# A modified ultrarush insect venom immunotherapy protocol for children

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## ABSTRACT

*The prevalence of insect venom allergy in the European population is ~5%. Hymenoptera venom allergy is an important epidemiological problem. Ten to 40 deaths are reported annually in Germany. In contrast to conventional dose increase schedules lasting a minimum of 5 days, shorter protocols reduce the patient's stay in the hospital and provide an earlier protection toward stings. Clinical studies on ultrarush protocols have been published for adult patients, but very little data are currently available for children. Therefore, we investigated the safety and tolerability of a shortened insect venom immunotherapy (VIT) in children and adolescents. Forty-three children and adolescents (aged 4–18 years) with insect venom allergy were treated in this study. Five children were hyposensitized according to the ultrarush protocol with nine injections (as suggested by Brehler* et al. *(Safety of a two-day ultrarush insect VIT protocol in comparison with protocols of longer duration and involving a larger number of injections. J Allergy Clin Immunol 105:1231–1235, 2000); 38 children received the modified ultrarush schedules with only eight subcutaneous injections. With both protocols the maintenance dose (100 μg) was achieved in 24 hours. Twenty-five patients (58.1%) showed no reaction after the injections. In 11 patients (25.6%), extensive erythema (>5 cm, maximum of 20 cm) was found at the injection site. Erythema and edema (>5 cm, maximum of 15 cm) were observed in seven patients (16.2%). The maintenance dose was well tolerated, with no systemic reaction in any patient. The modified ultrarush protocol for insect VIT used in this study showed very good tolerability and safety in children and adolescents. This dose regimen can increase compliance by shortening inpatient stay and reduces hospital costs.*
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Systemic allergic reactions to hymenoptera stings are reported in 0.8–5% of the total population in Central Europe. In Germany alone, 10–40 deaths are observed annually. Clinical manifestations range from local, to systemic reactions, to anaphylactic shock.[1,2] The allergic reactions are caused most often by allergies against toxins of honeybees (*Apis mellifera*) and common wasps (*Vespula germanica* and *Vespula vulgaris*). With a success rate of up to 100%, venom immunotherapy (VIT) has a convincingly protective effect.[3] Since the introduction of insect VIT in 1974, many dose increase protocols have been published. Conventional schedules require a minimum of 5 days whereas so called ultrarush protocols reach the maximum dose of 100 μg within 2 days.[4–7]

Studies with ultrarush protocols have been published for adult patients,[1,2,8] but very little data are currently available for children.[1] The purpose of our study was to investigate the safety of a shortened ultrarush protocol for children and adolescents, applying the maximum dose (100 μg) within 24 hours using a cumulative insect venom dose of 251.11 μg within 24 hours.

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## MATERIALS AND METHODS

Forty-three children and adolescents with insect venom allergy were treated in a prospective, open label study. Parents gave informed written consent to the simplified and shortened therapy protocol. All patients were monitored by the same physician in the hospital setting. Full emergency resuscitation equipment was readily available. The condition of the skin, heart rate, blood pressure, and respiratory rate were recorded before and 30 minutes after each injection. Local and systemic side effects were documented.

Sixteen patients were allergic to honeybees and 27 patients were allergic to common wasps. The patients were 4–18 years of age (mean, 9.5 ± 2.93 years); the demographic data are displayed in Table 1.

The interval between the last allergic reaction and the initiation of insect VIT was 5–12 months. Inclusion criterion was the history of a systemic reaction after a bee or wasp sting based on the criteria established by the European Academy of Allergy and Immunology Subcommittee on insect venom allergy.[9] The reactions were classified according to the grading scheme proposed by Mueller: grade 1 to grade 4.[10] VIT was recommended if

Table 1 **Demographic Data of Patients**

| | VIT | |
|---|---|---|
| | **Bee Venom** | **Wasp Venom** |
| Patients (no.) | 16 | 27 |
| Age (yr; mean) | 9.4 | 9.6 |
| Minimum | 4 | 4 |
| Maximum | 15 | 18 |
| Median | 9 | 10 |
| Sex (no.) | | |
| Male | 7 | 19 |
| Female | 9 | 8 |
| Prior sting reaction (Mueller grade[10]) | | |
| Grade 1 | 1 | 0 |
| Grade 2 | 12 | 15 |
| Grade 3 | 3 | 12 |
| Grade 4 | 0 | 0 |

there was a history of an immediate systemic reaction after sting and demonstration of immunoglobulin E (IgE)–mediated allergy by skin tests and/or the presence of specific IgE antibodies to the respective venom. The concentration of specific IgE fluroimmunoassay (CAP-FEIA; Pharmacia Diagnostics, Freiburg, Germany) was expressed in kilounits per liter and was ranked as negative below 0.35 kU/L. Children were treated with a lyophilized bee venom or *Vespula* species preparation (Venomil; Bencard/Allergy Therapeutics, Munich, Germany). All injections were applied subcutaneously to the lateral part of the upper arm. Patients did not receive a pretreatment with antihistamines.

Five children were hyposensitized according to the ultrarush protocol with nine injections suggested by Brehler *et al*.[2] With this dose regimen 100 $\mu$g of insect venom is reached after 24 hours with the eighth injection. A second injection of the maximum dose is applied 2 hours later.

The remaining 38 children received a shortened ultrarush protocol with only eight injections (Table 2). The injections were administered at 30- to 60-minute intervals (0.01–80 $\mu$g), the maximum dose (100 $\mu$g) was given once in the morning of the 2nd day (24 hours). The cumulative venom dose was 251.11 $\mu$g. The treatment was consolidated by 100 $\mu$g of booster injections given after 7 and 21 days and then in intervals of 4–6 weeks (100-$\mu$g maintenance dose) on an outpatient basis.

