

Treatment Failures With Whole-Body Extract Therapy of Insect Sting Allergy

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• Whole-body extracts (WBEs) remain in widespread use for therapy of insect sting anaphylaxis two years after the approval of Hymenoptera venoms. We have reviewed our experience with WBEs in our patient population. Of 250 patients who received WBE, 115 had subsequent stings. Systemic allergic reactions occurred in 65%, large local reactions in 23%, and no reaction in 12%. There was no consistent change in the severity of systemic reactions during WBE treatment. Systemic reactions occurred less commonly in younger persons or after at least two years of WBE treatment. We conclude that WBE is not effective for the prevention of allergic insect sting reactions. The natural history of the disease may account for its apparent efficacy in young people or those having prolonged WBE therapy. Venom immunotherapy is safe and rapidly effective and is the only protective treatment recommended.

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THE DIAGNOSIS and treatment of insect sting allergy have for half a century been based on the use of crushed whole-body extracts (WBEs) of stinging insects of the order Hymenoptera. These were more readily available than insect venoms and were thought to share the "intrinsic bee protein" responsible for allergic reactions to stings.¹ The past decade has seen a technical revolution in the field that has contributed to a more precise understanding of the problem. Although insect venoms do contain antigens common to the insect bodies and WBE, the allergens responsible for the clinical expression of the disease reside solely and specifically in the venoms.^{2,3} The specific clinical and immunologic efficacy of venom immunotherapy has been proved be-

yond reasonable doubt.^{4,5} Nevertheless, WBE therapy remains in widespread use in this country (Maurice W. Giboney, BSc, Hollister-Stier Laboratories, Spokane, Wash, personal communications, June 1, 1980, and Jan 1, 1981). As summarized in a recent physician-sponsored petition to the Food and Drug Administration, the rationale for this practice is based on the belief that (1) venom immunotherapy is potentially hazardous; (2) increased blocking IgG antibody levels associated with venom treatment have not been established as the protective mechanism; (3) the expense of treatment encourages noncompliance with recommended treatment; and (4) WBE can provide protection for 95% of patients.

However, evidence has accumulated in recent years that casts considerable doubt on this rationale. We have reviewed the adverse effects of venom immunotherapy and find them no greater than those associated with WBE treatment or with immunother-

apy for pollinosis.^{5,7} Increased serum levels of allergen-specific IgG antibodies have been associated with the clinical and immunologic efficacy of allergen immunotherapy,^{5,6,7-10} even in individual patients (Golden et al, unpublished data, March 1981), and may confer passive protection by transfusion.¹¹ The cost of venom immunotherapy is higher than for WBE, but in addition to the expense of obtaining the venoms, this also reflects the cost of marketing an allergenic extract of quality-controlled and uniform-specific allergenic potency.

The underlying theme, however, is the wide belief that WBE is efficacious. In fact, the literature contains several surveys supporting the efficacy of WBE.¹²⁻¹⁴ Although each of these admits the existence of patients who have similar or worse allergic sting reactions during WBE treatment, reports of such treatment failures are so few as to belie the extent of the problem.^{15,16}

Reasonable expectation of complete protection with venom immunotherapy and our increasing but still incomplete understanding of the natural history of the disease have shed new light on optimistic assessments of the efficacy of WBE. In this light, we present 75 cases of treatment failure with WBE and examine the interpretation of effective immunotherapy.

METHODS

The records of all patients assessed for insect sting allergy at the Johns Hopkins Center for Allergic Diseases, Baltimore, from 1975 to 1980, were reviewed. Those who had given a history of treatment with

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WBE for at least six months were examined for the outcome of stings received during treatment. Detailed information regarding dosage and regimen of treatment was often not available, but all had been receiving maintenance (booster) doses of WBE at regular intervals and had believed themselves protected. Identification of the culprit is unreliable and was not analyzed. Data on therapy self-administered at the time of sting were not always available.

Allergic reactions were diagnosed by our previous historical criteria.¹⁰ Large local reactions were described as areas of induration increasing in size over 12 to 24 hours to at least 8 cm and persisting two to seven days. The severity of sting reactions was graded on a scale of 0 to 4 as follows: large local only, 0; cutaneous symptoms only, 1; respiratory or vascular symptoms (with or without cutaneous symptoms), 2; respiratory and vascular symptoms (with or without cutaneous symptoms), 3; and loss of consciousness (with or without any other symptoms), 4.

