

Patients still reacting to a sting challenge while receiving conventional Hymenoptera venom immunotherapy are protected by increased venom doses

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Background: Up to 20% of patients allergic to Hymenoptera venom are not protected by conventional venom immunotherapy (VIT) with 100 µg of any single venom.

Objective: We sought to evaluate the efficacy of an increased venom dose in patients allergic to Hymenoptera venom still reacting systemically to a sting challenge despite immunotherapy with 100 µg of venom every 4 weeks.

Methods: In this retrospective study patients were included who still had reacted systemically to a sting challenge with a living bee or wasp despite VIT with a maintenance dose of 100 µg every 4 weeks. The maintenance dose was increased to 150 or 200 µg every 4 weeks, and a second sting challenge was performed. If a patient reacted again, the dose was further increased. Baseline mast-cell tryptase levels were assessed by using a fluoroenzyme immunoassay in stored patient sera.

Results: While receiving a maintenance dose of 100 µg of venom every 4 weeks for 7 to 38 months, 18 patients reacted systemically to a bee sting and 22 reacted to a wasp sting. After an increase of the maintenance dose to 150 µg, 2 of 4 patients allergic to bee venom (BV) and 6 of 6 patients allergic to yellow jacket venom (YJV) no longer reacted systemically to the sting challenge. The respective rates of full protection were 13 of 14 and 15 of 16 in patients with an increase of the maintenance dose to 200 µg from the start. Of those 4 individuals not protected by the first dose increase, one patient allergic to BV (prior dose of 150 µg) and one patient allergic to YJV (prior dose of 200 µg) did not react systemically to a further sting challenge while receiving 200 µg of BV or 250 µg of YJV, respectively. One patient allergic to BV who had a systemic reaction to the sting challenge while receiving 150 µg was not protected after a dose increase to 200 µg; she later received a dose of 400 µg of BV, and no further sting challenge was performed. The patient allergic to BV who still reacted systemically after a first dose increase to 200 µg was a female patient with urticaria pigmentosa. She had repeated systemic adverse

reactions to further BV immunotherapy, necessitating discontinuation of the treatment; however, she tolerated well VIT with 200 µg of YJV. In all other patients, no unusual adverse reactions to the increased venom doses were observed. Baseline serum tryptase levels were elevated above 13.5 µg/L (95th percentile in normal subjects) in 9 (28.1%) of 32 patients.

Conclusions: The majority of patients allergic to Hymenoptera venom who still reacted systemically to a sting challenge despite VIT with a dose of 100 µg every 4 weeks can be fully protected by an increased maintenance dose. This dose increase is well tolerated by most patients. The rather high proportion of patients with elevated baseline serum tryptase levels necessitates further investigation of a possible association between mastocytosis and treatment failure of conventionally dosed VIT. (*J Allergy Clin Immunol* 2001;108:1027-32.)

Key words: Hymenoptera venom allergy, venom immunotherapy, sting challenge, treatment failure, venom dose

In central Europe nearly exclusively stings of honey bees (*Apis mellifera*) or yellow jackets (*Vespula germanica* and *Vespula vulgaris*) lead to systemic anaphylactic sting reactions. Venom immunotherapy (VIT) is highly effective in preventing further systemic anaphylactic sting reactions in patients with Hymenoptera venom allergy. However, protection is not achieved in all patients by using the usual regimen. The percentage of patients not protected at re-stings varies significantly between different studies. Some authors found all patients were protected at sting challenge.^{1,2} However, in the majority of studies reporting larger numbers of patients, 2.4%³ to 20.4%⁴ of those allergic to bee venom (BV) or yellow jacket venom (YJV) were not protected by VIT and still reacted systemically to a sting challenge.³⁻⁷ The differences between these studies with respect to the treatment efficacy seem to be mainly related to patient selection (eg, the percentage of patients treated with BV or YJV, age, severity of previous sting reactions, and different indications for treatment).

The further treatment of patients found to be not protected by VIT at a re-sting is of major importance. In one such patient it has been shown that an increase of the maintenance dose can provide full protection.⁸ Also, in patients with test parameters suspected to predict reduced treatment efficacy^{7,8} or routinely from the start of VIT,^{7,9} increased venom doses were used with success.

