

The Imported Fire Ant: Immunopathologic Significance

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The Imported Fire Ant: Immunopathologic Significance

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The imported fire ant is a major insect cause of generalized hypersensitivity in the southern United States. The alkaloids in the ant's unique venom also produce substantial morbidity due to local reactions, both toxin- and IgE-mediated. Immunotherapy—with whole body extracts as well as with venom—is given only to patients with systemic reactions.

In some parts of the southeastern and south central United States and Puerto Rico, hypersensitivity reactions to imported fire ant stings are more common than those to stings from other hymenoptera—bees, wasps, yellow jackets, and hornets. Imported fire ants are aggressive and will attack en masse any human or animal that encroaches on their nest. They infest both urban and rural areas and have been known to invade homes and sting sleeping occupants.

The reactions to the sting of the imported fire ant range from local pruritus and erythema to anaphylactic shock and death. Many patients experience a large local reaction rather than a systemic allergic response, and a few have delayed neurologic sequelae. Moreover, secondary infection of the sting site can result in substantial morbidity. Clinicians should be aware of the variable consequences of an imported fire ant sting, as not all of them require immunotherapy. This knowledge is also relevant for clinicians living outside the South, since they may be called on to treat patients who have been stung while on vacation.

The venom of the imported fire ant is substantially different from that of other hymenoptera. A major difference relates to the low protein content and unique structure of the allergenic proteins contained in imported fire ant venom. This makes it unlikely for allergic patients to cross-react from fire ants to other hymenoptera, or vice versa. Also noteworthy is the experience that venom extracts are clearly preferable to whole body extracts (made from ground whole insects) for diagnosis and immunotherapy of

hypersensitivity to bees and vespids, but imported fire ant whole body extract and venom appear to be equally efficacious.

Entomology

Many insects can cause systemic allergic reactions. In the order Hymenoptera, these include the families Apoidea (bees), Vespoidea (wasps, yellow jackets, and hornets), and Formicoidea (ants). Of the ants, only those in the genus *Solenopsis* (fire ants) and the genus *Pogonomyrmex* (harvester ants) are known to cause IgE-mediated allergy in humans. Harvester ants are native to North America and are concentrated primarily in the southwestern United States and Mexico.

North American fire ant populations are dominated by twentieth-century immigrants from South America. Included are two species that were brought through the port of Mobile, Ala. The black imported fire ant, *Solenopsis richteri*, is native to Uruguay and Argentina. It spread slowly through the Southeast via transportation of agricultural products and soil after it was introduced, circa 1918. The red imported fire ant, *S. invicta*, was introduced from Brazil and Paraguay in the 1930s (Figure 1). *S. invicta* quickly displaced *S. richteri* because it is more aggressive and better adapted to southern climatic condi-

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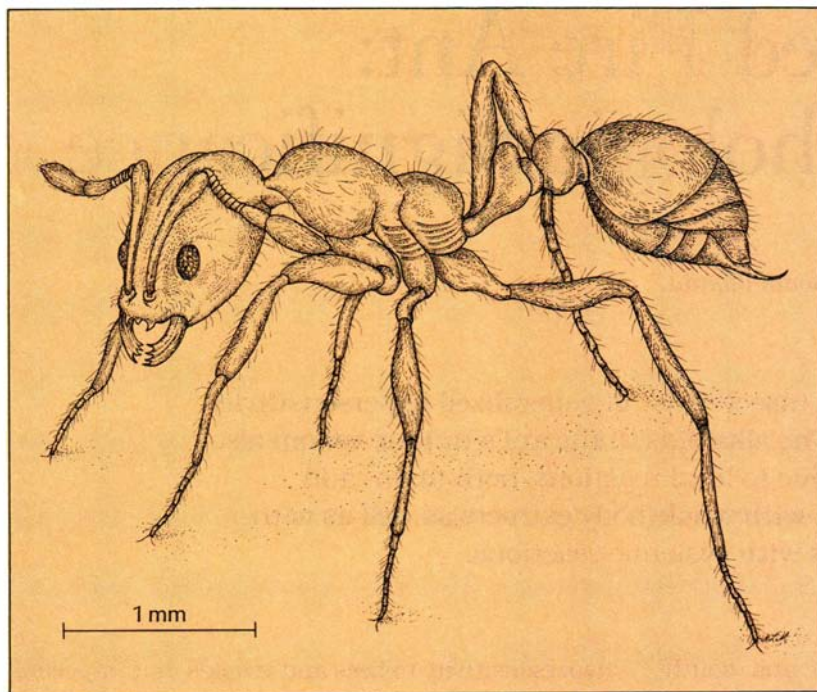


