series and discussion of published clinical trials. *Clin Transl Allergy.* 2017;31(7):27.
9. Wintenberger C, Boccon-Gibod I, Launay D, et al. Tranexamic acid as maintenance treatment for non-histaminergic angioedema: analysis of efficacy and safety in 37 patients. *Clin Exp Immunol.* 2014;178(1):112-117.

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Lessons from times of shortage: Interchangeability of venom preparations and dosing protocols

To the Editor,

The 2016/2017 venom shortage due to a manufacturing delay affecting products of a leading supplier persisted for several months and had an international impact. Suggested coping strategies included (a) economic use of venom preparations (eg, dose reduction, extension of injection intervals) and (b) change of suppliers.¹ Option one depends on a reserve stock of the products at shortage, leaving strategy two as the only way to deal with an extended loss of production. There is, however, a paucity of studies assessing the interchangeability of venom preparations, and concerns were raised regarding potential differences in standardization and allergenic potency. Temporary dose reductions of 25%-50% were recommended in order to minimize the risk of anaphylactic side effects upon change of venom preparations during ongoing venom immunotherapy (VIT).¹

The Allergy Center Mainfranken, a tertiary referral center, has used ALK venoms as the in-house standard for many years and was significantly affected by the shortage situation. We retrospectively describe a cohort of 102 patients who presented for VIT buildup in the course of 2017. During the shortage, the aqueous venom preparation Venomil™ (Bencard Allergie GmbH, München, Germany) was used for inpatient VIT buildup according to a standardized 3-day rush protocol comprising 9 injections and a total dose of 301.1 µg, which has been established for ALK-lyophilisiert SQ™ (ALK-Abelló, Hamburg, Germany) as the in-house standard.² A limited reserve stock of ALK-lyophilisiert SQ™ was used for children and putative high-risk cases (see Figure S1 for triage algorithm). All patients were subsequently switched to VIT maintenance with ALK-depot SQ™ (ALK-Abelló), a sufficient amount of which remained available throughout the shortage. Following buildup with Venomil™, the first depot injection was split into two equal doses of 50 µg given within 30 minutes. Patients treated with ALK-lyophilisiert SQ™ received a single dose of 100 µg. The severity of anaphylaxis was graded as mild, moderate, or severe as described previously.² Unspecific complaints during VIT buildup (eg, pruritus, dizziness, anxiety) were categorized as "subjective" as long as they were not accompanied by

TABLE 1 Patient cohort

	Total n = 102 (%)	ALK™ n = 58 (%)	Venomil™ n = 44 (%)	P-value*
<i>Vespula</i> VIT	81 (79.4)	41 (70.7)	40 (90.9)	0.014
Honeybee VIT	21 (20.6)	17 (29.3)	4 (9.1)	
Median age (y) (IQR)	51 (21)	53 (20.5)	48 (22.2)	0.174
Sex				
Male	57 (55.9)	35 (60.3)	22 (50.0)	0.321
Female	45 (44.1)	23 (39.7)	22 (50.0)	
Anaphylaxis at index sting				
Mild	19 (18.6)	8 (13.8)	11 (25.0)	
Moderate	51 (50.0)	20 (34.5)	31 (70.5)	
Severe	32 (31.4)	30 (51.7)	2 (4.5)	<0.001
Concurrent disease				
Cardiovascular	43 (42.2)	32 (55.2)	11 (25.0)	0.003
Pulmonary	13 (12.7)	7 (12.1)	6 (13.6)	1.00
Cardiovascular medication				
Any	37 (36.3)	29 (50.0)	8 (18.2)	0.001
ACE inhibitor	12 (11.8)	9 (15.5)	3 (6.8)	0.224
β blocker	15 (14.7)	14 (24.1)	1 (2.3)	0.002
Tryptase concentration ^a				
Median (µg/L) (IQR)	4.7 (4.3)	4.5 (5.2)	4.9 (3.3)	0.466
≥10.0 µg/L	13 (16.0)	10 (19.2)	3 (10.3)	0.360
≥20.0 µg/L	3 (3.7)	3 (5.8)	0 (0.0)	0.549
Total IgE				
Median (kU/L) (IQR)	64.3 (120.5)	77.7 (177.3)	61.9 (85.6)	0.643
≥100 kU/L	37 (36.3)	25 (43.1)	12 (27.3)	0.145

*Significant P-values are printed bold.

