

THE STING CHALLENGE TEST IN HYMENOPTERA VENOM ALLERGY: PROS AND CONS

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SUMMARY : This paper examines the main features of the deliberate sting challenge with regard to the type of insect, the advantages and disadvantages of its use in untreated and treated patients and after discontinuation of specific immunotherapy.

Key-words: Sting challenge - Diagnostic tool - Immunotherapy.

STING CHALLENGE PROCEDURE

Sting challenges are carried out by physicians to identify the type of reaction to a re-sting in patients with a previous history of a systemic reaction to hymenoptera stings.

In the vast majority of the European countries and in the U.S. deliberate insect sting challenges are not considered routine tests.

The outcome of the challenge is influenced by a number of factors such as patient reactivity which itself depends on venom sensitisation as well as other, only partially known, elements including the time interval between two stings, the patient's state of health, emotional frame of mind, instability of the kynin system and inflammatory diseases (1).

As for the insect biology, the amount of venom injected during a sting plays a determining role and depends on a number of variables: duration of the sting, season, actual volume of venom injected, actual venom allergen content, age of the insect (2).

In honeybees for example, the composition and the amount of the venom have been shown to depend on the insect's developmental age. After about one week

of a bee's life, its function changes from a "nurse bee" to a "guard bee", stationing herself at the hive entrance to identify and repel non-resident bees or other intruders; by this time the venom production mechanism has matured and provides the bee with a fully-loaded venom sac.

Also, the stinging technique which can produce unwanted irregularities could be much more standardised (3).

Evidence suggests that honeybees yield more reliable sting challenge results than do Vespids.

This can partially be explained since Vespids can squirt their venom without actually stinging for example when under threat of capture for use in the challenge. As a result the amount of venom delivered during a vespid sting tends to be subject to more variation than bee sting venom (4).

Moreover, the quantity of venom injected by a honeybee is much greater than that of a Vespid.

Probably due to the larger amount of venom, the reaction rate with the honeybee is considerably higher than that with the vespid sting challenge both in untreated patients and venom-immunotherapy treated patients

A further complication is that identifying and capturing Vespids can prove difficult.

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Whereas honeybees are easily identified and may be collected in the wild, or from a local cooperative beekeeper, the entomologic identification of Vespids has to be carefully carried out by an expert.

In-hospital sting tolerance has been found to be more predictive of the outcome of further stings than in-field challenges (5) where the positive identification of the offending insect is usually not possible, and the patient's description of the symptoms can be erroneous as it lacks objective assessment.

Some pediatric studies have replaced intentional sting challenge with venom extract challenge (6).

Well-tolerated venom immunotherapy is no reliable indication of the tolerance to a subsequent sting: Hunt demonstrated in 1978 that incremented subcutaneous doses of venom injected before a sting challenge failed to cause reactions in patients given a placebo and whole-body extract who subsequently responded to a sting challenge (7).

At that time the authors hypothesised that some components of the venom while delivered in a sting but lost in processing may increase local vascular permeability and so lead to an increase in the rate at which the venom protein is absorbed (7). This would appear to rule out venom-extract challenge as a reliable diagnostic tool.

STING CHALLENGE IN UNTREATED PATIENTS

Sting challenges have been performed in untreated patients, in order to assess clinical reactivity in subjects with no history of a systemic reaction (8), but a high risk of exposure to bee stings (beekeepers and their families), and in patients with a positive history and negative skin tests (9).

They have traditionally been used in both adults and children with systemic reactions to determine suitable candidates for immunotherapy (1, 10).

The prognosis after a systemic reaction is highly dependent on the severity of the initial reaction and the offending insect. The risk of another reaction ranges from less than 50% after mild systemic reactions and in wasp-allergic adult patients, to more than 70% in patients highly sensitised to honeybee venom (9, 10).

On the other hand, approximately 10% (vedere lavoro di Golden) of patients experiencing an anaphylactic

reaction to an insect sting have no detectable specific IgE or positive skin test results (9).

Because of this dichotomy between clinical reactivity and immunological, the selection criteria of individuals at risk for sting anaphylaxis and who need immunotherapy should be made more accurate.

When the indication for immunotherapy is based on the classic diagnostic tools (skin test, RAST and history, alone or in combination) there is a various degree of overtreatment (5).

Therefore, the prevention of overtreatment and its related costs represent the main reasons as to why certain specialists perform sting challenge in untreated patients.

Venom immunotherapy is unquestionably very expensive. However, sting challenges also incur high costs in some countries for patients, for medical insurance companies or for the Health Care System, since it needs to be performed where intensive care facilities are available.

The cost of venom immunotherapy should be evaluated in terms of the objectives that the patient and physician want to reach as well as the different degrees of patient acceptability of succumbing to an anaphylactic reaction.

Unlike inhalant allergen immunotherapy, the potential threat of death from an insect sting makes the risk of a systemic reaction unacceptable for physicians and patients alike. On the one hand the estimated 50-70% risk of sting anaphylaxis in untreated adults is far too high, whereas on the other a 5-14% risk of anaphylaxis with a history of a large local reaction is considered acceptable. However, the less well-defined "grey area" between these limits requires a joint patient-physician decision on what course of action to take.

The second reason for specialists performing sting challenges in untreated patients is to avoid the side effects of IT, though several studies show that the risk of systemic reactions associated with venom IT is not much greater than that associated with inhalant allergen IT, especially in vespid allergic patients treated with conventional, clustered and rush regimens (13, 14).

