

Clinical aspects of allergic disease

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

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Three hundred twenty-four patients with a history of yellow jacket- (n = 272) or honeybee- (n = 52) sting anaphylaxis were prospectively subjected to an in-hospital sting challenge. Plasma levels of specific IgE and IgG₄ skin venom tests, severity of previous reaction, sex, age, atopic constitution, histamine skin test results, location and number of previous stings, time interval between previous anaphylactic reaction and sting challenge, and time interval between sting challenge and onset of anaphylaxis were studied in relation to the clinical severity of a reaction after sting challenge. A recurrent anaphylactic reaction after sting challenge was observed in 25% of yellow jacket- and in 52% of honeybee-sensitive persons. The severity of this reaction correlated significantly with age and the time interval between sting challenge and onset of anaphylaxis only: older persons with faster reactions had more severe symptoms after sting challenge. None of the current criteria for insect-sting hypersensitivity (IgE, IgG₄ skin test) significantly related on an individual basis or in combinations to the reaction after sting challenge. We conclude that the current criteria to assess insect-venom hypersensitivity do not relate to the occurrence and severity of anaphylactic symptoms after an insect-sting challenge. (J ALLERGY CLIN IMMUNOL 1994;94:151-9.)

Key words: Insect-sting challenge, Hymenoptera, IgE, IgG₄ skin test, anaphylaxis, immediate hypersensitivity

Anaphylactic reactions to insect stings occur suddenly, are often frightening, and are the cause of death in a small number of otherwise healthy subjects. Therefore persons who have experienced such an anaphylactic reaction are afraid to get a

reaction again following a future sting. The occurrence and course of a future reaction is difficult to predict, mainly because the pathogenesis of insect-sting anaphylactic reactions has not been fully elucidated.¹⁻³ A key event in the pathogenesis of anaphylaxis is activation of mast cells or basophils,⁴⁻⁶ which may be induced by insect venom-specific IgE.^{1, 3, 7}

The current criteria to determine insect-sting hypersensitivity are skin tests with purified venoms and circulating levels of insect venom-specific IgE and IgG₄.^{1, 3} However, it has been demonstrated that these criteria do not accurately predict the clinical reaction *in individual patients* to a future field sting or sting challenge, in prospective studies,^{6, 8-18} as well as in retrospective studies.¹⁹⁻²³ Some investigators have even described patients with negative skin test results and without detectable levels of plasma IgE against the insect concerned, who nevertheless did have

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a pulmonary or cardiovascular reaction to a sting.^{6, 8, 13, 15} Approximately 10% of patients experiencing an anaphylactic reaction to an insect sting have no detectable specific IgE or positive skin test results against the insect concerned.^{4, 6, 8} Therefore non-IgE-dependent mechanisms may also contribute to insect sting-induced anaphylactic reactions. On the other hand, the majority of persons with venom-specific IgE or positive skin test results (5% to 45% of the general population) do not experience anaphylaxis after insect stings (prevalence, 0.02% to 4%^{19, 24-26}). Furthermore, in persons with detectable IgE or positive skin test results against the insect venom concerned, levels of specific IgE and IgG₄ or skin tests have been shown to correlate poorly with the outcome of a sting challenge after stopping venom immunotherapy.²⁷⁻³⁰ In addition, the natural history of insect-sting anaphylaxis indicates that many patients lose their sensitivity to future stings without having received any therapy.^{3, 6, 7, 20, 31, 32} These arguments illustrate that the current parameters of insect-sting hypersensitivity do not reliably predict the reaction after a future sting.

Other parameters that have been suggested to predict the outcome of a future sting are the severity of the previous reaction, sex, age, atopic constitution, histamine skin tests, location of the previous sting, number of previous stings, time interval between the previous and the future anaphylactic reaction, and time interval between the actual sting and onset of anaphylactic symptoms. However, the predictive value of (combinations of) these parameters remains to be established, in particular because these parameters have been studied only in prospective studies in relatively small numbers of patients,⁹⁻¹¹ or in large retrospective studies.¹⁹⁻²³ Recently, Reisman³³ stressed the importance of research on the predictive accuracy of plasma levels of specific IgG in clinical studies on allergic diseases.