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Abbreviations used

BV: Bee venom
VIT: Venom immunotherapy
YJV: Yellow jacket venom

It is part of our clinical routine to perform a sting challenge test in patients receiving VIT because this is the only method to recognize treatment failures.¹⁰ If a patient is found not to be fully protected by the usual treatment with 100 µg of venom every 4 weeks, the maintenance dose is increased. Here we report on the outcome in such patients, which was assessed with further sting challenges.

METHODS**Patients with Hymenoptera venom allergy**

Patients included had a history of a systemic anaphylactic reaction after a bee or yellow jacket sting. Severity was graded as follows¹¹: mild, only generalized skin reactions (severity grade 1); moderate, respiratory, cardiovascular, and/or gastrointestinal symptoms without signs of shock (severity grade 2); severe, full shock (severity grade 3). Threshold skin prick testing was done with BV (*Apis mellifera*) and YJV (*Vespula* species: *V vulgaris*, *V germanica*, *V pensylvanica*, *V maculifrons*, *V flavopilosa*, and *V squamosa*; Reless; ALK Scherax, Hamburg, Germany) at incremental concentrations of 0.1, 1.0, 10.0, and 100 µg/mL; if prick tests yielded no reaction, intradermal testing with 1.0 µg/mL venom was performed. Specific IgE antibodies in the serum to BV and YJV were initially determined by using Phadebas-RAST and then by using CAP-FEIA (Pharmacia & Upjohn, Freiburg, Germany).

Venom immunotherapy

Patients were treated with a lyophilized BV (*A mellifera*) or *Vespula* species (*V vulgaris*, *V germanica*, *V pensylvanica*, *V maculifrons*, *V flavopilosa*, and *V squamosa*) preparation (Reless, ALK Scherax). Dose increase was performed according to a rush protocol.¹² In brief, starting with a 100-fold lower concentration than that determined as eliciting the skin threshold test reaction, up to 5 injections of incremental venom doses were given daily on an in-patient basis. Usually, after 5 to 7 days of treatment, the maintenance venom dose of 100 µg was reached, and the patients were treated further with gradually increasing injection intervals until 100 µg of venom was injected every 4 weeks. After a nontolerated sting challenge, a dose increase was carried out after all symptoms had completely resolved and not earlier than 2 days after the reaction. Details of the dose increase to 150 or 200 µg are given in Table I. If a higher dose was necessary, the increase was carried out similarly in an individual way. Final maintenance doses were administered every 4 weeks.

Sting challenge tests

Sting challenge tests were performed with a living bee or yellow jacket, as described previously.¹⁰ In brief, the patients were hospitalized, and after exclusion of contraindications, they received the sting of a living bee or yellow jacket while being closely monitored under emergency department conditions. Reactions were documented and treated if necessary. In those who received treatment, the natural course of symptoms might have been more severe.

Selection of patients

From their files, all patients were selected who fulfilled the following criteria: patients allergic to BV, YJV, or both receiving a sting challenge test between May 1990 and September 1996 while

receiving a venom maintenance dose of 100 µg every 4 weeks; systemic anaphylactic reaction to the sting challenge; subsequent increase of the treatment dose; and second sting challenge while being treated with an elevated maintenance dose.

Measurement of mast-cell tryptase

If available, sera that had been kept frozen at -20°C after preparation from blood samples drawn apart from sting reactions were used to measure baseline mast-cell tryptase concentrations with a fluoroenzyme immunoassay (Unicap Tryptase; Pharmacia & Upjohn, Freiburg, Germany). Duplicate measurements were performed if the tryptase concentration was greater than 10 µg/L; in this case the mean value was considered. The assay detects both α- and β-tryptase. Tryptase levels of greater than 13.5 µg/L (95th percentile in normal control subjects) were considered to be elevated.

RESULTS

Forty patients (20 men and 20 women; 19-72 years old at the start of VIT) were included. The most severe sting reaction before VIT had been mild in 8 (20.0%), moderate in 8 (20.0), and severe in 24 (60.0%) patients. Sensitization to the eliciting venom could be shown by means of skin tests, assessment of venom-specific IgE antibodies, or both in all patients (Table II). According to history and test results, 13 patients were treated with BV, 18 with YJV, and 9 with both BV and YJV. A systemic reaction to the first sting challenge while receiving a maintenance dose of 100 µg of venom every 4 weeks for 7 to 38 months occurred in 18 patients to a bee sting and in 22 patients to a wasp sting. Fifteen (83.3%) of 18 reactions to BV had been mild, 2 (11.1%) of 18 had been moderate, and 1 (5.6%) of 18 had been severe. Reactions to YJV had been mild in 12 (54.5%) of 22, moderate in 8 (36.4%) of 22, and severe in 2 (9.1%) of 22 patients.