^aTryptase concentrations were available in a subgroup of 81 patients (Venomil™ group: 29 patients; ALK™ group: 52 patients) including all patients with severe anaphylactic index sting reactions.

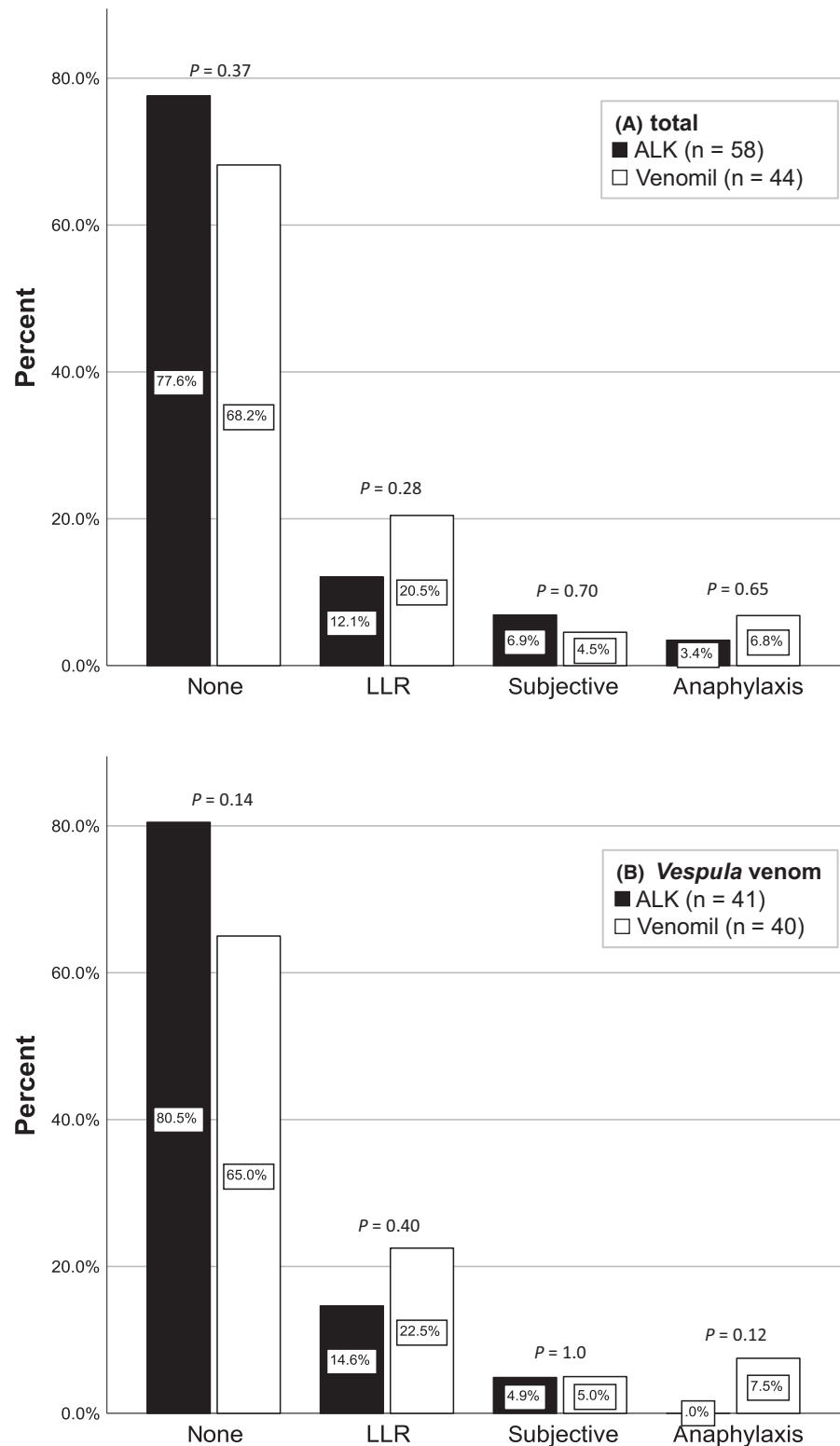


FIGURE 1 Side effects of venom immunotherapy (VIT) buildup according to a standardized 3-d rush protocol using aqueous venom preparations as supplied by ALK-Abelló (ALK-lyophilisiert SQ™) or Bencard (Venomil™). A, All cases including honeybee as well as *Vesputa* VIT (n = 102); B, *Vesputa* VIT only (n = 81). LLR, large local reaction (redness and swelling exceeding 10 cm and persisting for more than 24 h)

objective symptoms of anaphylaxis. SPSS 25.0 for Windows (SPSS Inc., Chicago, IL) was used for statistical analyses. Interval-scaled data were compared using the Mann-Whitney test; the Chi-squared test was conducted for categorical data. All tests were 2-tailed; *P*-values < 0.05 were considered significant.

Clinical baseline data are depicted in Table 1. 58 (56.9%) patients underwent honeybee or *Vesputa* VIT buildup with ALK-lyophilisiert

SQ™, and Venomil™ was used in 44 (43.1%) cases. The overall predominance of *Vesputa* venom allergic patients (79.4%) was significantly more pronounced in the Venomil™ group (90.9%, *P* = 0.014). As a consequence of the process of triage, patients treated with ALK-lyophilisiert SQ™ had more severe index sting reactions (*P* < 0.001) and were more likely to suffer from cardiovascular disease (*P* = 0.003) and to take antihypertensive medication (*P* = 0.001).

Side effects of VIT buildup are depicted in Figure 1 (see Table S1 for details). There was a tendency toward an increased incidence of large local reactions (Venomil™ 20.5%, ALK-lyophilisiert SQ™ 12.1%, $P = 0.28$) and systemic anaphylactic reactions (Venomil™ 6.8%, ALK-lyophilisiert SQ™ 3.4%, $P = 0.65$) in the Venomil™ group, which was more pronounced if only buildup cycles using *Vespula* venom were