In some centers in The Netherlands and a few other European countries, patients are selected for venom desensitization by sting challenge under controlled intensive-care conditions. For practical reasons, this has only been done in specialized centers. As described above, this procedure was initiated to withhold time-consuming immunotherapy from a large group of otherwise unnecessarily treated patients, as well as to administer venom immunotherapy to patients who would otherwise have been denied this important and effective therapy on the basis of negative skin test results or low plasma levels of specific IgE. In

addition, persons with a negative reaction to sting challenge performed for an anaphylactic reaction to a field sting in the past were asked about accidental field stings after this negative sting challenge. Preliminary data show that only 4% have an anaphylactic reaction to this later field sting, and in all of these only a mild one (to be published). The sting-challenge procedure enables the search for necessary less invasive tests, regarding their potency, to accurately predict the response to an insect sting in individual patients, as well as studies on the pathogenesis of insect-sting anaphylaxis.

We decided to study prospectively the relationship of the clinical severity of a sting-challenge reaction not only to skin tests, specific IgE, and IgG₄ (IgG₄ is thought to protect against IgE-mediated reactions³⁶), but also to the above-mentioned set of other parameters. Because of the national reference function of our hospital in The Netherlands, we were able to study a large number of patients. The results of 324 patients with a previous anaphylactic reaction to an insect sting are reported here. Stepwise logistic regression analysis was used to investigate whether a combination of laboratory and clinical parameters could predict the clinical response to an insect-sting challenge.

METHODS

Subjects

From 1982 until 1990, 324 patients (aged 7 to 72 years) with a history of an anaphylactic reaction to either a yellow jacket or a honeybee sting were subjected to a sting-challenge test to select patients for immunotherapy with purified venom. Correct insect identification was ensured by the patient's identification of the doctor's description of the three predominant Hymenoptera species (i.e., yellow jacket, honeybee, and bumblebee) in The Netherlands, supplemented by skin tests and determination of specific IgE. At the time of the challenge, all subjects were in good health; none were pregnant; and, more specifically, none had a cardiac disorder or used a β -blocker, antihistaminic, mast-cell stabilizing, or any other drug. Electrocardiograms, chest x-ray films, and results of routine blood examination were normal in all subjects. Atopic constitution was defined as a history of constitutional eczema, hay fever, asthma, or allergic reactions to medication, radioactive contrast media, or food. The patients were first seen in the outpatient clinic, where detailed oral and written information was given on the protocol of the study. After informed consent was obtained, the patients were entered in the study protocol, which had been approved by the medical ethical review board of the Eemland Hospital. Skin test results

TABLE 1. Relationship between the severity of the previous reaction and the reaction after sting challenge

Honeybee							Yellow jacket						
Previous reaction*	Reaction after sting challenge*						Previous reaction*	Reaction after sting challenge*					
	n	0	I	II	III	IV		n	0	I	II	III	IV
I	5	3	2				I	42	36	6			
II	12	5	6	1			II	52	39	11	2		
III	8	4	1		3		III	55	39	10	2	4	
IV	27	13	2	1	3	8	IV	123	89	12	2	1	19
Total	52	25	11	2	6	8	Total	272	203	39	6	5	19
		(48%)	(20%)	(4%)	(12%)	(16%)			(75%)	(14%)	(2%)	(2%)	(7%)

*Severity of anaphylactic reaction, as defined in Methods.

and specific IgE and IgG₄ were assessed in the outpatient clinic. The interval between these tests and the sting challenge ranged from 6 weeks to 1.5 years (median, 5 months).

Study protocol

The provocation procedure with living insects in the intensive care unit has been described before.^{6, 10, 13} Briefly, before the sting challenge, all subjects were hooked up to a constant heart rate-monitoring device, and a running intravenous line was maintained. A yellow jacket of the species *Vespula germanica* or *V. vulgaris* or a honeybee of the species *Apis mellifera* was induced to sting the lower left arm for a maximal period of 30 seconds. Then the insect was killed. Blood pressure was recorded automatically every 1 to 5 minutes. The severity of the anaphylactic reactions was classified according to the method of Mueller³⁴: 0, no systemic reaction (i.e., occurring at sites other than the sting site); I, skin symptoms (generalized urticaria, itching, erythema) or anxiety; II, gastrointestinal symptoms (stomach pain, nausea, vomiting) or angioedema; III, respiratory symptoms (dyspnea, difficulty in swallowing, hoarseness, stridor); IV, cardiovascular symptoms (*hypotension* defined as a decrease of 15 mm Hg or more in mean arterial pressure from initial value, requiring immediate intervention, with or without cyanosis, collapse, arrhythmias, or angina pectoris). Patients were classified according to the symptoms of the highest degree of severity, although symptoms of lower degrees may have been present.