Repeated bee-sting challenges

Data on repeated bee-sting challenges are shown in Fig 1. In 4 patients with systemic reactions to the first bee-sting challenge, VIT was continued with a dose of 150 µg of BV. After 13 to 42 months, the sting challenge was repeated, again causing systemic symptoms in 2 of 4 patients. In 14 patients reacting systemically to the first bee-sting challenge, the dose was increased to 200 µg of BV. When the sting challenge was repeated after 10 to 28 months, 13 of 14 patients were found to be protected, and one still reacted systemically.

Both patients not protected by 150 µg of BV began receiving a maintenance dose of 200 µg. When challenged again after 13 months, one was found to be protected, whereas the other again had a severe systemic reaction. In this patient the maintenance dose was increased to 400 µg because she had experienced severe reactions and had urticaria pigmentosa. VIT with 400 µg of BV was well tolerated and has been continued since then. A further sting challenge was not done.

In the patient not protected while receiving 200 µg of BV, a further increase of the dose was intended, but she started to have repeated, partially severe systemic reactions. This patient had histologically confirmed urticaria pigmentosa and also had a slight increase of mast cells in

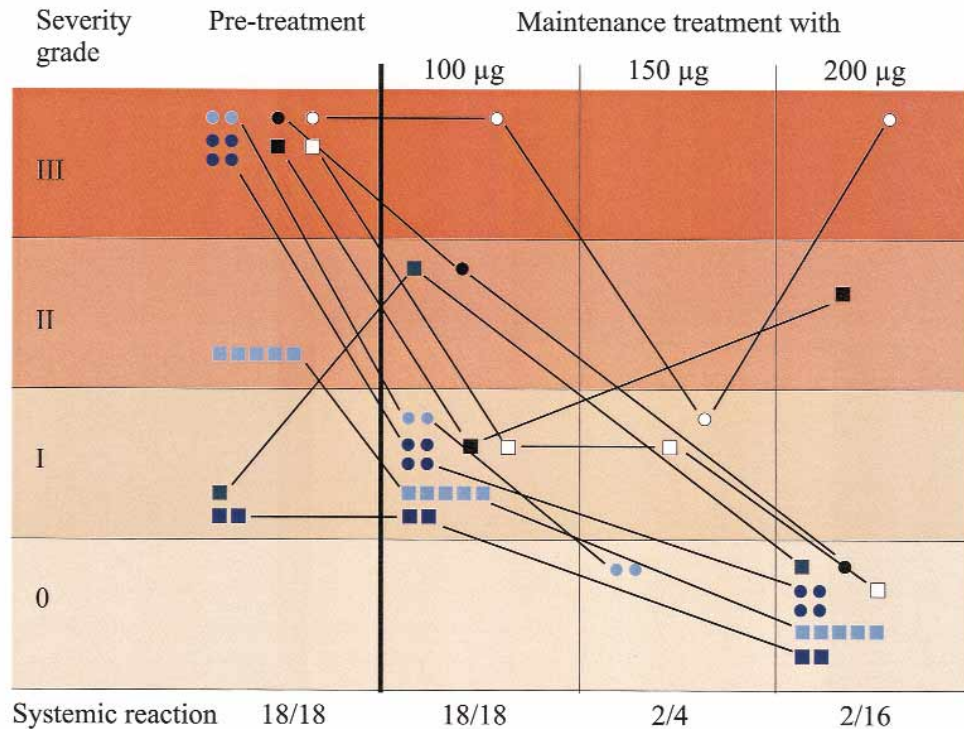


FIG 1. Severity grade of sting reaction of patients allergic to BV: pretreatment reaction and results of sting challenges during VIT.

the bone marrow. Premedication with antihistamines or corticosteroids did not improve the tolerance of treatment, and BV immunotherapy had to be stopped because she eventually had systemic reactions to gradually diminished BV doses as low as 50 µg. This patient also was allergic to YJV and had reacted systemically to a yellow jacket–sting challenge while receiving VIT with 100 µg of YJV; YJV immunotherapy with an increased dose of 200 µg was well tolerated, but she did not agree to a second yellow jacket–sting challenge.