Patients were categorized according to the most severe sting reaction experienced during treatment. Thus, an individual who had a large local reaction to one sting, a systemic reaction to another, and no reaction to a third sting would be classified as a systemic reactor. This is in keeping with the known variability of allergic reactivity.¹¹

Statistical comparison of systemic reactors and nonsystemic reactors with respect to age and duration of WBE therapy was performed by Student's *t* test and Fisher's exact test.

RESULTS

Among 1,072 patients who presented with complaints of insect sting allergy, we identified 250 who had received WBE treatment for at least six months and had positive venom skin test results at the time of our initial assessment. Of these 250 patients, 110 had been stung during treatment, and an additional five were stung within six months of their last booster injection. A total of 291 insect sting episodes were reported in these 115 patients. Fourteen patients (12%) had no reaction (NR) to 24 stings. Reactions no worse than prolonged large local (LL) swelling occurred in 26 patients (23%) on 71 stings (63 LL, eight NR). Seventy-five persons (65%) who had been stung experienced at least one systemic allergic reaction (SR) similar to that which had occurred before treatment. Of 196 stings in these 75 patients, 174 caused SRs, whereas 15 caused only

Reaction Type*	No. of Patients	Total Stings	Sting Reactions		
			SR	LL	NR
SR	75	196	174	15	7
LL	26	71	0	63	8
NR	14	24	0	0	24
Total	115	291	174	78	39

*Patients were classified according to the most severe sting reaction experienced during treatment. SR indicates systemic reaction; LL, large local reaction; NR, no reaction.

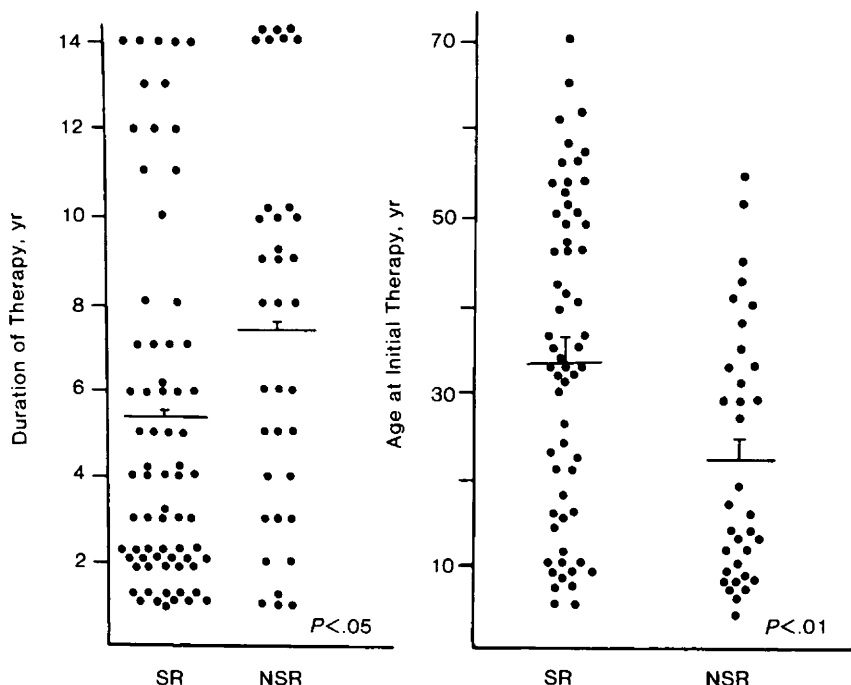


Fig 1.—Left, Duration of whole-body extract (WBE) therapy at time of our initial assessment is shown for systemic reaction (SR) and nonsystemic reaction (NSR). Mean±SEM is shown for each group. Statistical significance of difference in means (by median test and Student's *t* test) is shown. Right, Age at time that WBE therapy was initiated is shown for SR and NSR. Mean±SEM is shown for each group, as well as statistical significance of their difference.

LL, and seven resulted in NR (although each patient had at least one SR). The data are summarized in Table 1. Of 291 stings in 115 patients, 174 (60%) caused SRs, 78 (27%) caused LLs, and 39 (13%) caused NR.

Large local and nonreactors (collectively designated nonsystemic reactors [NSR]; NSR=LL+NR) were compared with systemic reactors with respect to duration of treatment and age at which WBE therapy was initiated (Fig 1). The mean (±SEM) duration of WBE therapy was 5.4 (±0.6) years for SR, and 7.7 (±0.9) years for NSR ($P<.05$). The mean age at which WBE therapy was begun was 33.7 (±2.3) for SR and 22.4 (±2.4) for NSR ($P<.01$). Age and duration of therapy were unrelated variables (by linear regression).