Assays

Specific serum IgE and IgG₄, as well as skin tests against the insect venom concerned, were determined as described before.¹⁰ Briefly, IgE levels were measured by the RAST method and expressed semiquantitatively in classes. The RAST classes related to the percentage

of bound radiolabeled anti-IgE (2% to 5% = class 1; 6% to 10% = class 2; 11% to 20% = class 3; 21% and greater = class 4).^{35, 36} In 3 of the 228 nonreacting patients, in 1 of the 50 with a grade I, and in 1 of the 8 with a grade II reaction, specific IgE levels were determined with a different assay than the one for the present study and were therefore not included. IgG₄ levels were measured with a similar assay, except that radiolabeled anti-IgG₄, instead of anti-IgE, was used. Results were expressed in units per milliliter. IgG₄ levels were not available (different assay) in 17 of the 228 nonreacting patients, in 3 of the 50 with a grade I, in 1 of the 8 with a grade II, and in 1 of the 11 with a grade III reaction. Skin tests against insect venom were determined by intracutaneous injections of 0.1 ml solutions of increasing concentrations of purified insect venom (ALK, Copenhagen, Denmark). Skin tests to histamine were determined by intracutaneous injections of 0.1 ml solutions of increasing concentrations of diluted 0.01% (wt/vol) histamine. A skin test result was determined by assessing the lowest concentration of insect venom or histamine at which an induration exceeding 5 mm and an erythema greater than 10 mm were observed.^{3, 11, 24} Skin tests were not available (different method) in 10 of the 228 nonreacting subjects, in 2 of the 50 patients with a grade I reaction, in 2 of the 8 with a grade II reaction, and in 2 of the 27 with a grade IV reaction.

Statistical analysis

Student's *t* test and the Mann-Whitney two-sample test were used to compare data between two groups. Differences between more than two variables were assessed by chi square tests or analysis of variance. Correlations between different groups of variables were assessed by Spearman rank order correlation tests. Stepwise logistic regression analysis was used to assess odds ratios and predictive values of multiple param-