evaluated, but did not reach statistical significance. Regardless of the culprit venom, systemic anaphylaxis during VIT buildup was invariably mild ($n = 4$) to moderate ($n = 1$) and promptly responded to treatment with intravenous antihistamines alone ($n = 3$) or combined with prednisolone ($n = 2$). The five patients with anaphylactic side effects invariably tolerated subsequent dose increase; the 100 µg maintenance dose was reached within the ongoing inpatient treatment in two cases and according to a modified outpatient protocol using the depot preparation in the remaining three. Transition from aqueous Venomil™ to aluminum hydroxide-adsorbed ALK-depot SQ™ was tolerated without symptoms in all 44 patients.

In addition to standard aqueous venom solutions (including Venomil™), so-called “purified” preparations (ALK-lyophilisiert SQ™) which may additionally contain aluminum hydroxide (ALK-depot SQ™) are available on the European market.^{3,4} All licensed products are derived from pure venom, but little information is available regarding specific downstream processing strategies applied by different manufacturers.⁵ A superior safety profile has been attributed to both aluminum hydroxide-adsorbed depot preparations⁶ and “purified” venoms^{3,6,7} which are claimed to be virtually free of low molecular weight components.⁴ Purification of bee venom, however, might entail an underrepresentation of certain allergens and thus increase the risk of treatment failure.⁵ While our study is likewise suggestive of a superior clinical tolerability of “purified” ALK-lyophilisiert SQ™ in the context of inpatient rush buildup, we were not able and did not aim to statistically compare safety profiles of different venom preparations (patients were not randomized into the two treatment groups, but sorted according to a process of triage). Our data, however, allow for some descriptive observations and may thus serve as an orientation in future shortage situations.