Figure 1. The worker ant of the genus *Solenopsis* is 3 to 6 mm long. To sting, the ant attaches its mandible to the skin, arches its back at the peduncle, and injects venom through a stinger at the tip of its abdomen. If left undisturbed, the ant will rotate on its mandible and sting repeatedly.

tions (Figure 2). Today, *S. richteri* is limited to a small area along part of the northern common border between Alabama and Mississippi. *S. invicta* has also largely displaced the native southern fire ant, *S. xyloni*, and the tropical fire ant, *S. geminata*, which was introduced to the United States in the sixteenth and seventeenth centuries. These two species are less aggressive than *S. invicta*, but their stings can result in severe systemic allergic reactions. Hybrids of *S. invicta* and *S. richteri* have also been identified. These hybrids occupy some of the territory (Georgia, Alabama, Mississippi) previously thought to be exclusive to *S. richteri*.

The imported fire ant is difficult to control with conventional insecticides and rapidly reinfests treated areas once the chemical has deteriorated. Soil temperature and moisture seem

to be the major two factors that limit its geographic spread. The northern boundary is extending northward but not rapidly, because of the inability of either species to withstand prolonged freezing temperatures. Favorable climatic conditions exist for extension of the current habitat to the entire West Coast and from Florida to Delaware on the East Coast. The desert conditions of Texas have hampered the westward spread of *S. invicta*, but isolated colonies have been identified and eradicated in Arizona, New Mexico, and California. The hybrids may be less cold sensitive than *S. invicta* and *S. richteri* and could therefore eventually spread north.

Epidemiology of Stings

Surveys indicate that up to 58% of the population in some areas of the southeastern and

south central United States are stung by imported fire ants each year. Anaphylaxis occurs in up to 1% of them. The prevalence of systemic allergic reactions is in all likelihood grossly underreported, since many persons who have systemic reactions do not realize the potential danger and therefore do not seek medical attention.

In a survey of a New Orleans suburb, Richard D. deShazo and co-workers found that 35% to 58% of residents had been stung within the past year. Wayne Yaeger reported that in one Georgia county, imported fire ants attack 13.8% of the exposed population each year, of whom 5% require medical attention for reactions ranging from mild local toxicity to life-threatening anaphylaxis. R. Fasser Triplett reported that 901 Mississippi physicians treated 12,438 ant stings in seven months. As many as 16% of the stung patients exhibited systemic allergic symptoms, with anaphylactic shock reactions occurring in 0.6%. South Carolina physicians surveyed by R. S. Lawrence reported 69 cases of anaphylaxis among 1,088 patients treated for stings over a two-year period.

Charles J. Hannan and colleagues have reported a seasonal variation in antigens of *S. invicta*. This variation may contribute to the higher rate of imported fire ant systemic reactions during the summer months.

Imported Fire Ant Venom

The venom produces a sharp, burning sensation—hence the name “fire ant.” The venom is chemically unique, in that it has an extremely low protein content and consists predominantly of toxic alkaloids. All

other venoms that have been characterized, including those of insects and vertebrates, do not contain alkaloids but are primarily concentrated, aqueous protein solutions. Indeed, there is more similarity between bee and rattlesnake venom than there is between bee and fire ant venom.

The venom of *S. invicta* has been characterized. Its alkaloid fraction consists of various water-insoluble 2,6-disubstituted piperidines, which account for 95% of the venom. The piperidine alkaloids possess direct tissue toxicity, as well as hemolytic, bactericidal, and insecticidal properties. They are able to activate the alternate complement pathway; however, skin testing, radioallergosorbent testing (RAST), and RAST inhibition have shown that the piperidines are not allergenic. They cause the typical delayed pustule.

The 5% aqueous fraction of the venom contains a small amount of solubilized protein. Less than 0.1% of the total venom weight consists of proteins, including those that are capable of causing systemic imported fire ant hypersensitivity. A single sting delivers 10 to 100 ng of protein. Various efforts to isolate the proteins and to characterize their antigenic and allergenic properties have been hampered by the difficulty in obtaining sufficient quantities of venom.

Most recently, Donald R. Hoffman and co-workers isolated four allergenic proteins from both commercial (collected by an electric shock method) and hand-milked pure *S. invicta* venom, using gel filtration and high-performance cation exchange chromatography. No other fraction of the venom was found to have IgE binding ac-

tivity. The four proteins were tested by RAST on the sera of 23 patients with imported fire ant hypersensitivity, and all had significant allergenic activity.