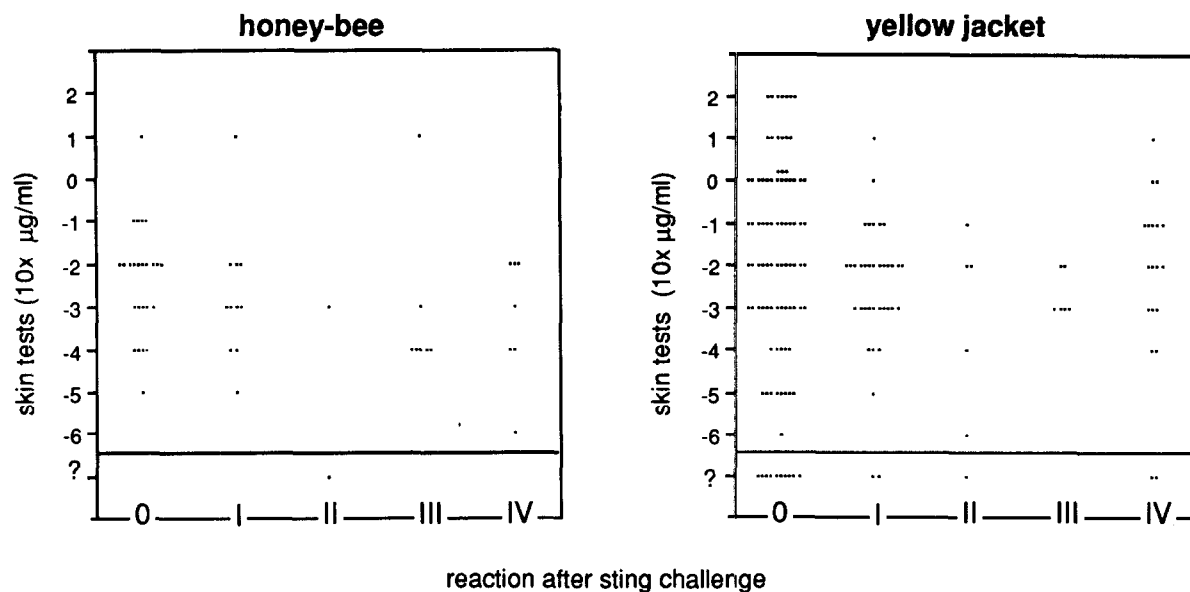


FIG. 1. Relationship between skin test results and the clinical reaction after sting challenge in 324 subjects. Values for skin tests (log scale) to insect venom are compared with the clinical reaction after insect-sting challenge in 324 individual subjects with a previous anaphylactic reaction to either a honeybee or a yellow jacket sting. (See Methods for skin tests and grades of reaction.) Each dot represents one subject. Question marks indicate subjects in whom the skin tests were not obtainable.

eters. A *p* value of less than 0.05 was considered to represent a significant difference, association, or regression.

RESULTS

Clinical course

The relationship between the clinical severity of the reaction to the sting challenge and the severity of the previous reaction in the 324 patients is shown in Table I. In 14 of the 52 (27%) patients sensitive to honeybees and in 31 of the 272 (11%) of the patients sensitive to yellow jackets, the reaction after challenge was similar to that after the previous field sting. In the majority of patients, the reaction after challenge was less severe or absent. Accordingly, most patients subjectively assessed that the current reaction was less severe than that after the previous field sting. None of the 324 patients had a reaction that was objectively of a higher Mueller grade, although 18 of the 324 patients indicated that the reaction after sting challenge was subjectively worse than the one experienced after the previous field sting. Patients sensitive to honeybees had more often a repeated grade III or IV reaction (31%) than did those sensitive to yellow jacket (13%; *p* < 0.0005, chi square test with Yates' correction).

Patients with an anaphylactic reaction to the

sting challenge received various combinations of an antihistaminic drug (clemastine, 1 mg/ml, administered intravenously to a maximum of 6 ml), fluid replacement ("Haemaccel"; Behringwerke AG, Wardorf, Germany; administered intravenously to a maximum of 2.5 L), and epinephrine (0.1 mg/ml, administered intravenously to a maximum of 5 ml). All 324 patients, including the 38 with a grade III or IV reaction, recovered uneventfully and left the hospital in a good clinical condition. The patients with grade III or IV symptoms at challenge subsequently started rush venom immunotherapy.³⁷ Most patients with no reaction or a grade I or II reaction did not receive additional therapy. However, when patients with grade I or II reactions felt uncomfortable with this regimen, they were offered either a rechallenge the following year, the use of an antihistaminic drug to be taken after a future sting, or venom immunotherapy.

Relationship of sting challenge to skin tests and specific IgE or IgG₄

Neither skin tests to insect venom nor classes of insect-specific IgE and levels of specific IgG₄ correlated significantly with the grades of clinical severity of the reaction after sting challenge (Figs. 1, 2, and 3, respectively). When the 19 patients