## RESULTS

Thirty-eight patients underwent our modified insect VIT between June 2002 and February 2005, receiving a total of 304 injections. A personal history of atopy was found in three patients (7.0%). Among the 43 patients, 25

Table 2 **Modified Ultrarush VIT**

| | **Time (hr)** | **Insect Venom ($\mu$g)** |
|---|---|---|
| Day 1 | 0 | 0.01 |
| | 0.5 | 0.10 |
| | 1.0 | 1.00 |
| | 1.5 | 10.00 |
| | 2.0 | 20.00 |
| | 2.5 | 40.00 |
| | 3.0 | 80.00 |
| Day 2 | 0 | 100.00 |

(58.1%) did not show any reaction during and after the VIT, 11 (25.6%) had an extensive reddening due to inflammation (>5 cm, maximum of 20 cm), and 7 (16.2%) showed a local reaction consisting of redness/swelling (>5 cm, maximum of 15 cm). The reactions were treated with local application of cold packs. The local reactions mainly occurred after a median single dose of 40–80 $\mu$g and a median cumulative dose of 151.11 $\mu$g. There was no difference between bee and wasp VIT. No systemic reaction occurred during the dose increase phase, and dose reduction due to adverse reactions was not necessary. The maintenance doses were well tolerated. No systemic or late reactions were observed. All patients were dismissed from the hospital on the 2nd day, with eight patients already discharged 4 hours after the first maintenance dose of 100 $\mu$g of insect venom.

## DISCUSSION

Immunotherapy treatment of patients with insect venom allergy is one of the most advantageous uses of VIT, with a reported effectiveness of 80% to nearly 100%.[3] The risks of insect venom allergy still are underestimated in the general population and by many physicians. In numerous protocols for insect VIT, the usual maintenance dose of 100 $\mu$g of venom is reached within different time periods. In conventional rapid schedules (rush), the maintenance dose is reached after 1 week, depending on the treatment scheme.

The ultrarush method is the shortest procedure for induction of insect VIT and was described for the first time by van der Zwan *et al*.[8] Since then, this schedule has been administered extensively. In ultrarush protocols, 2–5 days are necessary for the dose increase phase. The advantage is a rapid protection against insect stings during the insect flight period. Children usually require an inpatient stay for the dose increase phase.

An ultrarush protocol with a dose increase phase of only 24 hours was introduced by Brehler *et al.* for adult patients.[2] In this open retrospective study with 1055 patients (average age, 39 years), a decrease in the incidence and severity of adverse reactions was shown

with ultrarush insect VIT ($n$ = 403) when compared with several-day protocols.

Until now, ultrarush schedules mainly have been investigating adult patients; very few data have been published for children. Birnbaum *et al.*[1] investigated an ultrarush protocol in both children ($n$ = 51) and adults ($n$ = 207), with six injections on day 1 corresponding to a dose increase of up to 40 $\mu$g. A further increase was accomplished on day 15 with two injections of 50 $\mu$g. Finally, the maintenance dose (100 $\mu$g) was administered on day 45.

In our ultrarush protocol we modified the dose regimen recommended by Brehler *et al.*, cancelling the ninth injection, which may be omitted,[2] because there was no rationale with respect to a potential immunologic effect for the last injection. The maintenance dose of 100 $\mu$g was already reached with the eighth injection after 24 hours. The next injection (100 $\mu$g) was administered 7 days later. Our study, for the first time, investigated this ultrarush schedule in children and adolescents.

The modified ultrarush protocol in our study has proven very safe and well tolerated in children and adolescents with insect venom allergy. In 304 injections no systemic reaction occurred. The most frequent local reactions were erythema of 5–20 cm at the injection site. Up to the present time no systemic reaction has occurred in our patients.

In the study by Birnbaum *et al.*,[1] which included 51 children, systemic reactions during the dose increase phase occurred more frequently on day 1 than on days 15 and 45. The authors suggest that the dose increase phase on day 1 may be a risk factor for systemic reactions. However, the data from our study do not support this assumption. The study of Brehler *et al.*[2] is consistent with our results. These authors found a reduction in incidence and severity of adverse reactions if the dose increase phase is shortened to 24 hours.

The very short duration of the dose increase phase in our modified ultrarush protocol has several advantages over a longer regimen. With this ultrarush protocol only a 1- to 2-day hospital stay is necessary. Patients may be discharged on the 2nd day. Consequently, hospitalization costs are reduced.

Despite this positive experience, adverse incidents are possible in immunotherapy, demanding a high level of medical responsibility. It must be possible to perform adequate emergency treatment at any time. The influence of antihistamine pretreatment on systemic reactions associated with rapid insect VIT is controversial.[11,12] Scribner and Bernstein report weak evidence that pretreatment with antihistamines prevents systemic reactions.[13]

In ultrarush immunotherapy with a dose increase within a few hours, the immunologic effect is unclear. A shift from $T_{H2}$ to $T_{H1}$ is unlikely. Development of a refractory phase or anergy owing to the consumption of mediators or inhibition of IgE binding to mast cells would be a more conceivable explanation. The effect of immunotherapy also might depend on the total dose or on the dose per unit of time that is initially injected; however, up to now there is no evidence for either theory.

Optimal care of patients with an insect venom allergy consists of an integrated treatment concept that comprises acute treatment, an emergency kit, allergy diagnostics, and insect VIT. Up until now, observations indicated that our ultrarush immunotherapy procedure might increase compliance in children and adolescents, owing to a shortened length of hospitalization. Aside from being safe, it is well tolerated and reduces hospitalization costs.[2,6,14,15] We conclude that, generally, shorter rapid VIT protocols are better tolerated than those that span several days. These schedules will be favored equally by children and adults and, hopefully, contribute to a more extensive use of insect VIT.

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