The proteins have molecular weights ranging from 15,000 to 37,000 and have been designated *Sol i* I, II, III, and IV. *Sol i* II and III are the major proteins, respectively representing 67% and 20% of the venom protein. *Sol i* I represents 4% of the venom protein and *Sol i* IV 9%. Amino acid analysis showed that the proteins are structurally different and not derived from each other. *Sol i* II is a phospholipase that is both structurally and functionally different from phospholipases found in other hymenoptera venoms. Rabbit antisera raised against bee and vespid phospholipases did not react with *Sol i* II on immunoblot analysis.

Individual serum samples from the 23 allergic patients did not react equally to the four proteins; however, none of the allergens was dominant. The sera of some patients did not

show IgE binding activity to all four proteins, but each of the four showed the highest IgE binding activity for at least four serum samples. Linear regression analysis of RAST data showed that the IgE responses to the allergens were not related to each other.

Hoffman has also shown that venom from *S. richteri* contains three proteins, *Sol r* I, II, and III, which are similar to *S. invicta* proteins. *S. richteri* venom does not have a protein similar to *Sol i* IV. The venoms of the two species are highly cross-reactive on direct RAST and RAST inhibition studies.

We have obtained results similar to Hoffman's in a study of *S. invicta* whole body extract, performed in conjunction with S. Lennart Nordvall and S. Gunter Johansson in Sweden. An allergen extract made from ground whole ant is a complex mixture of venom and body antigens, most of which are not allergenic. Since the clinical efficacy of commercial whole body extracts may vary, we prepared our own extract and analyzed it

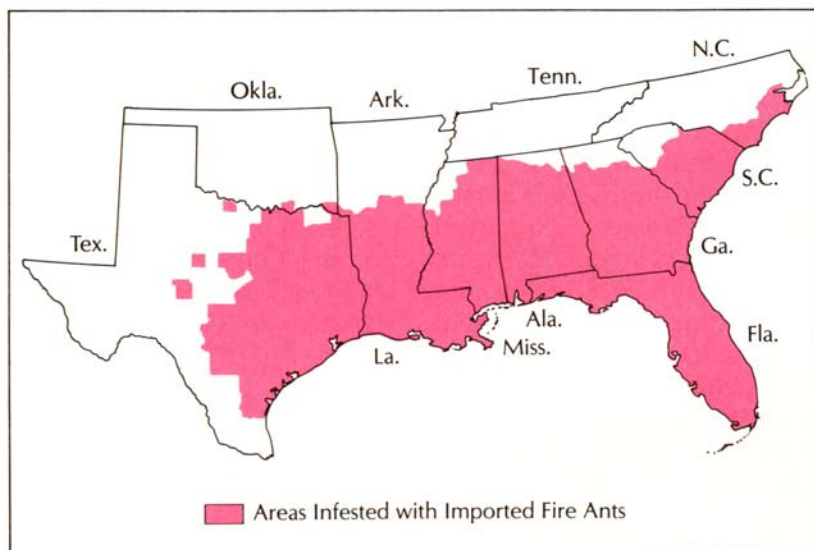


Figure 2. Parts or all of these southern states (and U.S. Caribbean possessions) are infested with imported fire ants, which may spread to other warm-weather states. A cold-tolerant hybrid adds the possibility of greater spread.



Figure 3. The sting of the imported fire ant results in an immediate wheal-flare response; within 24 hours, a characteristic sterile pustule appears at the sting site. If left undisturbed, the pustule usually resolves over three to 10 days.

with crossed immunoelectrophoretic techniques. Six allergens were identified, but in immunoblotting studies, only four bound to IgE from 24 patients with hypersensitivity to the imported fire ant. The four antigens had molecular weights ranging from 13,000 to 42,000, and as in Hoffman's study, two fulfilled criteria for major allergens. Three of the four allergens were easily identified in crossed immunoelectrophoresis of a commercial venom.

The venoms of bees and vespids contain systemically vasoactive and cytotoxic substances, in addition to their hypersensitivity-inducing proteins. Bee venom, for example, contains apamin, which is known to be a specific centrally acting neurotoxin. Bee and vespid stings can therefore also produce toxic, sometimes fatal, non-IgE-mediated reactions, including seizures, cerebral edema, vasculitis, pulmonary emboli, and renal failure. Unlike anaphylactic reactions, these toxic sequelae occur not immediately after the sting but a day or more later.