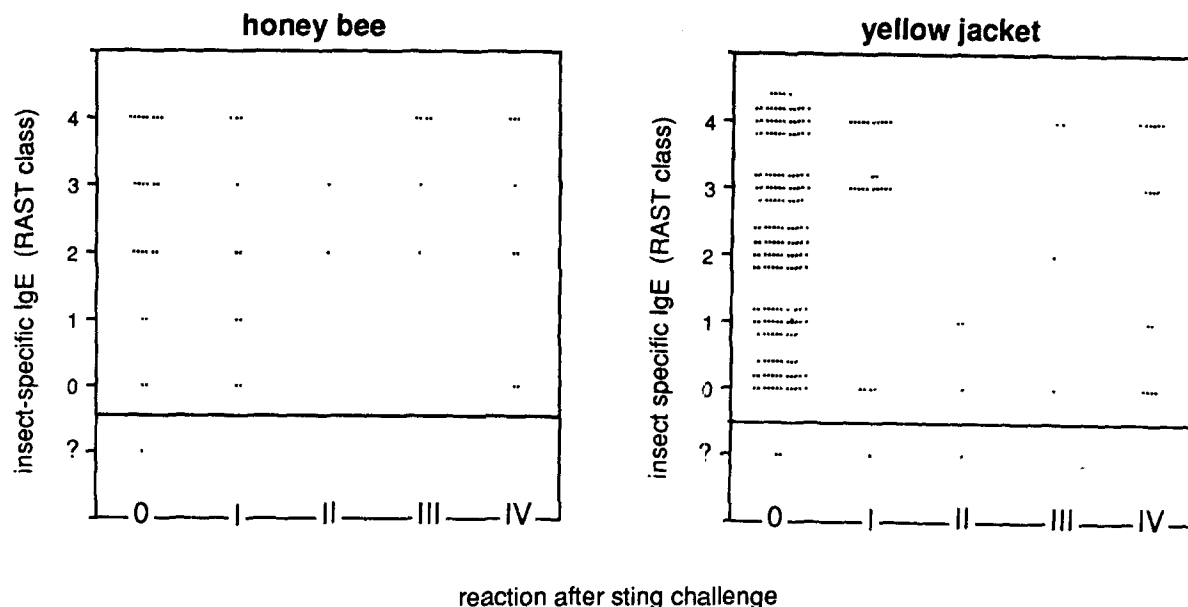


FIG. 2. Relationship between insect-specific IgE and the clinical reaction after sting challenge in 324 subjects. Individual results for levels of insect-specific IgE (RAST class) are compared with the clinical reaction after a sting challenge with either a honeybee or a yellow jacket sting. (See legend to Fig. 1 for explanation.)

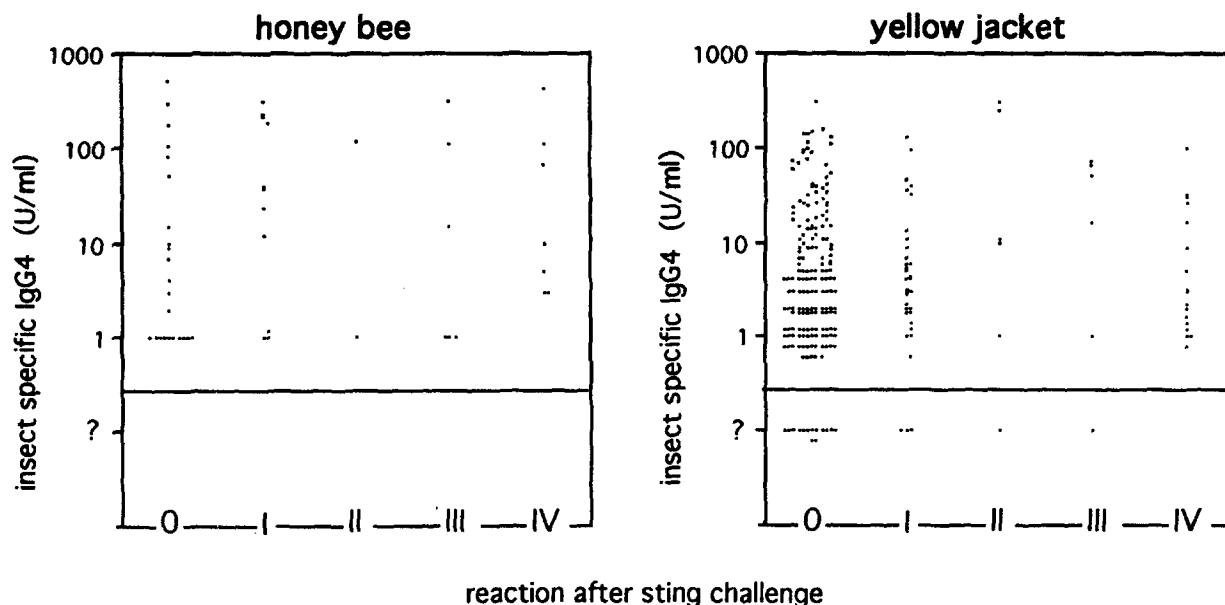


FIG. 3. Relationship between insect-specific IgG₄ and the clinical reaction after sting challenge in 324 subjects. Individual results for levels of insect-specific IgG₄ (U/ml, log scale) are compared with the clinical reaction after a sting challenge with either a honeybee or a yellow jacket sting. (See legend to Fig. 1 for explanation.)