Although not clearly related to gender, sting reactivity was significantly less when therapy was begun in childhood ($P<.02$) or lasted more than two years ($P<.02$). Figure 2 shows that there was no consistent change in the severity of allergic sting reactions as a result of WBE therapy.

Among the 115 patients who were stung during therapy, the product used for immunization was known in 28 cases, and all had received mixed stinging insect WBEs. The dose achieved was known in 25 cases: 16 received at least 0.2 mL of 1:10 dilution, four received solutions at a 1:20 or 1:50 dilution, four received a 1:100 dilution, and one received only a 1:1,000 dilution. Maintenance intervals varied from one to six weeks. Among the 25 patients whose treat-

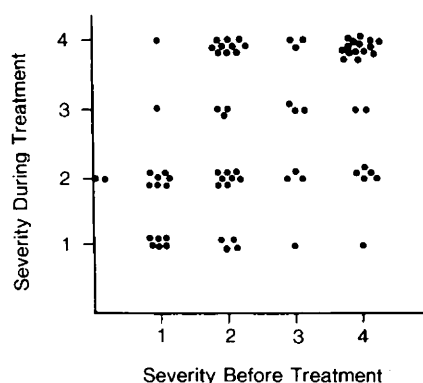


Fig 2.—Graded severity of allergic sting reactions before and during whole-body extract therapy is shown for each patient stung during treatment (see text for grade system).

ment doses were known, the outcome of subsequent stings was not different than for the total population: 20 had SR, one LL, and four NR. By reaction grade (see "Methods"), eight worsened, eight improved, and nine were unchanged. Two of the persons who improved (by virtue of NR) had self-administered epinephrine at the time of the sting. The outcome of stings in these 25 patients did not relate to the treatment dose achieved.

Table 2 summarizes the histories of 15 patients chosen because their treatment doses were known and also to make the age and sex distribution of the table representative of the total sample.

COMMENT

Whole-body extract therapy has gained wide acceptance as a satisfactory method of prophylaxis for insect sting allergy. While our referral population is undoubtedly biased toward treatment failure, we present here an assembly of 75 patients in whom this treatment was unsatisfactory, and, in one case, fatal. Ninety-five percent of these patients lived within an 80-km radius of Baltimore.

The importance of the therapeutic regimen has been emphasized in the literature on WBE but has never been perfectly clear. Until recently, the recommended approach¹⁴ was to build up to the highest tolerated maintenance dose, usually between 0.3 mL of 1:100 dilution and 0.2 mL of 1:10 dilution. This dose was then to be repeated monthly for one year, every two months the second year, every three months the third year, and then to be discontinued. Most of the per-

Patient / Sex / Age, * yr	WBE Therapy		No. of SR/Stings†	Reaction Grade§	
	Duration, yr	Dose†		Before	During
1/F/16	2	NA	2/2	2	3
2/M/18	2	1.0/1:50	1/1	1	1
3/M/8	6	0.5/1:10	1/1	1	2
4/F/46	6	0.5/1:100	2/2	3	2
5/F/39	1	0.4/1:10	1/3	1	2
6/M/51	1	0.45/1:10	1/1	4	4
7/M/46	2	0.5/1:10	1/1	1	2
8/F/32	2	NA	1/1	4	4
9/M/54	5	0.5/1:10	2/2	2	4
10/M/16	29	0.6/1:10	2/2	2	4
11/M/46	4	0.9/1:10	2/2	4	2
12/M/7	5	0.2/1:10	1/2	1	1
13/M/53	2	0.5/1:10	3/3	3	3
14/M/47	12	NA	2/2	2	4
15/M/10	7	0.9/1:10	1/1	1	2

*At time of initial WBE therapy.

†Dose, mL/Concentration (weight/volume). NA indicates not available.

‡SR indicates systemic reactions; stings, total number of stings during therapy.