The venom of the imported fire ant does not appear to have such nonallergenic generalized effects. Although its piperidine

alkaloids are toxic at the sting site, they seem to be detoxified locally and do not have cumulative systemic effects. Nonallergic adults routinely receive dozens and even hundreds of ant stings in a single exposure without any systemic symptoms. Indeed, a case report of a woman who sustained approximately 10,000 imported fire ant stings without any sequelae argues strongly against nonallergenic systemic effects of any kind.

Pustule

The intense inflammatory reaction and pustule that develop at the imported fire ant sting site probably result from the potent cytotoxins and hemolytics found in the alkaloid fraction of the venom. The toxins cause localized necrosis of the dermis and underlying connective tissue to create the characteristic sterile pustule that appears within 24 hours after almost all stings (Figure 3). The likelihood of pustule formation is probably a function of the amount of toxin injected. In the United States, this pustule is pathognomonic for *S. invicta* and *S. richteri* stings, except for an occasional pustule caused by native or tropical fire ants.

A 25- to 50-mm erythematous flare develops immediately after a sting, followed in a few minutes by a wheal that may enlarge up to 10 mm in diameter. The wheal-flare response is most prominent at 20 minutes and resolves within two hours. A vesicle containing clear fluid begins to form in four hours. The fluid becomes cloudy over the next several hours, and within 24 hours, the pustule is usually umbilicated and surrounded by a red halo and an area of edema. If undisturbed, the pustule will rupture or resolve over three to 10 days, leaving a superficial scar, macule, or fibrotic nodule.

Histologic studies indicate that imported fire ant venom causes histamine release at the sting site. Slight infiltration of lymphocytes, histiocytes, and plasma cells, local edema, and some necrosis begin within 30 minutes. At 24 hours, the pustule contains many necrotic polymorphonuclear cells, lymphocytes, and neutrophils. By 72 hours, these have been joined by plasma cells and eosinophils (Figure 4). At this time, the pustule's central floor area is obliterated, and the cellular infiltrate extends into the underlying necrotic tissue. The pustule fluid contains necrotic cellular debris and leukocytes, primarily neutrophils.

Being sterile, the pustule usually heals spontaneously. The intense pruritus, however, prompts many patients to scratch off the pustule's thin epidermal covering, creating a direct route for secondary infection, which can cause considerable morbidity; sepsis and death have been reported. Local sepsis and, in some patients (particularly those with diabetes mellitus or impaired circula-

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tion), local necrosis may require surgical debridement and skin grafting or, occasionally, partial or complete amputation of a limb.

There is no treatment that will alter the evolution of local toxicity and the necrotic pustule. In a study with rabbits, we determined that topical steroids, systemic steroids, systemic antihistamines, sympathomimetics, local abrasion and treatment with povidone-iodine solution, and aspiration of pustules did not alter the pustule's clinical or pathologic course. Prophylactic treatment with topical or parenteral steroids could not protect the animals against the immediate destructive action of the alkaloid cytotoxins.

The management of choice for the pustular lesion caused by the imported fire ant is repeated cleansing of the site with soap and water, covering the lesion to prevent excoriation, and immediate treatment of secondary infection. Topical anesthetics or oral antihistamines may be used for pruritus.

Large Local Reactions

As with other hymenoptera stings, large local reactions are common after imported fire ant stings, developing in perhaps 15% to 50% of patients. Triplett reported that almost 50% of 12,438 stung patients had localized swelling, and another study of 226 stung patients showed that 17% had swelling greater than 25 mm in diameter at the sting site.

DeShazo and co-workers have characterized the large local reaction that occurred in 36 of 65 stung patients. The immediate wheal-flare reaction evolved in-

