

Investigational and clinical use of the sting challenge

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Purpose of review

The sting challenge has been an important tool in advancing our knowledge about allergy to stings from insects in the order Hymenoptera. While some European centers have advocated its use in the past as a routine diagnostic procedure to select patients requiring venom immunotherapy, this practice has been abandoned because of the poor reproducibility of the test. In this review, the possible use of the sting challenge in clinical practice is discussed in the light of current knowledge of the limitations of the test. Its use in recent studies is also discussed, with an emphasis on the implications of the test's variability.

Recent findings

Several studies have attempted to quantify the risk of recurrence of anaphylactic reactions to hymenoptera stings under various clinical circumstances on the basis of the outcome of a single sting challenge. Many of these studies were carried out with small patient numbers, and consequently must be interpreted with caution.

Summary

While the sting challenge with a living insect is still the best available test for ascertaining clinical reactivity to insect venoms, the reproducibility of this procedure is modest. The outcome of single sting challenges in individual patients should therefore be interpreted with caution, in both the research setting and clinical practice.

Keywords

allergy, Hymenoptera, hypersensitivity, sting challenge

Curr Opin Allergy Clin Immunol 3:283–285. © 2003 Lippincott Williams & Wilkins.

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Current Opinion in Allergy and Clinical Immunology 2003, 3:283–285

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1528-4050

Introduction

Although sting challenge with a living insect is the gold standard for the diagnosis of allergic reactions to stings from insects in the order Hymenoptera, difficulties with this test continue to hamper our understanding of both the test itself and the allergy for which it is used. This review examines the usefulness of this test and considers various aspects of the inconsistency of clinical responses to insect stings. Its role as a research tool and its possible use in clinical practice are discussed.

Why challenge patients suspected of hymenoptera allergy?

A sting challenge with a living insect is considered the best available test for assessing clinical reactivity to insect stings, for two reasons. First, as with other anaphylactic allergies, a significant number of sensitized individuals show no clinical reactivity when exposed to the allergen in question. This 'asymptomatic sensitization' has been shown in many studies in the past, although estimates of the frequency of this phenomenon in hymenoptera allergy have varied widely (from just over 40% to almost 80%). In one recent publication by Golden and co-workers [1], only 21–24% of history-positive sensitized patients reacted to a subsequent sting challenge. Second, an absence of sensitization does not preclude clinical reactivity. This problem seems particularly prevalent in the US, where this phenomenon was documented in 14% of patients in the recent study mentioned above.

Why challenge with living insects?

Challenges with purified venom from the culprit insect give positive responses far less frequently than challenges using a living insect. This was documented in the original study demonstrating the efficacy of venom immunotherapy [2], in which all patients, including those treated with a placebo, were challenged with purified venom (resulting in no clinical responses) prior to the sting challenge with a living insect (which resulted in responses in 58% of placebo-treated patients). A recent study in children allergic to yellow-jackets seems [3] to confirm this finding: only one patient of 104 children challenged with purified venom showed a systemic reaction. The reason for the lack of efficacy of purified venom as a challenge material/procedure is unknown, but it is certainly one of the most important unanswered questions in this field. The consequence of this observation is that challenges must be carried out with living insects, with all the disadvantages that this entails, including the following: an inability to grade

challenges incrementally (with the resulting increased risk of severe reactions); an inability to use blinded challenge protocols (with the resulting interpretive difficulties); inconsistency of clinical responses, because of the variability of the insects; seasonal (un)availability of insects; and the aversion of some patients to the test.

Inconsistency of clinical responses to sting challenge

Inconsistency of clinical responsiveness to sting challenges has been found on two levels: differences in response rates in patient groups studied at different centers and/or at different time points; and differences in the occurrence and severity of reactions following sting challenge in the same patient on different occasions.

That sting-challenge response rates may vary widely over time may readily be appreciated when one considers that the aforementioned recent study by Golden [1], with a 24% response rate, and the study by Hunt *et al.* [2], published in 1978, which found a 58% response rate, are from the same center. Wide variation in response rates in contemporaneous studies in different locations has also been found. Over a 10-year period from 1980 to 1990, the response rate in patients studied at our center [4] was 39%, whereas the rate was only 25% at another center in the Netherlands [5]. These studies illustrate that unknown patient (selection) factors and/or insect factors and/or variable technical factors related to the sting challenge itself result in different estimates of clinical risk in otherwise comparable populations. With regard to the procedure, it may be noted that while there have been numerous studies on venom composition and delivery as well as other aspects of the challenge procedure, there have been no studies demonstrating that these factors actually influence the frequency of sting-challenge responses.