with a grade IV reaction were assessed after yellow jacket sting challenge, eight of them had skin tests of 10 to 0.1 $\mu\text{g/ml}$, and six of them had IgE RAST class 0 or 1. When the 203 patients who did not react to a yellow jacket sting chal-

lenge were assessed, 13 of them had skin tests of 0.0001 to 0.0000001 $\mu\text{g/ml}$ and 72 of them had IgE RAST class 3 or 4. Similar observations were made for the patients sensitive to honeybees. This relationship was assessed by rank order correla-

tion tests on the different groups indicated in Figs. 1, 2, and 3, as well as by comparing the previous reaction with that after the challenge. In addition, no differences were observed between patients sensitive to yellow jackets or honeybees.

Relationship of the severity of the sting challenge reaction to other parameters

Severity of the previous reaction, sex, atopic constitution, histamine skin test results, location of the previous sting, time interval between the previous anaphylactic reaction and the challenge, and the number of previous stings—none of these correlated with the clinical severity of the sting challenge. Nor did these parameters discriminate between patients who did and patients who did not show a systemic reaction to the sting challenge (data not shown).

Age, however, was significantly related to the severity of the sting challenge reactions. Patients who had a grade IV reaction after sting challenge were significantly older than patients who had a grade I reaction: for patients allergic to honeybees, 48 ± 11 versus 28 ± 15 years (mean $\pm$ SD; $p < 0.01$) and for patients allergic to yellow jackets, 49 ± 10 versus 42 ± 12 years ($p < 0.05$).

The time interval between the sting and the onset of the clinical symptoms was also significantly related to the severity of the clinical reaction after sting challenge. Patients with a grade IV reaction experienced clinical symptoms earlier than did patients with a grade I, II, or III reaction after sting challenge: for patients allergic to honeybees, 5 minutes (median; range 2 to 7 minutes) versus 16 minutes (range, 2 to 49 minutes; $p < 0.005$) and for patients allergic to yellow jackets, 8 minutes (range, 1 to 28 minutes) versus 18 minutes (range, 2 to 91 minutes; $p < 0.01$).

Stepwise logistic regression analysis was performed on the patients separately. The first denominator investigated was whether an anaphylactic reaction developed after the sting challenge. For patients sensitive to yellow jackets, the combination of higher age at challenge and higher specific IgE significantly yielded a higher chance that an anaphylactic reaction would develop after challenge (Odds = $-3.06 + [0.27 \times \text{IgE in RAST}] + [0.03 \times \text{Age in years}]$). For patients sensitive to honeybees, none of the parameters related to this denominator.

The second denominator investigated was whether a potentially life-threatening reaction (grade III or IV) developed after the sting challenge. For patients sensitive to yellow jackets,

only the severity of the previous reaction significantly correlated with this denominator (Odds = $-7.00 + [1.38 \times \text{Grade of previous reaction}]$). For patients sensitive to honeybees, the combination of the severity of the previous reaction and the skin test to insect venom were positively correlated with the chance of developing a grade III or IV reaction to the sting challenge (Odds = $-9.01 + [1.64 \times \text{Grade of previous reaction}] + [-0.74 \times \text{Log of skin threshold to insect venom}]$).

DISCUSSION

Hypersensitivity to insect stings may be effectively treated with venom immunotherapy. Based on the natural history of declining insect-sting hypersensitivity in most subjects, it is difficult to decide which patients should receive immunotherapy. The current criteria to assess insect-sting hypersensitivity are skin tests with purified venom and plasma levels of insect venom-specific IgE and IgG₄.^{1,3} This prospective study in 324 subjects with a history of insect-sting anaphylaxis shows that neither absolute grades of skin tests nor plasma levels of specific IgE or IgG₄ predict the clinical response to an in-hospital sting challenge in individual patients, and therefore it is very likely that they do not predict the response to a field sting. Previous studies in a limited number of patients (90 in reference 10, 106 in reference 11, and 21 in reference 12) have shown that immunologic criteria (e.g., venom-specific IgE and skin test results) do not predict the occurrence of anaphylactic reactions after an in-hospital sting challenge. Our results, obtained in a larger number of patients (324), confirm these findings. In addition, we demonstrate that neither these immunologic criteria nor the combination of these immunologic criteria with clinical parameters predict the occurrence or the clinical course of a reaction after sting challenge. Thus the present data do not justify the use of these parameters to identify insect-sting sensitivity in the individual patient or to determine which patients are eligible for insect-venom desensitization.