With the exception of the above patients, the BV dose increase was well tolerated. There was only one other patient who experienced a single mild systemic reaction, and 2 patients had single occurrences of subjective systemic symptoms, such as palmoplantar itching or shivering.

Repeated yellow jacket–sting challenges

Data on repeated yellow jacket–sting challenges are shown in Fig 2. The YJV dose was increased to 150 µg in 6 patients and to 200 µg in the remaining 16 patients. At the second yellow jacket–sting challenge performed after 12 to 24 months, only one of the patients, who was receiving a YJV maintenance dose of 200 µg, again experienced a systemic reaction. In this patient the YJV dose was raised to 250 µg, and no systemic sting reaction occurred when she was challenged again after a further 12 months of immunotherapy with 250 µg of YJV.

The YJV dose increase caused single mild or moderate reactions in each patient, and another patient reported a single occurrence of subjective systemic symptoms.

TABLE I. Treatment protocol for dose increase

Dose (µg)	Day	Hour
100	1	0
20		0.5
120		2
30		2.5
150	2	0
20		0.5
170		2
30		2.5
200	3	0*

*If no systemic reaction occurred, the patient was discharged 3 hours later.

Baseline serum tryptase levels

Sera from 32 patients were available. Baseline serum tryptase levels of greater than 13.5 µg/L were found in 9 (28.1%) patients, ranging from 14.0 to 47.8 µg/L (Table II). In the patients allergic to BV with urticaria pigmentosa, the tryptase concentrations were 26.6 or 22.3 µg/L, respectively.

DISCUSSION

In this retrospective study nearly all patients who had still reacted systemically to a sting challenge while receiving VIT with a maintenance dose of 100 µg of venom every 4 weeks were found to be protected after an increase of the treatment dose.

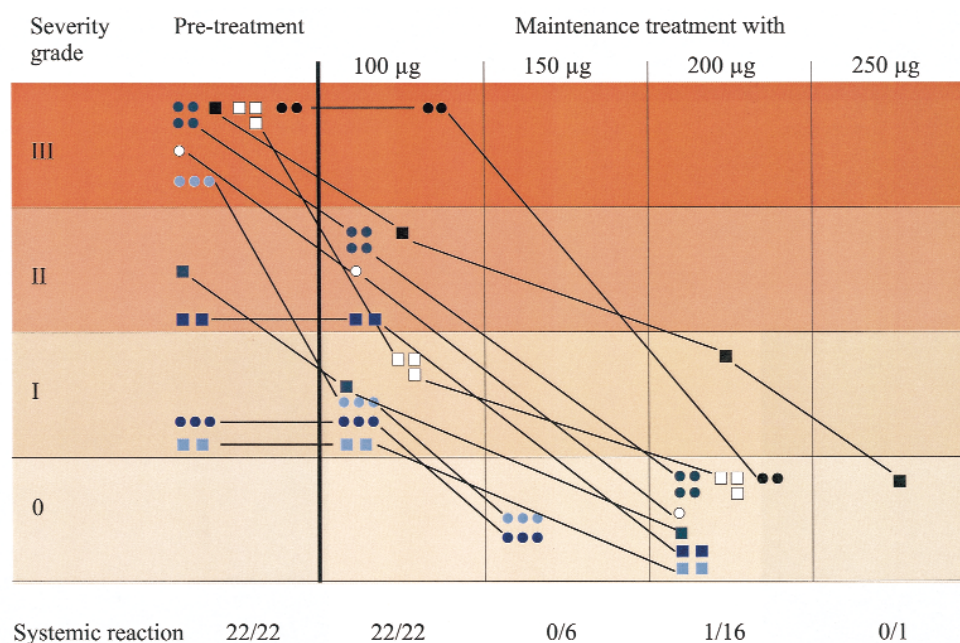


FIG 2. Severity grade of sting reaction of patients allergic to YJV: pretreatment reaction and results of sting challenges during VIT.