Moreover, sting challenges provide an opportunity to study the pathophysiology of anaphylaxis *in vivo*, by monitoring related events and in particular the release of mediators (15, 16).

Another opportunity offered by sting challenges could be the evaluation of the natural history of large local

reactions since conclusions today are based on field sting results from only about 150 patients, without distinguishing between insects (12, 17).

The principal argument against the diagnostic use of intentional sting challenges is the ethical side of the issue (18-20).

As far as we know, no actual deaths after a diagnostic sting challenge have occurred to date. However, in addition to severe systemic reactions (21), one near fatal reaction has been reported (22), leading the majority of authors to the conclusion that patients with a high risk of serious anaphylaxis should not be intentionally re-challenged and should be given immunotherapy on the basis of their history and skin test reactivity, knowing that some of them may not need therapy (18, 20).

Although some studies show that the results of the in-hospital sting challenge provide a good prediction of tolerance to a subsequent field sting (5,23), it seems that a single negative sting challenge may not be used to select patients for venom immunotherapy, since 21% of adult patients (24) and 13% of children (25) with a first negative challenge had anaphylactic responses after the second one.

The risk then, is that a negative challenge may lull patients and physicians into a false sense of security and thereby resulting in the delay or omission of appropriate preventive and therapeutic measures.

Sensitisation *de novo* or boosting of already existing sensitisation could be an important risk of the sting challenge test. It has been shown that after hymenoptera stings there is an increase in the skin test reactivity and serum specific IgE to the relevant venom; from the natural history of insect allergy we know that one tolerated sting followed by another 2-4 weeks later will result in the highest incidence of systemic reactions (26).

Although, there are no conclusive data indicating that sting challenge tests could increase clinical reactivity. However, it can be assumed that such a mechanism might be responsible for some systemic reactions at a second challenge in untreated patients who did not reacted to a previous one.

In conclusion, at the moment there is no *in vitro* or *in vivo* test that can predict with certainty the clinical reactivity of a sting-sensitive subject. Therefore, even with the inclusion of a challenge test our current diagnostic tools are far from perfect and the selection of patients for venom immunotherapy must be based on a combination of medical and non-medical criteria,

such as for example the degree of exposure and also the alteration in the patient's life style.

On the other hand, the benefits for the majority of patients at risk outweigh the risks and inconveniences of immunotherapy for the minority who might not even react.

STING CHALLENGE IN TREATED PATIENTS

In numerous studies sting challenges have been performed during immunotherapy, in order to evaluate the therapeutic efficacy of the treatment; in larger populations of patients, 80% to more than 95% of patients on maintenance treatment turned out to be protected at the sting challenge (1).

Since systemic reactions can occur even with immunotherapy, the sting challenge allows us to identify those patients who need a higher maintenance dose than the usual 100 mcg, before an unprotected field sting (27) and to evaluate efficacy after increasing the maintenance dose (28).

In order to reduce the costs and the disadvantages of venom immunotherapy, sting challenge could be more extensively used for progressively prolonging the interval between maintenance injections, instead of risking an anaphylactic reaction when immunotherapy is discontinued after a predetermined period (29, 30).

Since preliminary data indicate that venom IT is able to improve patients' quality of life (31), especially in those patients who were in-field restung (32), it might be advisable to use a deliberate sting challenge within a therapeutic framework in order to neutralise the placebo effect by proving the efficacy of immunotherapy through a tolerated re-sting.

The only argument against a sting challenge in treated patients is the fact that a re-sting might not necessarily re-occur in the patient's lifetime. However, if this were so, immunotherapy would not be necessary in the first place.

STING CHALLENGE AFTER STOPPING IMMUNOTHERAPY

Sting challenges have been performed after the discontinuation of immunotherapy in order to monitor the persistence of its therapeutic efficacy, to identify the main parameters that can predict a relapse after stop-

ping immunotherapy and consequently to evaluate the ideal duration of the treatment (1, 33-35).

Sting challenges done in patients off immunotherapy for 1-5 years with a treatment duration of at least 3 years induced systemic reactions in 0-17%, with less favourable results in honeybee allergic patients than in Vespid allergic subjects where adults fared worse than children (1).

Thanks to the use of sting challenges, from the latest studies it seems that the protection offered by three and five year courses of immunotherapy does not differ in the first years of the treatment, but the longer treatment gives superior long-term results, especially in adults and in patients with a history of severe reactions (35, 37, 38).

As previous studies have shown, the discontinuation of immunotherapy still raises some unanswered questions such as the number of challenges that could be performed and whether a sting challenge could re-sensitise patients leaving them at a subsequent risk of a sting reaction.

Some Authors have shown that the severity of the re-sting reaction may increase with repeated re-exposure (36, 38); on the other hand Golden, performing two sequential sting challenges a month apart, concluded that venom sensitivity decreases with time and a re-sting does not increase the risk of reactions in patients who had completed at least 5 years of maintenance venom immunotherapy (32).

For the time being all that can be said is that the possibility of re-sensitization can neither be confirmed nor ruled out, it is therefore advisable to prolong immunotherapy for at least six months after the last challenge.

CONCLUSION

The deliberate sting challenge is generally accepted as a tool to evaluate the efficacy of IT.

In the vast majority of the countries, especially for ethical reasons, it is not recommended as a diagnostic test in untreated patients with a history of systemic reaction, in order to identify those who need IT.

Due to the potential risk of patient's re-sensitization, the administration of a sting challenge after stopping IT remains a controversial issue.

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