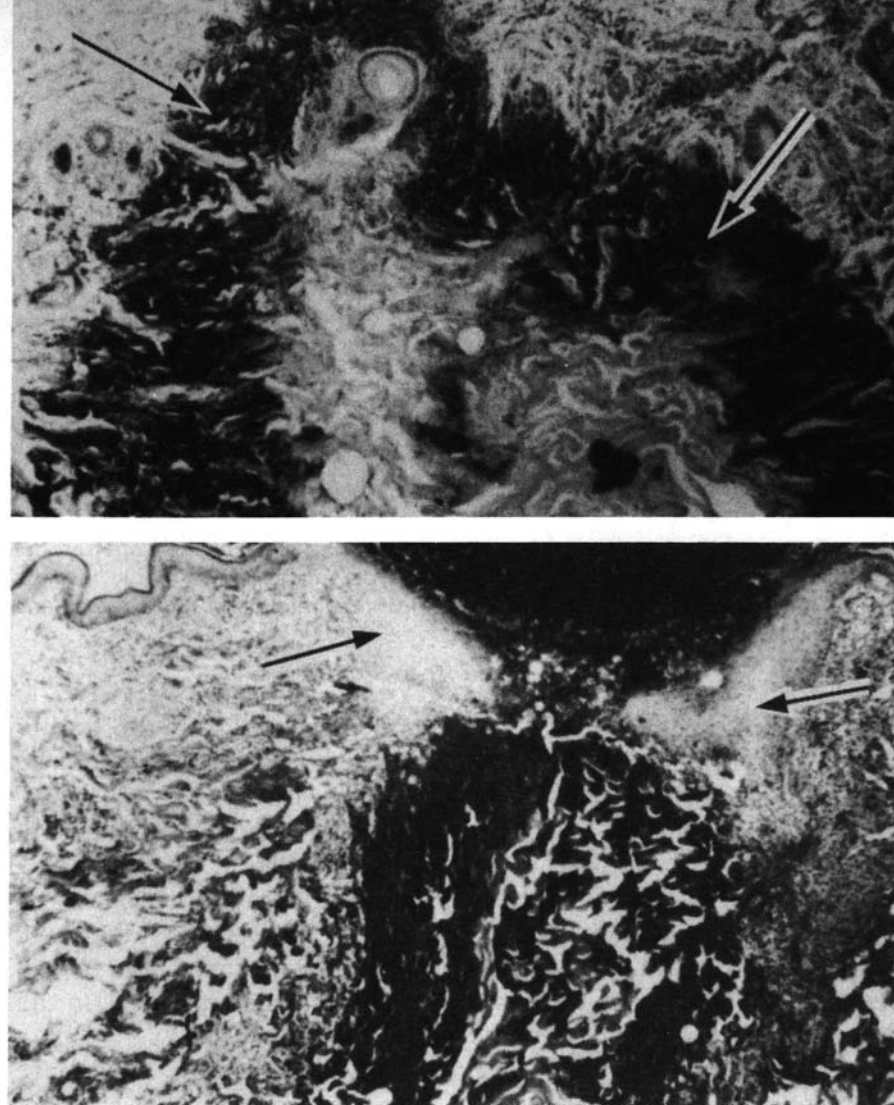


Figure 4. H&E-stained rabbit skin shows intense eosinophil-neutrophil infiltrate (arrows) in reticular dermis abscess 48 hours after fire ant sting (top). Five days later, necrosis has decreased, the epidermis has thickened (arrows), and macrophages are seen at the abscess's edge (bottom).

to pruritic, often painful, erythematous, edematous lesions within one to two hours (Figure 5). The size of the wheal-flare response at 20 minutes directly correlated with the size of the large local reaction at six hours. The second reaction peaked at 24 hours and resolved in 48 hours.

On the basis of the temporal sequence and histopathologic studies, deShazo called the large local reaction an IgE-mediated late-phase response. Pathologically, it resembled late-phase reactions that develop after intradermal injections of ragweed or insulin, characterized by dense fibrin deposits with trap-

ping of edema in the reticular dermis around the pustule. Eosinophils were present at 24 hours in the pustular fluid of the dual reactors but not in the single reactors. None of the patients had a systemic allergic reaction (Figure 6). It also is possible that the large local reaction is a form of dermal hypersensitivity mediated by nonimmunologic mechanisms.

In a study of 133 patients from the Buffalo, N.Y., area who had large local reactions to bee and vespid stings, Paul M. Mauriello and co-workers found that such patients are likely to have similar reactions when they are stung again, with very