- No severe side effects were observed in 102 cycles of VIT buildup according to a standardized 3-day rush dose increase schedule,² implying that the protocol is reasonably safe regardless of the venom used. The risk of IgE-mediated side effects during VIT buildup depends on the number of injections and cumulative daily doses applied.⁸ Rush protocols proposed by different manufactures considerably differ, though there is no reason for product-specific, diverging recommendations from an immunological or clinical point of view. A product-independent harmonization of buildup schedules would be very helpful to facilitate the interchange of venom preparations in shortage situations and permit comparability of data.
- The change of suppliers during transition from buildup with Venomil™ to maintenance with ALK-depot SQ™ was invariably tolerated without any side effects. Our findings are in accordance with previous observations from a series of *Vespula* venom allergic patients who received Venomil™ for VIT buildup

and were subsequently switched to ALK-depot SQ™ without any dose adjustment.⁹ We conclude that switching to a venom of a presumably higher grade of “purification” is reasonably safe. Extra precautions might be appropriate if “purified” venoms are replaced by potentially more allergenic preparations during ongoing VIT.

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CONFLICTS OF INTEREST

AT reports personal fees from ALK-Abelló. JS has no conflict of interest.

Keywords

buildup, Hymenoptera, immunotherapy, maintenance, *Vespula*

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REFERENCES

1. Golden DB, Bernstein DI, Freeman TM, Tracy JM, Lang DM, Nicklas RA. AAAAI/ACAAI joint venom extract shortage task force report. *J Allergy Clin Immunol Pract*. 2017;5(2):330-332.
2. Stoevesandt J, Hosp C, Kerstan A, Trautmann A. Safety of 100 µg venom immunotherapy rush protocols in children compared to adults. *Allergy Asthma Clin Immunol*. 2017;13:32.
3. Sturm GJ, Varga EM, Roberts G, et al. EAACI guidelines on allergen immunotherapy: hymenoptera venom allergy. *Allergy*. 2018;73(4):744-764.
4. 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.
5. Blank S, Etzold S, Darsow U, et al. Component-resolved evaluation of the content of major allergens in therapeutic extracts for specific immunotherapy of honeybee venom allergy. *Hum Vaccin Immunother*. 2017;13(10):2482-2489.
6. Bilò MB, Antonicelli L, Bonifazi F. Purified vs. nonpurified venom immunotherapy. *Curr Opin Allergy Clin Immunol*. 2010;10(4):330-336.
7. Bilò MB, Severino M, Cilia M, et al. The VISYT trial: venom immunotherapy safety and tolerability with purified vs nonpurified extracts. *Ann Allergy Asthma Immunol*. 2009;103(1):57-61.

8. Brehler R, Wolf H, Kütting B, Schnitker J, Luger T. Safety of a two-day ultrarush insect venom immunotherapy protocol in comparison with protocols of longer duration and involving a larger number of injections. *J Allergy Clin Immunol*. 2000;105(6 Pt 1):1231-1235.
9. Worm M. Verträglichkeit der spezifischen Immuntherapie während der Umstellung von lyophilisiertem Wespengift auf ein Depotpräparat. *Allergologie*. 2009;32(4):143-145.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Untreated allergic rhinitis is a major risk factor contributing to motorcar accidents

To the Editor,

Allergic rhinitis is a common allergic disease with increasing prevalence, recent estimates suggesting an incidence in excess of 30% of individuals in the European Union.^{1,2} While often trivialized, allergic rhinitis is crucially linked to impairments in information processing and changes in attention-related cognitive processes.³ This has a measurable impact on performance at work or school but an under-investigated implication is the effect of untreated allergic rhinitis on driving motor vehicles.

A recent study has assessed the effect of nasal provocation of seasonal allergic patients on driving performance.⁴ The results showed that when individuals were symptomatic and untreated, their driving ability was significantly impaired. When engaging in a secondary memory task during driving, their performance deteriorated further. The magnitude of impairment was relevant and comparable to that seen with a blood alcohol level of 0.5%, the legal limit in many countries.⁴

While this is an excellent clinical study, it does not necessarily represent the real-life situation in chronic disease where sleep disturbances may exacerbate impairment of psychomotor performance, including driving.⁵⁻⁷ We now present the results of a real-life survey of 513 regular car drivers with seasonal allergic rhinitis on the effect of their disease on their ability to drive and the measurements they took to reduce the possibility of accidents.

