

Rush Hymenoptera venom immunotherapy: A safe and practical protocol for high-risk patients

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Background: Hymenoptera venom immunotherapy in allergic patients is a well-established treatment modality for the prevention of systemic anaphylactic reactions caused by insect stings. A variety of therapy regimens exists, from conventional to rush and ultrarush modalities that operate on continuous or intermittent schedules.

Objective: The aim of this study was to report the 8-year experience with our rush venom immunotherapy regimen in predominantly high-risk patients and to compare data on safety and convenience with the results of 26 studies published from 1978 to 2001.

Methods: One hundred one patients allergic to bee, yellow jacket, or hornet venom were treated with rush Hymenoptera venom immunotherapy. Diagnosis and selection of patients for venom immunotherapy were carried out according to the recommendations of the European Academy of Allergology and Clinical Immunology. We used a 4-day regimen, and the incidence and nature of systemic reactions (SRs) were documented. Fifty-two patients were treated with honeybee venom, and 49 were treated with yellow jacket venom.

Results: One hundred (99%) patients reached the maintenance dose. We observed 8 injection-related SRs (0.47% of all injections given) in 7 (6.9%) patients. The number of SRs was higher in patients treated with bee venom extract (12%) compared with in patients receiving yellow jacket venom extract (2%).

There was no significant difference in the risk of SRs between female and male patients. The incidence of SRs was considerably lower than the average of 17.8% reported in the literature. **Conclusion:** With a rush immunotherapy regimen over a time period of 8 years in predominantly high-risk patients, the incidence of SRs was low, despite the high number of patients with bee venom allergy, who are more likely to have side effects. Epinephrine as rescue medication was never necessary, and the regimen proved to be safe and convenient for both the patients and the medical staff. (*J Allergy Clin Immunol* 2002;110:928-33.)

Key words: Honeybee venom, Hymenoptera venom allergy, rush immunotherapy, side effects, yellow jacket venom

Systemic hypersensitivity reactions to Hymenoptera stings are reported to occur in 0.8% to 5% of the general population.¹ In Austria these reactions are mainly caused

Abbreviation used
SR: Systemic reaction

by allergy to venom constituents of honeybees (*Apis mellifera*), yellow jackets (*Vespula germanica* and *Vespula vulgaris*), or, rarely, European hornets (*Vespa crabro*). A field sting might be life-threatening for patients with insect venom allergy.

Immunotherapy offers full protection in 83% to 95% of persons with a history of anaphylactic reactions after an insect sting.²⁻⁶ However, systemic reactions (SRs) during the initial phase of treatment are quite common, occurring in up to 67.3% of cases.⁷⁻³² Currently, 4 quite different treatment schedules with numerous variations are in use in specialized centers. The main regimens are termed conventional (increasing doses in weekly intervals for outpatients), rush (induction phase over 4-7 days for inpatients), ultrarush (the maintenance dose is reached within 1-2 days), or cluster (a modified rush approach schedule, which involves giving several injections at 15- to 30-minute intervals during the first visits and reaches a maintenance dose in about 6 weeks). In rush protocols patients receive higher doses of venom in a shorter time period and thus reach the maintenance dose of 100 µg faster than in conventional schedules; this might be of great importance before the onset of the flying season of insects (Fig 1). In recent years, ultrarush therapy is being used to an increasing extent, although it is associated with a potentially higher frequency of SR.³³ However, some modalities are reported to be well tolerated.^{26,34}

At our department, we offer patients with venom allergy who need venom immunotherapy the option between a conventional (slow) and a rush protocol. The incidence and nature of side effects during the rush protocol are reviewed in the present study.

