# Hymenoptera sting challenge of 348 patients: Relation to subsequent field stings

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**Background:** *Patients with a history of a serious anaphylactic reaction after a Hymenoptera sting are usually given venom immunotherapy. Because the natural history of Hymenoptera sting anaphylaxis is often of a declining severity, there is a chance of overtreatment.*
**Objective:** *Identification of patients at risk for a future anaphylactic reaction may reduce the number of patients who need venom immunotherapy.*
**Methods:** *We investigated the relation between the grade of hypersensitivity to an in-hospital sting challenge and the reaction to a subsequent accidental field sting. From 1982 through 1992, 348 patients with mild or no symptoms after a sting challenge were not given venom immunotherapy. All patients were asked by letter whether they had experienced a subsequent field sting. In case of a sting, the severity of the reaction was further evaluated.*
**Results:** *Information could be obtained from 327 patients: 129 had been re-stung, and 110 of them had only had a local reaction. Thirteen patients had experienced mild systemic symptoms, and six patients had experienced serious manifestations. In two of the latter group hypotension was observed.*
**Conclusion:** *In 95% of patients with a previous anaphylactic reaction, the result of the in-hospital sting challenge provided a good prediction of tolerance to a subsequent Hymenoptera field sting. (J Allergy Clin Immunol 1996;97:1058-63.)*

***Key words:*** *Sting challenge, Hymenoptera, immunotherapy, anaphylaxis*

Most stings by Hymenoptera species only lead to a local reaction: redness, swelling, itching, and pain. Yet, in a minority of persons (0.02% to 4%) an anaphylactic, sometimes life-threatening, reaction may occur.[1-6] Patients with a history of an allergic reaction to a field sting by either a honeybee or a yellow jacket may receive venom immunotherapy to prevent future anaphylactic events. Venom immunotherapy is usually given for at least 3 years and offers protection in 90% to 95% of cases.[7-11] This success rate may, however, be overestimated; the symptoms after a previous sting may have been aggravated by hyperventilation or a vasovagal collapse. Even more important is the fact that insect sting anaphylaxis is a self-limiting disease in a great number of cases.[12-15]

*Abbreviation used*
ICU: Intensive care unit

Several methods have been explored to identify patients at risk for a future anaphylactic reaction after an insect sting. However, levels of insect-specific IgE and $IgG_4$ and results of skin testing and the basophil degranulation test have not been shown to correlate significantly with the severity of the allergic reaction to a Hymenoptera sting.[16, 17] Several studies on the natural history of Hymenoptera sting anaphylaxis have demonstrated that most patients exhibit identical symptoms after consecutive stings or even show a less severe or no reaction.[12-15] This finding has led to the introduction of the in-hospital sting challenge as a diagnostic procedure. In some hospitals it is used to assess the grade of venom hypersensitivity and to determine whether venom immunotherapy should be given.[18, 19]

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**TABLE I.** Severity of anaphylactic symptoms after an insect sting

| Müller grade | Symptoms |
|---|---|
| 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, stridor, hoarseness) |
| IV | Cardiovascular symptoms (cyanosis, hypotension, collapse, arrhythmias, angina pectoris) |

Adapted from Müller. J Asthma Res 1966;3:331-3.

Between 1982 and 1992 we sting-challenged 490 patients with a live honeybee or yellow jacket in the intensive care unit (ICU) of our hospital for diagnostic purposes. Three hundred forty-eight of 490 patients had mild systemic or no symptoms and consequently did not receive venom immunotherapy. To determine the negative predictive value of an in-hospital sting challenge, we analyzed the severity of subsequent field sting reactions in these 348 patients.

## METHODS

The in-hospital sting challenge was performed with an insect of the species that had induced systemic symptoms in the past. All sting challenges were conducted in the ICU with cardiac rhythm and blood pressure monitoring. An intravenous catheter was inserted into the right arm. Medication and medical and nursing staff were on hand. The insects were caught from a nest or apiary on the balcony of the ICU and were applied to the dorsal aspect of the left lower arm within a minute. The patients remained in the ICU for at least 1 hour and spent the next 2 hours in the waiting room. The period of observation was longer when a systemic reaction occurred.

Grading of the systemic reaction was performed according to the classification system proposed by Müller[20] (Table I). In case of a local reaction after challenge, patients were discharged without treatment. After a Müller grade I or II reaction, patients were allowed to choose no therapy, an antihistaminic drug to be taken after a future sting, or venom immunotherapy; none of them chose the latter option. In all cases of a grade III or IV reaction, rush venom immunotherapy was started the next day.[21]

All 348 patients who had not received venom immunotherapy were asked by letter whether they had been stung again in the field by the same insect species after the in-hospital sting challenge. Correct insect identification was promoted by a detailed description of the three predominant Hymenoptera species (i.e., yellow jacket, honeybee, and bumblebee) in the Netherlands. When a field sting had occurred, the patient was asked to fill in a detailed questionnaire devised to estimate the severity of the reaction. In case of a systemic reaction to the field sting, we interviewed the patient by telephone in order to further evaluate this field sting reaction. If the patient had sought medical advice after the sting, we obtained information from the physicians consulted.