TABLE II. Characteristics of patients with systemic anaphylactic sting reactions (n = 40)

	BV allergy	YJV allergy
n	18	22
Age range (y)	19-67	25-72
M/F ratio	11:7	9:13
Additional VIT with "other" venom	5	4
Most severe symptoms of previous sting reactions		
Mild	3 (16.7%)	5 (22.7%)
Moderate	5 (27.8%)	3 (13.6%)
Severe	10 (55.5%)	14 (63.7%)
Pretreatment skin test reaction to Hymenoptera venom used for VIT		
id: 0.1 µg/mL	2	0
Prick: 100 µg/mL	3	7
10 µg/mL	8	10
1 µg/mL	4	1
0.1 µg/mL	1	3
Not available		1
Pretreatment specific serum IgE antibodies to venom used for VIT		
Class 0	1	3
Class 1-2	8	8
Class 3-4	7	9
Class 5-6	2	
Not available		2
Baseline serum tryptase levels		
<13.5 µg/L	7	16
≥13.5 µg/L	6 (14.0, 16.1, 16.3, 16.4, 22.3, 26.6)	3 (15.1, 21.3, 42.5)
Not available	5	3

Most patients tolerated this regimen without notable adverse reactions. Only one patient, who had reacted systemically to the sting challenge while receiving 200 µg of BV, had repeated, partially severe reactions to further VIT with BV. Eventually, BV immunotherapy had to be stopped because despite premedication with antihista-

mines or corticosteroids, she continued to react systemically also to gradually diminished BV doses as low as 50 µg. However, she tolerated well YJV immunotherapy with a maintenance dose of 200 µg. This patient also had urticaria pigmentosa and an elevated baseline serum tryptase level, and the increased number of mast cells in

mastocytosis may be held responsible for her intolerance of BV immunotherapy. If in patients with mastocytosis systemic reactions occur during VIT, they may be particularly severe and relapsing.^{13,14} However, in a series of 10 patients with mastocytosis who were allergic to Hymenoptera venom, VIT did not cause unusual adverse effects.¹⁵ In our study, apart from the patient not tolerating BV immunotherapy, there were 8 further individuals with elevated baseline serum tryptase levels who tolerated the venom dose increase without unusual side effects. As reported recently, increased baseline serum tryptase levels in patients with Hymenoptera venom allergy are mostly indicative of mastocytosis.¹⁶ In this retrospective study it was not possible to assess the patients with raised baseline serum tryptase levels for the presence of mastocytosis.

In this study we found a surprisingly high proportion of patients with elevated baseline serum tryptase levels. In a few patients with mastocytosis who were allergic to Hymenoptera venom,^{15,17} VIT was proved to be effective. However, our findings suggest a causal relationship between mast-cell disease and treatment failures of VIT. In a yet unpublished evaluation of 182 consecutive unselected patients receiving BV or YJV treatment and undergoing a sting challenge, we found elevated baseline serum tryptase levels in only 7.1% of the cases. The possible association between elevated baseline tryptase levels and failure of VIT needs further clarification in a prospective study. Elevated levels of baseline serum tryptase may indicate patients allergic to Hymenoptera venom who are at particular risk of severe reactions.^{16,18} Therefore we recommend measurement of baseline serum tryptase levels and exclusion of cutaneous mastocytosis in all patients with a history of systemic sting reactions.

In 4 patients allergic to BV and 6 patients allergic to YJV, the first dose increase was to 150 µg. With this maintenance dose, all patients with YJV allergy, but only half of the patients with BV allergy, were found to be protected when a second sting challenge was performed. In most patients the increase of the maintenance dose was to 200 µg from the start, which fully protected 13 of 14 patients with BV allergy and 15 of 16 patients with YJV allergy. At a third sting challenge, further increases of the maintenance dose to 200 µg of BV or 250 µg of YJV, respectively, were found to be effective in 2 patients. In all 22 patients with YJV allergy and in 16 of 18 patients with BV allergy, final protection proved by a sting challenge was achieved. These findings suggest that an increase of the maintenance dose is more successful in YJV than in BV allergy. A dose of 150 µg might be sufficient in most patients with failure of conventional YJV immunotherapy, whereas in BV allergy the first step of a dose increase should be 200 µg. However, because this was a retrospective study, further systematic investigations are necessary with regard to this issue.