METHODS

All patients receiving rush venom immunotherapy between January 1, 1994, and April 30, 2001, were included in a retrospective, descriptive study (clinical data in Table I). The hospital records of the patients were evaluated. Anaphylactic reactions caused by field stings were classified according to the system of Ring and Messmer.³⁵ The causative insect was identified by the patient (sometimes in cooperation with the physician). Fourteen patients were unable to identify the stinging insect: 12 did not recognize the insect, and 2 made inconclusive statements. The nature of sensitization was con-

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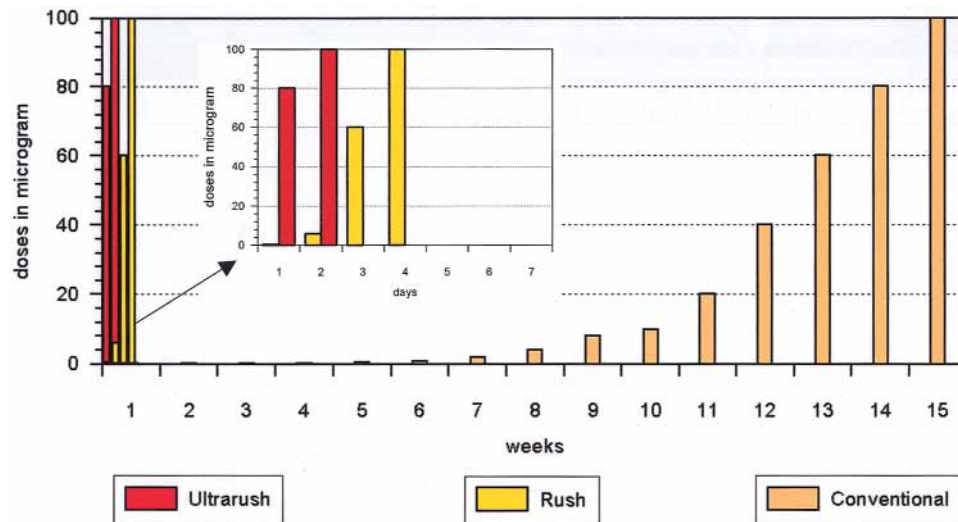


FIG 1. Schedules for ultrarush, rush, and conventional protocols in specific immunotherapy with insect venoms.

TABLE I. Clinical data of patients receiving rush venom immunotherapy

	Bee venom allergy	Yellow jacket venom allergy	European hornet venom allergy
No. of patients	52 (51%)	47 (47%)	2 (2%)
Age (y)			
Range	5-71	4-61	41-61
Mean	33.1	35.7	51.0
Sex			
Male	31	25	1
Female	21	22	1
Grade of field sting reaction*			
I	7 (13%)	5 (11%)	0
II	23 (44%)	14 (30%)	0
III	22 (42%)	27 (57%)	1 (50%)
IV	0	1 (2%)	1 (50%)

*Classification according to the method of Ring and Messmer³⁵ (Table VI).

TABLE II. Treatment protocol for increased dosing of rush venom immunotherapy

Day 1	Day 2	Day 3	Day 4
0.001	0.8	8	80
0.01	1.0	10	100
0.1	2.0	20	
0.2	4.0	40	
0.4	6.0	60	

Values are given in micrograms; injections are given in 60-minute intervals.

firmed by means of standardized end point titration skin prick tests (1, 10, and 100 µg/mL solutions of purified venom extracts; ALK-Abello) and intradermal tests (0.05 mL of 0.01, 0.1, and 1 µg/mL solutions), as well as by detection of specific IgE antibodies in the patients' sera (CAP-FEIA).

The rush immunotherapy regimen took 4 days, during which patients were hospitalized and kept under strict observation. The dosing was adapted from several similar regimens, as published earlier,¹ starting with very low concentrations because of the many

high-risk patients and then increasing gradually in intervals of 60 minutes (Table II). A total of 17 injections of the respective venom preparations (ALK-Lyophilisate SQ801/2) were administered subcutaneously until the maintenance dose of 100 µg was reached. Every morning, 60 minutes before starting the injection series, Fenistil (dimetinden maleate, 4 mg, a first-generation H1-receptor antagonist for intravenous use similar in its pharmacokinetics and pharmacodynamics to diphenhydramine, which is also recommended in the United States for parenteral treatment of anaphylaxis) diluted in 100 mL of saline solution was administered intravenously. After rush immunotherapy had been concluded, the patients received monthly injections of 100 µg of bee or yellow jacket venom (ALKdepot SQ801/2, aluminum hydroxide-adsorbed venom, ALK-Abello) over a period of at least 3 years.