Twenty-one of 348 patients (6%) could not be reached, because they had moved to another address, which was unknown to their former general practitioner. The patients who had experienced a subsequent field sting, those who had not, and those who could not be traced were compared in terms of sex, age, level of venom-specific IgE at the time of sting challenge, and severity of the field sting reaction that preceded the in-hospital sting challenge. IgE levels were measured by means of a RAST and expressed semi-quantitatively 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% to 40%, class 4+; >40%, class 5+).[22]

**TABLE II.** Characteristics of patients allergic to honeybee or yellow jacket who had been dismissed without venom immunotherapy from 1982 to 1992

| | Re-stung ($n$ = 129) | Not re-stung ($n$ = 198) | No follow-up ($n$ = 21) |
|---|---|---|---|
| Sex | | | |
| Male (%) | 54 | 43 | 29 |
| Female (%) | 46 | 57 | 71 |
| Mean age (yr) | 43 | 46 | 43 |
| Insect species | | | |
| Honeybee (%) | 19 | 10 | 10 |
| Yellow jacket (%) | 81 | 90 | 90 |
| Specific IgE | | | |
| Unknown (%) | 2 | 6 | 5 |
| None (%) | 19 | 18 | 14 |
| 1+ (%) | 18 | 13 | 10 |
| 2+ (%) | 20 | 21 | 24 |
| 3+ (%) | 22 | 17 | 14 |
| 4+ (%) | 18 | 25 | 33 |
| 5+ (%) | 1 | — | — |
| Severity of symptoms* | | | |
| Grade I (%) | 20 | 15 | 19 |
| Grade II (%) | 19 | 21 | 33 |
| Grade III (%) | 21 | 20 | 19 |
| Grade IV (%) | 40 | 44 | 29 |

Patients were divided into three groups: those who had and those who had not been re-stung and those who could not be traced for further follow up.

*Experienced after the field sting that had preceded the in-hospital sting challenge (estimated according to the Müller classification system[20]).

**TABLE III.** Patients sensitive to honeybee or yellow jacket not receiving venom immunotherapy because of a previous in-hospital sting challenge but who had systemic symptoms after a subsequent field sting

| | | | Reaction to sting | | | |
|---|---|---|---|---|---|---|
| | | | Field 1 | Hospital | | Field 2 |
| Patient No. | Insect species | Specific IgE | Symptoms | Clinical signs | Complaints | Complaints and course |
| 1 | hb | 1+ | Collapse in hospital, no signs of shock | None | None | Collapse, hypotension (60/40 mm Hg), pulse rate not documented, epinephrine given by doctor, recovery uneventful |
| 2 | yj | 4+ | Chest pain | None | Anxious | Palpitations, vertigo, no doctor, aspirin |
| 3 | yj | 1+ | Headache, palpitations, urinary incontinence | None | Palpitations, headache | Anxiety, palpitations, tendency to collapse, epinephrine given by neighbour |
| 4 | yj | 4+ | Angioedema, dysphagia, stridor, palpitations, vertigo | None | Vertigo, nausea | Perioral stiffness, dyspnea, palpitations, vertigo, no medication given by doctor |
| 5 | yj | 3+ | Nausea, tendency to collapse | Hyperventilation | Dyspnea | Vertigo, heart beats fast, no doctor, no medication |
| 6 | yj | 0 | Unconscious, urinary incontinence | None | None | Vertigo, sweating, fast pulse rate and low blood pressure (measured by doctor but not documented), epinephrine, recovery uneventful |
| 7 | yj | 4+ | Angioedema, anxiety, unconscious, involuntary loss of urine, diarrhea | None | None | Nausea, stomach pain |
| 8 | yj | 4+ | Urticaria, angioedema | None | Generalized itching | Angioedema, generalized itching |
| 9 | yj | 2+ | Tendency to collapse, no palpitations | None | None | Urticaria |
| 10 | yj | ne | Generalized itching, unconscious, no palpitations | None | None | Urticaria |
| 11 | hb | 3+ | Urticaria, tendency to collapse, no palpitations | None | None | Generalized itching |
| 12 | hb | 1+ | Urticaria, slow heart rate, vertigo, dyspnea, urge to defecate | None | None | Nausea, urge to vomit and defecate, no medication |
| 13 | yj | 1+ | Urticaria, tendency to collapse, no palpitations | None | None | Angioedema, doctor's visit, aspirin |
| 14 | yj | ne | Angioedema, palpitations | None | Nausea | Angioedema |