There are 2 studies comparing the efficacy of VIT with different maintenance doses. Golden et al⁶ showed that 21.1% of 19 patients treated with 50 µg of Hymenoptera venom, but only 2.7% of 147 patients treated with 100

µg, again reacted systemically to a sting challenge. Müller et al,⁷ treating 119 patients allergic to BV with a maintenance dose of 100 µg and another 29 with an increased dose of 200 µg, found treatment failure rates of 26.1% or 10.3%, respectively, when sting challenges were performed. Irrespective of the absolute rate of protection, it is evident that higher maintenance doses are more efficient.

In the United States patients with allergy to various members of the Vespidae family are often treated with mixed vespoid venoms. This mixed vespoid venom includes equal amounts of 100 µg of YJV and each of 2 *Dolichovespula* venoms, resulting in a total dose of 300 µg. Because cross-reactivity to different vespoid venoms is frequent,¹⁹⁻²² this increased dose may enhance efficacy, and this could explain to a certain degree the differences of protection achieved by VIT in various studies. However, even a dose of 50 µg of any single venom was shown to be effective.^{6,23}

To our knowledge, up to now, only one patient was reported in whom the VIT dose was increased to achieve protection after failure of a lower dose.⁸ This increased maintenance dose of 200 µg of BV every 2 weeks was well tolerated and protected this patient from a further systemic reaction to a sting challenge. Also, in patients who had experienced repeated systemic adverse reactions to VIT, increase of the venom doses to 200 µg resulted in good tolerance of the treatment.⁸

Evidently, in some patients the response-modifying effect of VIT cannot be achieved with the routine 100-µg dose, and they need higher doses. Up to about 20% of patients with venom allergy treated with the conventional 100-µg dose have been found to be not protected at sting challenge.³⁻⁷ The use of increased maintenance doses from the start should be considered in certain patients who are at a particular risk of further stings because of intense exposures (eg, beekeepers, gardeners, and fruit sellers) or because of very severe anaphylactic reactions caused by older age,^{24,25} cardiovascular disease,^{26,27} or mastocytosis.^{14,16,18,28} Because VIT seems to be less effective in BV than in YJV allergy,⁷ a higher routine maintenance dose has to be considered, especially for patients with BV allergy.

In conclusion, the vast majority of patients allergic to Hymenoptera venom who still react to a sting while receiving conventional VIT at a dose of 100 µg every 4 weeks can be fully protected by an increased maintenance dose. This therapeutic regimen is well tolerated by most patients. VIT with an increased maintenance dose from the start should be considered in patients at particular risk of further Hymenoptera stings or of very severe sting reactions.

REFERENCES

1. Mosbech H, Malling H-J, Biering I, Böwadt H, Søborg M, Weeke B, et al. Immunotherapy with yellow jacket venom. *Allergy* 1986;41:95-103.
2. Nataf P, Guinépain MT, Herman D. Rush venom immunotherapy: a 3-day programme for hymenoptera sting allergy. *Clin Allergy* 1984;14:269-75.
3. Chipps BE, Valentine MD, Kagey-Sobotka A, Schuberth KC, Lichten-