We determined the incidence and nature of, as well as rescue medication for, side effects during the induction phase. Furthermore, we compared patients who had allergic reactions to venom during rush immunotherapy with those who tolerated therapy without hypersensitivity reactions to detect any potential risk factors. Additionally, we matched our results with those of 26 studies published from 1978 to 2001.

TABLE III. Systemic hypersensitivity reactions during the initial phase

	Bee venom	Yellow jacket venom
Grade of reaction*		
I	3	0
II	2	1
III	2	0
IV	0	0
No. of injections	885	833
Injections with SR	7	1
Risk of SRs per injection	0.79%	0.12%

*Classification according to the method of Ring and Messmer³⁵ (Table VI).

TABLE IV. Incidence of SRs in the different age groups

Age group (y)	RVIT	%	SR	% of all patients	% of age group
1-10	7	7	1	14	14.3
11-20	17	17	0	0	0
21-30	14	14	1	14	7.1
31-40	24	24	3	43	12.5
41-50	20	20	2	29	10.0
51-60	15	15	0	0	0
61-70	3	3	0	0	0
71-80	1	1	0	0	0
Total	101	100	7	100	

RVIT, Rush venom immunotherapy.

RESULTS

One hundred one patients with insect venom allergy received rush immunotherapy, resulting in a total of 1718 injections. Fifty-two patients were allergic to bee venom, 47 to yellow jacket venom, and 2 to European hornet venom. The latter patients, who had cross-reactivity to yellow jacket venom, received immunotherapy with yellow jacket venom extract. Thus 52 patients were vaccinated with bee venom, and 49 were vaccinated with yellow jacket venom.

One hundred (99%) of 101 patients reached the maintenance dose, 96 of them within 4 days and 4 within 5 days. Several patients experienced intermittent or persistent local reactions, such as urticaria or swelling at the site or sites of injection. No specific treatment except a change of the injection site was required. We observed SRs after 8 (0.47%) injections in 7 (6.9%) patients. SRs occurred in all stages of the protocol. The majority of patients only had local reactions, with most SRs being mild or moderate (Table III). The most severe symptoms were angioedema, bronchial asthma, and tachycardia. Treatment with antihistamines, medium-dose corticosteroids, and β -mimetics was sufficient to stop any progression, and the administration of epinephrine was never required. Rush immunotherapy could be continued in all 7 patients who needed treatment for SRs (ie, 3 patients on the same day and the remaining 4 on the following day). Three (6.8%) SRs occurred in the 44 treated female patients, and 4 (7.0%) of the 57 treated male patients had SRs. We were unable to confirm the female

preponderance of SRs reported in other studies.^{10,12,13,26} Additionally, the severity of side effects was not higher in women than in men; the mean grade was 2.0, with a range of 1 to 3 in both sexes. The small number of reactions might, however, invalidate such statistics. There was no direct correlation between the severity of the sting reaction that led to the initiation of venom immunotherapy and the occurrence of SRs during therapy regarding frequency and severity of these reactions. A high degree of sensitization (as indicated by high levels of specific IgE antibodies) did not increase the risk of SRs during the induction phase.

The frequency and severity of SRs in patients treated with bee venom compared with that seen in those treated with yellow jacket venom was remarkable in that 7 (86%) of 8 SRs were caused by bee venom, and the risk for an SR was 0.79 per injection with bee venom compared with 0.12% for yellow jacket venom. Twelve percent of patients receiving bee venom had SRs compared with 2% of those receiving yellow jacket venom. With regard to severity, bee venom caused 3 grade 1 reactions versus none in the yellow jacket venom group, 2 grade 2 reactions versus 1 in the yellow jacket group, and 2 grade 3 reactions versus none in the yellow jacket group. This different hazard of bee venom compared with yellow jacket venom is confirmed in the literature.^{10-13,19,26,36} The risk of side effects is presumed to be higher in elderly patients (51-71 years of age). However, no elderly patient had SRs during initial therapy in our study, a phenomenon that has been reported elsewhere as well.²⁶ The majority of events occurred in patients aged 31 to 50 years (Table IV). One patient did not reach the maintenance dose by means of rush venom immunotherapy but continued treatment with a conventional protocol, finally reaching the dose of 100 μ g. This 8-year-old boy felt sick on day 2 of immunotherapy and started to vomit. Non-vaccine-related gastroenteritis was diagnosed. Two days later, the patient was free of clinical symptoms, and the inflammation parameters decreased. Rush immunotherapy was resumed the next day. On day 4 of the treatment, the patient had generalized urticaria immediately after receiving a dose of 80 μ g. The last injection of 100 μ g was not administered. The patient continued with conventional therapy 2 weeks later, receiving 100 μ g of venom and experiencing no complications.