Several points of discussion must be addressed at this stage. First, the specificity of the insects concerned. In The Netherlands, people usually get stung by only three species of Hymenoptera—yellow jacket (*V. germanica* or *V. vulgaris*), honeybee (*A. mellifera*), and bumblebee (*Bombus terrestris*). Bumblebee stings are rare and mainly observed in workers in the greenhouse industry. Honeybee stings are mainly observed in beekeep-

ers or their immediate family or neighbors. The confounding problems related to the different (sub-)species of wasps, such as those in the United States,⁷ do not occur in The Netherlands. Another confounding factor might be the method of skin tests and both IgE and IgG₄ assays. We used, however, the internationally advised intracutaneous skin test^{6, 10, 13} with purified venom (ALK, Copenhagen, Denmark) and the standard tests for IgE and IgG₄.^{35, 36} Standardization of the sting challenge procedure is another important issue. All patients were stung in the left volar lower arm with a newly obtained insect from one nest each season. Insects were caught in an identical manner, and within 30 seconds after being caught, each insect was induced to sting. Each sting lasted 30 seconds and was performed in a strictly standardized way in all patients; after this, the insect was killed.^{6, 10, 13} This standardization was used to minimize the possible influences from different nests and handling of insects.³⁸

Another point of discussion is the time interval between skin test, IgE, or IgG₄ determination and the sting challenge. This period varied from 6 weeks to 1.5 years (median, 5 months). A lack of correlation among these three parameters and the clinical reaction after sting challenge might be due to fluctuation in values caused by this time interval.^{17, 23} We do not consider this possibility to be likely, because IgE and IgG₄ levels in blood samples obtained immediately before the sting challenge (in 250 patients, data not shown) did not differ significantly from the previously obtained outpatient clinic values.

An important issue is the comparison of a reaction after a sting challenge to that after a field sting. The emotional state may influence different mediator systems in a patient (e.g., by releasing neuropeptides or catecholamines³⁹), mediating the clinical severity of a reaction. In addition, the description of symptoms after a field sting is markedly influenced by subjective interpretation, whereas an in-hospital sting challenge can be assessed in a more objective way (e.g., by assessing redness, angioedema, wheezing, stridor, cyanosis, cardiac arrhythmias, and hypotension). Nonetheless, we think that a strictly controlled sting challenge yields relevant objective information with regard to insect-sting hypersensitivity in individual patients.

In this study, no increase in Mueller class was observed between the previous reaction and that after sting challenge. In addition, 48% of subjects previously sensitive to honeybees and 75% of

those previously sensitive to yellow jackets did not show an anaphylactic reaction at all after the challenge. Most patients with an anaphylactic reaction after challenge subjectively indicated that this reaction was less severe than the previous one (after a field sting), although approximately 5% indicated that their symptoms were worse than before. These latter patients, however, did not show objective symptoms indicative of a more severe class of reaction (Table I). The differences in response after sting challenge compared with the previous field sting have been observed after repeated field stings as well.^{17, 19-21, 23} Finally, most studies on field stings were retrospective studies, in which an unknown number of patients with no reaction or a less severe reaction after the second field sting may not have been included.^{17, 19, 20, 21, 23} This self-limiting nature of insect-sting anaphylaxis in most patients further illustrates the relevance of the challenge procedure. The reason that most patients with a previous anaphylactic reaction after an insect sting did not have a recurrent anaphylactic reaction after the following sting is intriguing. A possible explanation is that those patients who fail to react to repeated stings have spontaneously (i.e., as a natural consequence of the venom injected with their most recent sting) achieved the state of clinical nonreactivity, which other patients achieve only after undergoing prolonged venom immunotherapy. The mechanism for this spontaneous nonreactivity may be related to the induction of anti-idiotypic antibodies or to changes in the modulating effects of cytokines, which determine sting outcome. Thus these speculative changes might be stimulated by stings, as well as by immunotherapy. Apparently, more studies are needed to substantiate these speculations.