**TABLE III.** Cont'd

| Patient No. | Insect species | Specific IgE | Reaction to sting: Field 1 Symptoms | Hospital: Clinical signs | Hospital: Complaints | Field 2: Complaints and course |
|---|---|---|---|---|---|---|
| 15 | yj | ne | Anxiety, urticaria | None | None | Urticaria |
| 16 | yj | 4+ | Angioedema, generalized itching | None | Generalized itching | Angioedema, generalized itching, dysphagia, doctor's visit, no medication |
| 17 | yj | 1+ | Angioedema, urticaria, unconscious, no palpitations | None | Anxiety, vertigo | Urticaria |
| 18 | yj | 2+ | Urticaria, palpitations, vertigo | None | None | Urticaria |
| 19 | yj | 2+ | Anxiety, vertigo, tendency to collapse | Hyperventilation | Anxiety, generalized itching | Anxiety, nausea, vertigo, no signs of shock at medical examination |

*Field 1,* Field sting reaction that led to in-hospital sting challenge; *Field 2,* field sting reaction that occurred after in-hospital sting challenge; *hb,* honeybee; *yj,* yellow jacket; *ne,* not examined.

## RESULTS

Completed inquiries were obtained from 327 patients who did not receive venom immunotherapy. One hundred twenty-nine of these 327 patients had experienced one or more field stings by the same insect species in the years after the in-hospital sting challenge. The characteristics of patients who were re-stung, those who were not re-stung, and those who could not be traced are shown in Table II.

One hundred and ten of 129 patients who had been restung (91 patients with a local reaction and 19 patients with a mild systemic reaction after in-hospital sting challenge) had experienced a local reaction after a subsequent field sting, whereas 19 patients had experienced systemic symptoms (Table III). Six of them reported serious complaints. According to information obtained from their physicians, only patients 1 and 6 had experienced hypotension. Both had recovered uneventfully. The complaints of patients 3, 4, and 5 were subjectively identical to those experienced after sting challenge, whereas no signs of an anaphylactic reaction had been observed at that time. In spite of her serious complaints, patient 2 did not require a doctor's visit or medication for her recovery. Thus in 123 of 129 patients (95%) the result of the in-hospital sting challenge provided a good prediction of tolerance to a subsequent accidental field sting.

## DISCUSSION

Patients with a history of an anaphylactic reaction after a field sting by either yellow jacket or honeybee can be effectively treated by means of venom immunotherapy. Ninety to ninety-five percent of patients appear to be protected after at least 3 years of venom immunotherapy.[7-11] Systemic side effects of venom immunotherapy occur in approximately 10% of patients; life-threatening adverse reactions are rare.[23] Because venom immunotherapy is costly and laborious, it is usually only given to patients at risk of experiencing potentially fatal symptoms after a future field sting. When the decision to initiate venom immunotherapy is only based on symptoms described by the patient, the chance of overtreatment is considerable. Complaints caused by hyperventilation or a vasovagal collapse may mimic respiratory or cardiovascular symptoms of an anaphylactic reaction. Therefore a reliable screening test is obviously needed to predict the severity of a future field sting reaction. At present, sensitive in vitro tests are not available. The only in vivo test available is an in-hospital sting challenge with a live insect.

The aim of our study was to determine how many patients who did not have a serious systemic reaction (Müller grade III or IV) at the time of in-hospital sting challenge had a dangerous anaphylactic reaction after a subsequent field sting. Unfortunately, 21 patients could not

be traced for follow-up. We cannot exclude a higher frequency of serious anaphylaxis in this group. The fact that the characteristics of these patients did not markedly differ from those of the 327 patients who could be traced (Table II) makes a higher frequency less probable. According to our results the negative predictive value of in-hospital sting challenge could be as high as 0.95 (123 of 129). We therefore consider it a useful screening test, which could help to determine whether a particular patient needs venom immunotherapy.

For several reasons some investigators oppose the use of an insect sting challenge for diagnostic purposes. First, a sting challenge may theoretically lead to sensitization. This assumption has not been proven. Second, a sting challenge may evoke a serious systemic reaction. In The Netherlands, approximately 2000 patients have been challenged without fatal complications. Up to now, no lethal reactions after insect sting challenge have been reported in the literature. Third, the amount of Hymenoptera venom that is delivered to the skin may vary from one sting to another. However, no publications have claimed that the severity of an anaphylactic reaction depends on the amount of Hymenoptera venom delivered to the patient. Fourth, the development of a local reaction or mild systemic symptoms after insect sting challenge does not completely exclude the development of serious systemic symptoms after a future sting.[24] This finding is confirmed by our data. It is important to inform patients about the risk of a serious systemic reaction after a subsequent accidental field sting. This risk should, however, be viewed in relation to the possibility that venom immunotherapy may be given to patients who actually do not need it. Furthermore, there is also a chance of side effects during venom immunotherapy, and venom immunotherapy appears to be ineffective in at least 5% of cases.[7-11] At present, many of our patients who have been thoroughly informed about the advantages and disadvantages of both sting challenge and venom immunotherapy prefer a diagnostic in-hospital sting challenge.

In conclusion, there is an obvious need for a screening test to rule out a serious systemic reaction to a future Hymenoptera sting.[25] When performed under intensive care conditions in specialized centers, the in-hospital sting challenge with a live insect appears to have the highest negative predictive value.

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