DISCUSSION

The decision of which treatment schedule to best choose for the individual patient (ie, a rapid regimen, in which the targeted maintenance dose might be reached within 6 hours and associated with a higher frequency of local reactions and SRs, or a slow, conventional regimen, in which the patient remains unprotected for a long time) should take into account not only medical factors but also logistic, financial, and other considerations that are specific to the individual and his or her family. We put patients on the (intermediate) fast schedule who (1) are at high risk of future severe reactions (according to case

TABLE V. Frequency of SRs during the initial phase: Summary of published studies

Reference	No. of patients	SR (%)	Regimen	Comments
Urbanek et al, 1978 ³¹	11	64.0	R	
Yunginger et al, 1979 ³⁰	20	55.0	R	
Chipps et al, 1980 ²²	44	6.8	C	
Gillmann et al, 1980 ¹⁴	23	13.0	C	
Golden et al, 1980 ²³	64	16.0	C	
Bar-Sela and Levo, 1981 ¹⁵	13	7.7	C	
Ramirez et al, 1981 ¹⁶	18	0	C	
Thurnheer et al, 1983 ²⁰	21	38.1	R	
	21	38.1	C	
Van der Zwan et al, 1983 ³²	11	0	UR	6 h
Przybilla et al, 1987 ²¹	290	37.6	R	
Bernstein et al, 1989 ²⁹	33	12.0	CI	
Lockey et al, 1990 ²⁸	1410	12.0	C	
Berchtold et al, 1992 ⁷	52	67.3	R	
Muller et al, 1992 ¹²	205	36.1	R + C	
Tarhini et al, 1992 ²⁷	100	0	CI	
Birnbaum et al, 1993 ¹¹	46	28.2	R	4 d
	21	28.6	UR	6 h
	217	6.9	CI	210 min; maximum dose, 40 µg
Wyss et al, 1993 ¹⁹	35	8.6	C	
Bernstein et al, 1994 ¹⁷	77	5.2	CI	
Youlten et al, 1995 ¹⁰	109	7.5	C	
Brockow et al, 1997 ⁸	121	11.6	R	
Laurent et al, 1997 ¹⁸	97	26.8	R	
Teudler et al, 1997 ²⁴	20	50.0	R	
Mosbech and Muller, 2000 ¹³	840	20.0		Various regimens
Brehler et al, 2000 ²⁶	317	22.4	R	7-9 d
	335	13.7	R	3-6 d
	403	10.7	UR	2 d
Reimers et al, 2000 ⁹	54	38.9	CI	
Westall et al, 2001 ²⁵	68	38.0	R	
Our study	101	6.9	R	
Total	5197	17.8		

R, Rush venom immunotherapy (inpatient); C, conventional venom immunotherapy or similar outpatient regimens; UR, ultrarush venom immunotherapy (intensive care patients); CI, cluster schedule (outpatient).

TABLE VI. Classification of anaphylactic reactions³⁵

Grade	Skin	Gastrointestinal tract	Respiratory tract	Circulation
I	Pruritus, urticaria, flush			
II	Pruritus, urticaria, flush	Nausea	Dyspnea, rhinorrhea	Tachycardia, hypotension
III	Pruritus, urticaria, flush	Vomiting, incontinence	Bronchospasm, cyanosis	Loss of consciousness
IV	Pruritus, urticaria, flush	Vomiting, incontinence	Respiratory arrest	Cardiac arrest

history and test results); (2) are at high risk for side effects of venom immunotherapy (eg, elderly persons with coexisting internal disease); (3) need protection soon (in the weeks before the insect flying season starts); (4) are living in rural areas, where no specialists are available or take the responsibility; (5) are highly sensitized and anxious; or (6) are highly sensitized children for whom responsibility can not be delegated to a physician's office. The selection of patients for our regimen was thus for severe cases—ie, predominantly high-risk patients, rather than young, healthy, and low-sensitized patients, were included.