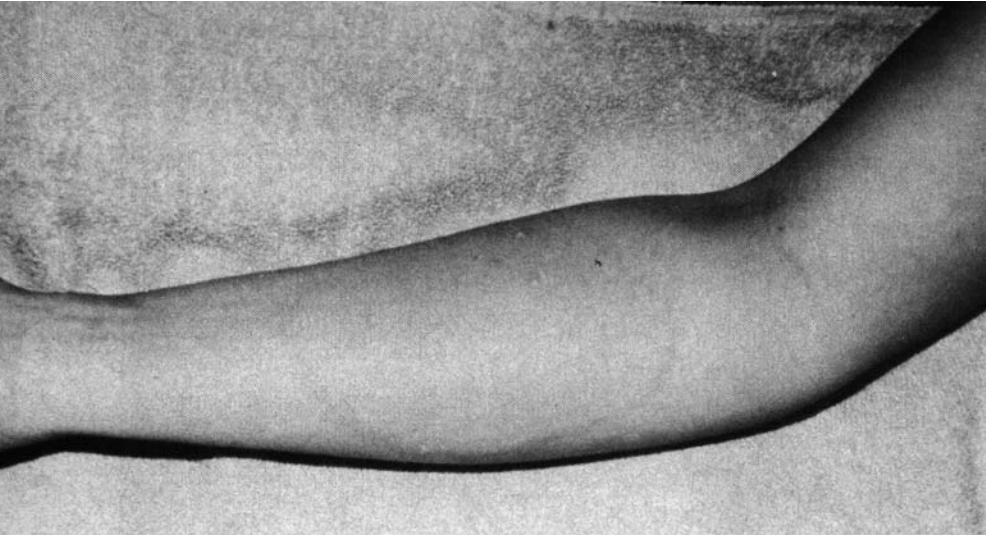


Figure 5. Large local reaction often results from the sting of the imported fire ant. In this patient, shown six hours after three stings from a single fire ant, much of the forearm is covered by a pruritic, painful, erythematous, and edematous lesion. The reaction peaked in size at 24 hours.

cur. It thus appears reasonable to recommend imported fire ant immunotherapy for patients who experience a seizure after a sting if they have appropriately positive skin tests.

Hypersensitivity Reactions

In a classic review, Robert B. Rhoades and co-workers studied 104 cases of imported fire ant hypersensitivity that were documented by either typical pustule formation or positive skin tests. Patients sustained one to 100 ant stings (average, 10), and onset of anaphylaxis was almost immediate (average, 13 minutes). The characteristic pustule was identified in 86%. Prominent features of the hypersensitivity reactions included diffuse erythema, pruritus, urticaria, or angioedema, respiratory distress (secondary to laryngeal edema or bronchospasm or both), nausea, dizziness, hypotension, circulatory collapse, coma, and death.

Whether atopic disease predisposes to anaphylaxis remains controversial. A history of allergy was documented in 28 of 83 patients (34%) in Rhoades's study. However, large epidemiologic studies of patients who are allergic to bees and vespids have found no increased incidence of atopy.

Allergic reactions are more common in children than in adults. John Strimas and co-workers studied 19 children, aged 15 to 39 months, with imported fire ant hypersensitivity and found that they have higher serum levels of specific IgE antibodies to the fire ant than do adults.

Treatment is no different from that for any other anaphylactic reaction—primarily epinephrine and antihistamines

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little risk of systemic anaphylaxis. Only one of 130 twice-stung subjects had a systemic anaphylactic reaction. Neither skin testing nor determination of serum levels of venom-specific IgE was able to predict subsequent large local reactions, and venom immunotherapy did not prevent them. Similarly, a review of 118 patients with bee and vespid sting anaphylaxis showed that only five had had a large local reaction to an earlier sting.

The results of these studies suggest that in the absence of associated systemic symptoms, skin testing, RAST, or prophylactic immunotherapy is unnecessary for patients with a large local reaction to an imported fire ant sting. Therapy for a large local reaction consists of symptomatic treatment with oral corticosteroids, antihistamines, or both. Steroids may not be helpful unless begun within 48 hours of the sting. They should be continued for three to five days.

Neurologic Sequelae

Neurologic manifestations secondary to the imported fire ant sting are rare. They usually involve the central nervous sys-

tem, develop 24 to 96 hours after the sting, and may not be associated with an earlier reaction. We have reported neurologic sequelae in five patients: a right radial mononeuropathy, a focal motor seizure, and three grand mal seizures. The neurologic disorder resolved in all five patients.

The neuropathy may have been the result of local neurotoxic effects of piperidine alkaloids in the venom, nerve compression by local edema and swelling, or direct injury to the nerve or its vascular supply. Focal motor seizures are not typical of anaphylactic convulsions. In two patients, the grand mal seizure occurred immediately after the sting and may have been the presenting manifestation of a hypersensitivity reaction. In the third patient, the grand mal seizure occurred more than six hours after the initial collapse and treatment for anaphylaxis.