Initiated and funded by the company autoscout24, Berlin, Germany, a nationwide survey was performed in Germany involving a representative sample of 513 regular car drivers who suffered from seasonal allergic rhinitis. The group comprised 262 males and 251 females between the ages of 18 and 65. The drivers were asked three questions by trained interviewers by telephone. In the questions, rather than using the term seasonal allergic rhinitis, the German term "hay fever" was used, which is the commonly known term in that country. In addition to counting the number of respondents for each answer, the replies were divided into sex and into age groups 18-29, 30-39, 40-49 and 50-65 years.

The first question asked was "Do you think that hay fever impairs your ability to drive?" More than three quarters of the respondents said that it did with 13% saying that it is sometimes so

bad that they have to refrain from driving (Figure 1). There was no significant sex or age difference between the answers.

The second question asked was "Have you ever had an accident attributed to your hay fever or have you ever experienced a near-accident situation which can be attributed to this?" To this question, 36 respondents (7%) replied yes, they had. Interestingly, approximately twice as many men than women and twice as many respondents under rather than over 40 years old responded yes to this question.

The third question asked was "What measures do you take to relieve your hay fever symptoms while driving?" Multiple answers were allowed here. The results (Figure 2) showed that while the majority (57%) of respondents kept the windows and roof closed while driving, it is surprising that less than half took anti-allergic drugs, such as H₁-antihistamines, or turned the air conditioning to recirculating before driving. Furthermore, 46 respondents (9%) did nothing to relieve their hay fever symptoms before driving. The only sex difference in these answers was that more men than women equipped their car with a pollen filter. With regard to age, fewer of the younger age group kept their windows and roof closed or equipped their car with a pollen filter than the other age groups. However, this younger age group were more likely to take anti-allergic drugs than their older counterparts.

The primary findings of this survey are that more than three quarters of the individuals with seasonal allergic rhinitis interviewed replied that their disease bothered them when driving and 7% stated their disease had contributed to an accident or near-accident situation. However, less than half took drug therapy to relieve their symptoms before driving.

The figure of 7% of the respondents reporting an accident or near-accident situation may seem small, but is it? Approximately 60% of the 500 million people living in the European Union hold a valid driving licence.⁸ If it is assumed that around one-third of these 300 million citizens has seasonal allergic rhinitis then that gives a figure approximately 7 000 000 accidents or near accidents. All of these could have been prevented by appropriate treatment as detailed in the ARIA guidelines.⁹

Almost as disturbing is that 60% of respondents failed to take pharmacotherapy to relieve their symptoms before driving. This is