We treated 101 patients with a history of SRs after an insect sting and with proven immunologic sensitization using a 4-day rush protocol. One hundred (99%) of them reached the maintenance dose; the one exception was not related to therapy but was caused by a concurrent unrelated infectious disease process. Only 6.9% of patients had SRs, with a 0.47% risk of anaphylactic reaction per injection. None of these reactions was life-threatening, and no epinephrine was needed as emergency treatment. Thus our treatment regimen is a compromise between ultrarush regimens with numerous side effects requiring intensive care conditions and conventional treatment

modalities with the problems of slow success and side effects in an outpatient setting. MEDLINE reports a total of 82 publications on rush immunotherapy from 1982 to 2001, in which various regimens were applied and controversial results were achieved. The present retrospective study concurs well with a number of similar published reports (Table V). The frequency of SRs in the different centers is of interest, ranging from 0% to 67.3%.⁷⁻³² These discrepancies might have several reasons. First, side effects are not reported in a standardized manner. Thus the high numbers reported in some studies^{7,9,12} might have resulted from the fact that the authors interpreted all subjective and mild SRs, such as sensation of heat, anxiety, and general itching, as SRs. Yet others only report a few severe reactions. In the present study we registered SRs in 6.9% of the treated patients and a 0.47% risk per injection. These figures are acceptable and far below the average of 17.8%.

Second, the small numbers of SRs reported in some studies might have been due to the fact that the patients were given antihistamines as premedication. Several studies investigated the efficacy of antihistamine pretreatment.⁷⁻⁹ Whereas all investigators observed a decrease in cutaneous symptoms, such as pruritus, urticaria, and angioedema only, Brockow et al⁸ reported a significant reduction in local and even systemic adverse reactions. Because there is no mention of a greater risk in antihistamine-pretreated patients, it would be appropriate to recommend this modality in the future. Some authors even attribute an enhanced efficacy of rush venom immunotherapy to this pretreatment.³⁷

Third, the different regimens of treatment are associated with different ratios of side effects. When comparing 26 publications in regard to regimens and SRs, we found 14 conventional or cluster regimens with an average of 11.2% SRs, 13 rush protocols with 25.6% SRs, and 3 ultrarush schedules with 11.3% SRs; the overall frequency of SRs was 17.8%. The conventional and cluster regimens seem to be the safest modalities and also the most convenient protocols. They thus should be instituted in patients in whom immunotherapy and the risk of an outpatient treatment is justifiable. Whereas for such patients a conventional regimen with weekly intervals between injections is usually chosen in Europe, a modified rush approach is now frequently used in the United States. Both modalities are safe if performed by specialists, and both seem to induce protection in most patients. We see an advantage for our fast approach in high-risk patients and persons who need immediate protection. Ultrarush regimens have been infrequently reported^{11,26,32-34} and were usually applied in a small number of patients only.^{11,32,33} The assumption that such protocols are associated with a greater incidence of SRs^{13,38} is reflected by the fact that they are usually performed under intensive care conditions. Thus the protocols are delicate, expensive, and unattractive for the patients. Additional studies in larger patient populations will be required before final conclusions can be made.

Finally, published data on this subject are difficult to compare because patient selection for treatment varies

considerably in different centers. In several studies even patients with generalized urticaria but no SRs are included. So-called dangerous protocols are applied in young and healthy individuals rather than in elderly patients.

In conclusion, Hymenoptera venom immunotherapy with newer treatment modalities is both successful and safe. The incidence of severe SRs is low, and the majority of reported reactions are mild. In the present study the incidence of SRs was very low, the treatment conditions were convenient for the patients, and the costs of treatment were acceptable for the public health system.

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