Most neurologic problems associated with other hymenoptera stings consist of transient alterations of consciousness associated with anaphylactic shock immediately after a sting, but delayed neuropathies and encephalopathies also oc-

(see table). When necessary, other drugs and supportive care may be required.

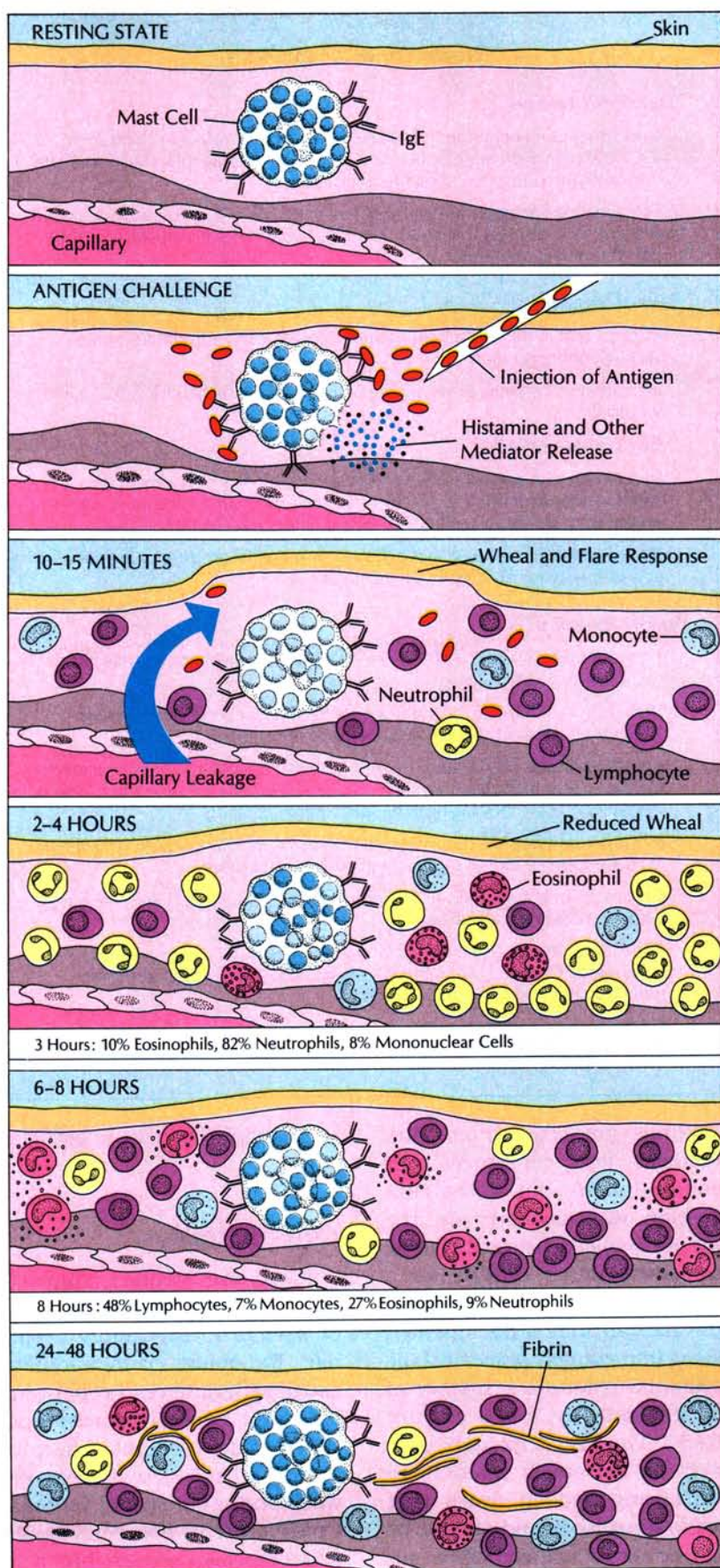
Anaphylactic Death

Fifty to 60 deaths from bee and vespid stings are documented in the United States each year, but this is thought to represent only 25% to 50% of real mortality. Fatal anaphylactic reactions to the imported fire ant sting are less frequent nationally than are those to other hymenoptera, but the true incidence remains unknown. In many parts of the South, however, the imported fire ant is the leading cause of insect-induced anaphylactic death.

A survey by Rhoades and colleagues documented 31 fatal reactions to imported fire ant stings. Death was rapid, and victims ranged in age from infancy to 65 years. Most of the deaths were caused by fewer than five stings, although some involved 20 or more stings.