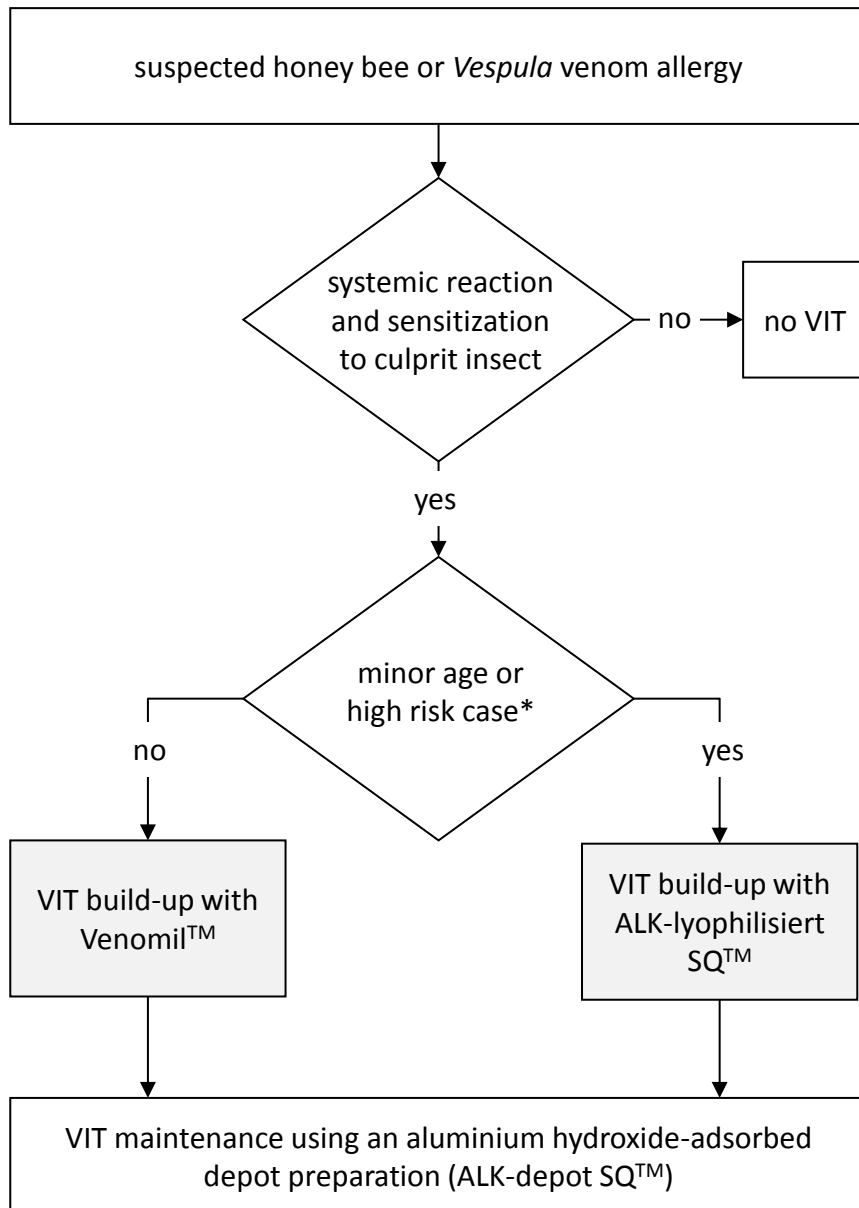


TABLE S1 Side effects of venom immunotherapy and their treatment

	ALK-Iyophilisiert SQ™			Venomil™		
	total (%)	<i>Vespula</i> (%)	bee (%)	total (%), <i>P</i> -value ¹	<i>Vespula</i> (%), <i>P</i> -value ¹	bee (%), <i>P</i> -value ¹
side effect						
none	45 (77.6)	33 (80.5)	12 (70.6)	30 (68.2), .37	26 (65.0), .14	4 (100.0), .53
large local reaction ²	7 (12.1)	6 (14.6)	1 (5.9)	9 (20.5), .28	9 (22.5), .40	0 (0.0), 1.0
subjective	4 (6.9)	2 (4.9)	2 (11.8)	2 (4.5), .70	2 (5.0), 1.0	0 (0.0), 1.0
anaphylaxis	2 (3.4)	0 (0.0)	2 (11.8)	3 (6.8), .65	3 (7.5), .12	0 (0.0), 1.0
treatment						
not required	49 (84.5)	35 (85.4)	14 (82.4)	36 (81.8), .79	32 (80.0), .57	4 (100.0), 1.0
oral antihistamine	3 (5.2)	3 (7.3)	0 (0)	5 (11.4), .29	5 (12.5), .48	0 (0.0), ND
iv antihistamine	6 (10.3)	3 (7.3)	3 (17.6)	1 (2.3), .14	1 (2.5), .62	0 (0.0), 1.0
iv antihistamine + steroid	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.5), .18	2 (5.0), .24	0 (0.0), ND

¹*P*-values refer to comparison of respective ALK™ and Venomil™ groups

²local redness and swelling exceeding 10 cm and persisting for more than 24 hours

ND, not determinable

FIGURE S1 Triage algorithm assigning patients to VIT build-up with ALK-lyophilisiert SQTM (in-house standard) or VenomilTM (alternative while standard at shortage).

*serum tryptase value exceeding 20 µg/L, age ≥ 65 years, significant cardiovascular comorbidities, and honeybee venom allergy were considered indicators of high risk. Minor age, though not a risk factor for treatment-related adverse events, was considered a reason to provide standard treatment.

VIT, venom immunotherapy