The reproducibility of a single negative sting challenge in a particular individual has been found to be low: 21% of patients not reacting to a first challenge went on to react to a second subsequent challenge [4]. Although this last phenomenon has been observed in sting-challenge (and also in field-sting) studies in untreated patients, it has also been reported recently in field-sting studies after discontinuation of immunotherapy [6], where risk estimates based on initially negative field stings were found to be lower than cumulative risk based on subsequent positive reactions. It is therefore probable that sting-challenge reaction reproducibility is also a problem in patients during or after immunotherapy. There is very little data on repeated sting challenges in treated patients. In a study of mostly honeybee-allergic patients treated with venom immunotherapy at 3-month intervals [7], sting challenges were performed both during and after this therapy. This study attempted to

verify protection after stopping venom immunotherapy by repeated sting challenges, but were able to recruit only five patients willing to undergo this procedure twice. No patients reacted to the second challenge, but because the numbers are small it is uncertain what the risk of a sting reaction in this group was, and unclear whether all patients not reacting to the second sting challenge were protected.

In our own study in untreated patients [4], 39% reacted to a first sting challenge. Of the non-reactors, 21% went on to react to a second challenge. Assuming that the initial population consists of a group of non-allergic patients with a negligible chance of a positive reaction to a challenge (such as those with non-anaphylactic symptoms due to hyperventilation, vasovagal reactions, etc.) and a second truly allergic group with a risk for recurrence during the challenge, an estimate can be made of the relative size of these two groups and the risk of a reaction in the allergic group. With the data cited above, this results in a population with approximately 40% non-allergic individuals (with negligible risk) and 60% allergic patients who have a collective risk of 70% of a recurrence during a sting challenge. An estimate can also be made of the expected frequency of reactions to a third sting challenge (8.3%) and a fourth challenge (2.7%).

In our patient population, therefore, three negative sting challenges reduce the risk to approximately 2.7%, and we are currently using this procedure in cases where the sting challenge is used to exclude patients from immunotherapy. This is also the approach used in a study by Schuetze and colleagues [8•], who recently reported only 6.3% systemic reactions to field stings following negative sequential sting challenges in untreated honeybee-allergic children. It should be stressed, however, that patient selection in different centers may vary considerably, as may be anticipated from the differences in reactorship frequencies to a first sting challenge cited previously, and this could alter the outcome of risk estimation using repeated sting challenges. It may also be concluded that a single negative sting challenge may overestimate clinical protection in individual patients. Thus, reports concluding that individual patients are protected following an increase in the maintenance dose of venom immunotherapy [9], following bumblebee venom immunotherapy [10], and following venom immunotherapy in patients with urticaria pigmentosa and/or systemic mastocytosis [11] must be interpreted with caution, as repeated sting challenges in these individual patients were not done.

Sting challenge versus field stings

The relative merits of the sting challenge and field stings as the primary indicator of risk and risk reduction with treatment have been debated in the past. Critics of the

sting challenge have maintained that the test is artificial and may overestimate risk, which in turn could result in overtreatment. Others have pointed out that because of difficulties with insect identification and objectivity of reactions, field stings may underestimate risk and result in undertreatment. There is little direct data on this issue. Recently published studies in which field stings and sting challenges were used [7,12] are too small to allow for meaningful conclusions. In a report by Müller *et al.* [13], lasting protection from honeybee stings after cessation of immunotherapy was seen significantly more often in patients who tolerated a sting challenge than in those who tolerated a field sting during immunotherapy. In general, field stings cannot be used as a diagnostic test and have the further disadvantage of inferior safety, making the sting challenge the preferred method to compare and assess risk in venom-allergic patients.

Who should we sting challenge?

Outside the research setting, sting challenges during treatment are used in some centers to select patients who may safely stop venom immunotherapy after 3 years [13]. The question of whether sting challenges should be performed in untreated patients has been a matter of controversy in the past. There is general consensus that a single sting challenge cannot be used safely to exclude patients from venom immunotherapy, because of the poor reproducibility of the test [14]. Given the risks involved, it is worth considering whether any patients at all should undergo this test. In our opinion, carefully selected patients may benefit from this test and it should thus be considered in special cases. Generally speaking, the test may be indicated when there are serious doubts as to the need for venom immunotherapy (because of uncertainty about whether an insect, or which insect, was involved and/or whether the reaction was anaphylactic in nature), as well as in circumstances that necessitate a high degree of diagnostic certainty (such as for patients living in remote areas). In addition to those patients with the generally acknowledged contraindications (beta-blocker treatment, pregnancy, serious cardiovascular or respiratory disease, acute inflammatory disease [14]), we feel that patients with mastocytosis should be excluded, as this condition has been associated with fatal outcomes after field stings in treated patients [15]. Patients who have had severe reactions have the greatest risk of a severe reaction to the sting challenge, and therefore this test is relatively contraindicated in such cases. Fortunately, there is usually no reason to perform this test in these patients. The test should take place in centers experienced in its use.

Conclusion

While the sting challenge with a living insect is still the best available test for ascertaining clinical reactivity to insect venoms, the reproducibility of this procedure is

modest. Whether factors affecting test outcome are related to the insect, the patient, or a combination of both is unknown and is an important focus for future research in this area. Given these limitations, the outcome of single sting challenges in individual patients should be interpreted with caution, in both the research setting and clinical practice. Although this test is inappropriate for most untreated patients, it may be a useful adjunctive diagnostic procedure for carefully selected cases, provided the limitations of the test are taken into account.

References and recommended reading

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- of outstanding interest

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