In this study we demonstrate that patients sensitive to honeybees may experience a repetitive grade III and IV reaction more often than those sensitive to yellow jackets (3 of 8 and 8 of 27 vs 4 of 55 and 19 of 123, respectively; Table I). This may be explained by the fact that a honeybee may inject more venom with one sting.^{14, 17} In addition, most honeybee-sensitive patients were beekeepers, their immediate family members, or neighbors. They had been stung more frequently by the same insect species before than those patients sensitive to yellow jackets; they were aware of the risk of being stung again and therefore not as easily frightened by an insect sting as other patients; and they reported to their doctors less

frequently with only a minor anaphylactic reaction. Thus patients sensitive to honeybees who report to their doctor may be more at risk than patients sensitive to yellow jackets for an anaphylactic reaction after a future sting.

Because the absolute grades and levels of the "classical" criteria for insect-venom sensitivity (skin tests, high levels of specific IgE, and low levels of IgG₄) were not related to the clinical severity after a sting challenge in individual patients, we investigated combinations of parameters to predict the severity of a reaction after a sting challenge. Severity of the previous reaction, sex, atopic constitution, histamine skin test results, location of the previous sting, and the number of previous stings did not, on an individual basis, relate to the severity of the reaction. The only parameters significantly associated with a grade IV reaction were age and the time that elapsed between the sting challenge and the onset of symptoms.

The distribution of skin test grades is the same for all persons who have had an insect-sting anaphylactic reaction, regardless of the severity of their previous reaction or the reaction after sting challenge. Much lower values were obtained in volunteers who had never been stung by an insect of this species before.^{6, 39} Because the skin test itself was not an inclusion criterion for this study (only a previous insect-sting anaphylactic reaction), we think we have not left out special groups of subjects. The overall results of the sting challenge reactions are indeed lower than those in most other published studies, but this most probably reflects the prospective nature of our study (including patients diagnosed by history alone) versus other, mostly retrospective, studies (including patients diagnosed by history *plus* skin test results and plasma IgE levels). Although our results clearly indicate that in patients with previous insect-sting anaphylaxis there is no relationship between the severity of a reaction after sting challenge and plasma levels of specific IgE or IgG₄ or skin test results, the data do not exclude these immunologic parameters as a risk factor for anaphylactic reactions after a future sting. To establish this latter issue, the incidence and the severity of a reaction after an insect sting may be prospectively studied in persons who have never had insect-sting anaphylaxis before and who have either negative skin test results and no detectable venom-specific IgE or positive skin test results and elevated levels of IgE.

Patients eligible for venom immunotherapy are those who are at risk for developing pulmonary

(grade III) or cardiovascular (grade IV) symptoms after a sting. We tried to identify this group of patients with stepwise logistic regression analysis. For both insect species, the clinical severity of the previous anaphylactic reaction appeared to be the best parameter, although insufficient for clinical practice, to predict a future grade III or IV reaction on challenge and most likely also on future field stings.^{21, 23} The combination of age and specific IgE best predicted the occurrence of any anaphylactic reaction after a second yellow jacket sting, whereas this was not observed for honeybee-sensitive patients. Only for patients sensitive to honeybees did skin tests significantly add some predictive value to the severity of the previous reaction in the prediction of a pulmonary or cardiovascular reaction. No other parameters related to the clinical severity of a reaction after sting challenge. The reason for this difference between persons sensitive to honeybees and persons sensitive to yellow jackets is not clear.

In conclusion, we observed that neither skin tests to venom nor levels of specific IgE or IgG₄ alone or in combinations predict the outcome of a reaction after an insect-sting challenge in patients with a previous insect-sting anaphylactic reaction.

This article is dedicated to Dr. J. Kees van der Zwan, who died before the study could be published. As a general internist with special interest in intensive care medicine, Kees van der Zwan initiated clinical research on insect-sting anaphylaxis in The Netherlands, as early as 15 years ago. The data in this study, as well as in previous publications, were acquired through his dedicated and continuous efforts.

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