§Systemic reaction before and during WBE therapy. Sting reactions were graded as follows: large local only, 0; cutaneous symptoms only, 1; respiratory or vascular symptoms (with or without cutaneous symptoms), 2; respiratory and vascular symptoms (with or without cutaneous symptoms), 3; and loss of consciousness (with or without any other symptoms), 4.

sons described herein were treated along these guidelines and were led to expect protection, except that treatment was extended in many cases owing to continued allergic sting reactions. It was not until 1977 that Mueller¹³ published his recommendations that the maintenance dose must be at least 0.2 mL of 1:10 dilution and should be continued beyond the third year with annual booster injections. In fact, of the 25 patients in this review whose doses were known, 16 (65%) received the maximum dose and still had the same results as the group as a whole: 80% had SR (six worse, six same, one better than pretreatment systemic reactions).

The medical literature through 1976 reported clinical efficacy of 95% for WBE therapy.¹²⁻¹⁴ The basis of these reports bears careful analysis, since much of the perceived efficacy may lie in (1) the definition of reasonably expected goals of "effective" treatment and (2) an insufficient knowledge of the natural history of the disease. The past decade has seen advances in the understanding of insect sting allergy and its treatment that have changed the frame of reference for the assessment of therapeutic efficacy.

The efficacy of WBE therapy has been defined by criteria developed for the assessment of pollen immunotherapy. Whole-body extract treat-

ment has been called successful when, after two years of regular injections, the patient suffers a systemic reaction of lesser severity than pretreatment reactions. These criteria are inappropriate for insect sting allergy where the morbidity associated with anaphylactic reactions is almost completely preventable after only a few weeks of venom immunotherapy.^{4,5,10} Successful immunotherapy for this disease must now be defined as inducing a total lack of systemic allergic reaction to a sting. It is in this light that we present 75 WBE treatment failures. It is not possible to reassess retrospectively reports of WBE efficacy, since patients who were "improved" may well have had systemic symptoms of any severity. The treatment failures described herein showed no such tendency toward improvement during therapy (Fig 2): 22% had milder reactions, 34% had worse reactions, and 44% had reactions similar to their pretreatment reactions.

The failure of WBE therapy has often been attributed to treatment with insufficient doses or for too short a time. However, many of the treatment failures presented here received very high doses for prolonged periods of time. Mueller et al¹⁴ have suggested that reactions to stings become less likely after at least two years of therapy. Our data indi-

cate that there may be some validity to this suggestion. Although there were numerous individual exceptions, Fig 1 (left) shows that NSR patients had a longer mean duration of therapy than SR patients. Of those who received six to 24 months of treatment, 82% had SR compared with 58% with three to 29 years of therapy. The significance of this difference ($P<.01$ by Fisher's exact test) indicates that the passage of time may be associated with a slight decrease in the risk of reaction. Whether this is due to WBE treatment or to the natural history of the disease is not clear, since spontaneous loss of sensitivity does occur⁷ and is not uncommon in children.¹⁸ Also, other unknown factors may influence the natural course of the disease, and the outcome of any given sting is influenced by the species of the insect and any self-medication, both of which are not documented. The data support reports that WBE is only as effective as placebo in short-term⁴ and long-term treatment.¹⁹

The age of patients at the time of initial WBE treatment (Fig 1, right) is an important consideration in view of our increasing appreciation of the natural history of insect sting allergy. Patients at risk (as judged by history and venom skin tests) do not always react to a sting. In adults, only 30% to 60% will react,^{4,17,20} whereas the reaction rate in untreated children (younger than 17 years) may be as low as 15%.¹⁸ In the affected population described in the largest review of WBE therapy,¹² 41% were younger than 20 years. The recommended regimen for WBE treatment was based on observations of a population of which 84% were younger than 20 years.³ There is reason to believe that the outcome of a sting may be age dependent (Golden et al, unpublished data,

March 1981)¹⁸ and that this factor must be considered for accurate assessment of treatment efficacy. The mean age of the NSR group in this report was significantly less ($P<.01$) than that of the SR group (Fig 1, right). In fact, of those who began WBE therapy before age 17 years, only 48% had SR to subsequent stings, compared with 73% of patients who began treatment after age 17 years ($P<.02$ by Fisher's exact test). This is consistent with the previously observed age dependence of reactivity and illustrates the potential for overestimation of the clinical efficacy of treatment in young persons.

We conclude that WBE treatment is not effective for the prevention of allergic insect sting reactions. Furthermore, its apparent efficacy in some patients may be due in part to the natural history of the disease rather than to the WBE injections, since only 15% to 60% of untreated patients react to a challenge sting, in an age-dependent fashion. Venom immunotherapy is safe and is highly effective within a few weeks and must, therefore, be emphasized as the only recommended form of prophylaxis for insect sting allergy.

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