- stein LM. Diagnosis and treatment of anaphylactic reactions to Hymenoptera stings in children. *J Pediatr* 1980;97:177-84.
4. Przybilla B, Ring J, Griebhammer B, Braun-Falco O. Schnellhyposensibilisierung mit Hymenopterengiften. Verträglichkeit und Therapieerfolg. *Dtsch Med Wochenschr* 1987;112:416-24.
5. Urbanek R, Forster J, Kuhn W, Ziupa J. Discontinuation of bee venom immunotherapy in children and adolescents. *J Pediatr* 1985;107:367-71.
6. Golden DBK, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Dose dependence of Hymenoptera venom immunotherapy. *J Allergy Clin Immunol* 1981;67:370-4.
7. Müller U, Helbling A, Berchtold E. Immunotherapy with honeybee venom and yellow jacket venom is different regarding efficacy and safety. *J Allergy Clin Immunol* 1992;89:529-35.
8. Bousquet J, Ménardo J-L, Velasquez G, Michel F-B. Systemic reactions during maintenance immunotherapy with honey bee venom. *Ann Allergy* 1988;61:63-8.
9. Bousquet J, Knani J, Velasquez G, Menardo JL, Guilloux L, Michel FB. Evolution of sensitivity to Hymenoptera venom in 200 allergic patients followed for up to 3 years. *J Allergy Clin Immunol* 1989;84:944-50.
10. Ruëff F, Przybilla B, Müller U, Mosbech H. The sting challenge test in Hymenoptera venom allergy. *Allergy* 1996;51:216-25.
11. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977;1:466-9.
12. Przybilla B, Ring J. Hyposensibilisierungsbehandlung der Hymenopterengiftallergie: Aspekte der Indikationsstellung und Dosierung. *Allergologie* 1986;9:2-10.
13. Kors JW, Van Doormaal JJ, De Monchy JGR. Anaphylactoid shock following Hymenoptera sting as a presenting symptom of systemic mastocytosis. *J Internal Med* 1993;233:255-8.
14. Oude Elberink JNG, de Monchy JGR, Kors JW, van Doormaal JJ, Dubois AEJ. Fatal anaphylaxis after a yellow jacket sting, despite venom immunotherapy, in two patients with mastocytosis. *J Allergy Clin Immunol* 1997;99:153-4.
15. Fricker M, Helbling A, Schwartz L, Müller U. Hymenoptera sting anaphylaxis and urticaria pigmentosa: clinical findings and results of venom immunotherapy in ten patients. *J Allergy Clin Immunol* 1997;100:11-5.
16. Ludolph-Hauser D, Ruëff F, Fries C, Schöpf P, Przybilla B. Constitutionally raised serum concentrations of mast cell tryptase and severe anaphylactic reactions to Hymenoptera stings. *Lancet* 2001;357:361-2.
17. Biedermann T, Ruëff F, Sander CA, Przybilla B. Mastocytosis associated with severe wasp sting anaphylaxis detected by elevated serum mast cell tryptase levels. *Br J Dermatol* 1999;146:1110-2.
18. Schwartz LB, Bradford TB, Rouse C, Irani A-M, Rasp G, van der Zwan JK, et al. Development of a new, more sensitive immunoassay for human tryptase: use in systemic anaphylaxis. *J Clin Immunol* 1994;14:190-204.
19. Findlay SR, Gillaspie JE, Lord R, Weiner LS, Grant JA. *Polistes* wasp hypersensitivity: diagnosis by venom-induced release of histamine in vitro. *J Allergy Clin Immunol* 1977;60:230-5.
20. Wicher K, Reisman RE, Wypych J, Elliot W, Steger R, Mathews RS, et al. Comparison of the venom immunogenicity of various species of yellow jackets (genus *Vespula*). *J Allergy Clin Immunol* 1980;66:244-9.
21. Reisman RE, Wypych JI, Mueller UR, Grant JA. Comparison of the allergenicity and antigenicity of *Polistes* venom and other vespid venoms. *J Allergy Clin Immunol* 1982;70:281-7.
22. Grant JA, Rahr R, Thueson DO, Lett-Brown MA, Hokanson JA, Yunginger JW. Diagnosis of *Polistes* wasp hypersensitivity. *J Allergy Clin Immunol* 1983;72:399-406.
23. Reisman RE, Livingston A. Venom immunotherapy: 10 years of experience with administration of single venoms and 50 µg maintenance doses. *J Allergy Clin Immunol* 1992;89:1189-95.
24. Lockey RF, Turkeltaub PC, Baird-Warren IA, Olive CA, Olive ES, Peppe BC, et al. The Hymenoptera venom study I, 1979-1982: demographics and history-sting data. *J Allergy Clin Immunol* 1988;82:370-81.
25. Przybilla B, Ring J. Hymenoptera venom allergy. In: Ring J, Przybilla B, editors. *New trends in allergy III*. Berlin: Springer; 1991. p. 335-49.
26. Müller UR. Insect sting allergy: clinical picture, diagnosis and treatment. Stuttgart: Gustav Fischer; 1990.
27. Mosbech H. Death caused by wasp and bee stings in Denmark 1960-1980. *Allergy* 1983;38:195-200.
28. Price LA, Safko M. Bee venom allergy in a patient with urticaria pigmentosa. *J Allergy Clin Immunol* 1987;79:407-9.