Anaphylactic death is more common among adults than among children, particularly in the elderly and those with coronary artery disease. Postmortem findings, while nonspecific, are typical of other hymenoptera-induced pathology. Primary

Figure 6. Local reactions to imported fire ant stings resemble the late-phase reactions that develop after intradermal injection of antigen. In this schematic synthesis of work done in a number of laboratories, the immediate response triggered by antigen involves antigen-IgE-mediated degranulation of the mast cell, release of histamine and other mediators, and recruitment of inflammatory cells. Various chemotactic factors activated during the acute reaction induce the cellular infiltration and fibrin deposits that characterize the late phase.



Treatment of Anaphylaxis

Immediate Measures

Give aqueous epinephrine 1:1,000, 0.3 to 0.5 ml (0.01 ml/kg in children) SC or IM. Repeat once or twice if necessary at 15- to 20-minute intervals to maintain normal blood pressure and control symptoms.

Mix aqueous epinephrine 1:1,000, 0.1 ml to 0.3 ml in 10 ml of normal saline, and give IV over several minutes. Repeat as necessary for anaphylactic shock not responding to therapy.

General Measures

Place patient in the recumbent position. Elevate lower extremities or use Trendelenburg position.

Establish and maintain airway (endotracheal tube or tracheostomy may be required).

Give oxygen as needed.

Start IV line with normal saline for fluid replacement and as a route for additional medication. If severe hypotension exists, rapid infusion of volume expanders is necessary (colloid-containing solutions or saline).

Place a venous tourniquet above the reaction site (insect sting or injection) to decrease systemic absorption of the antigen.

Specific Measures

Aqueous epinephrine 1:1,000, 0.1 to 0.3 ml, at the site of antigen injection will delay its absorption.

Diphenhydramine, 60 to 80 mg (5 mg/kg/24 hours) can be given IV over 3 minutes if the patient is not responding to initial therapy.

Aminophylline, 6 mg/kg administered over 20 minutes IV, should be given if the patient has bronchoconstriction. Make appropriate adjustments in dose if the patient is currently taking a theophylline preparation.

If hypotension persists, dopamine, 400 mg in 500 ml D5W, should be given IV at an appropriate rate to maintain normal blood pressure.

Glucocorticoids are usually not helpful in acute anaphylaxis. They may be useful in protracted anaphylaxis.

Cimetidine, 300 mg administered IV over 5 minutes, may reverse refractory anaphylaxis. Caution: Transient hypotension and bradycardia have been reported after rapid IV administration.

Glucagon, 2 to 5 units given IV over 2 minutes, may be useful when a β -blocker is complicating anaphylaxis.

findings are acute pulmonary changes and cerebrovascular congestion. In some cases, congestion was also seen in the kidneys, spleen, adrenal glands, and liver. Other criteria for a postmortem diagnosis of anaphylaxis include a documented sting immediately preceding the systemic reaction, a history of hypersensitivity, and a positive RAST. The RAST, in particular, may be extremely valuable in explaining sudden death that occurs outdoors and should be performed routinely when in-

sect anaphylaxis is a possible cause.

Cross-reactivity

There are striking similarities among the venom proteins of insects in the family Vespidae. Extensive cross-reactivity exists with different hornet venoms and between hornet and yellow jacket venoms. There is limited cross-reactivity between wasp and other vespid venoms. Cross-reactivity between vespids and bees also occurs, but this

is unusual. About 50% of patients who are hypersensitive to one vespid will have cross-reactivity to another.

The low protein content of imported fire ant venom and the unique structure of its allergenic proteins suggest that cross-reactivity would be unlikely. Clinical experience also indicates that a person who is allergic to bees, wasps, yellow jackets, or hornets probably is at no greater risk for a systemic reaction to a fire ant sting than a person with no history of hymenoptera hypersensitivity.

Some studies do hint at the possibility of at least some cross-reactivity, however. In Rhoades's report of 104 patients, eight had a history of hypersensitivity to other insects. Another five patients who were newcomers to the South or from the North had a systemic reaction to their first imported fire ant sting, which indicated that they might have been initially sensitized through a cross-reacting antigen, possibly of another insect.

Rhoades also reported a high incidence of skin-test and RAST cross-reactions between persons hypersensitive to imported fire ants and those sensitive to other hymenoptera. Similarly, J. E. Moffitt and co-workers found that 34 of 47 patients allergic to bees and vespids had positive skin tests to imported fire ant venom, and 11 of 19 were RAST-positive to imported fire ant venom. Hoffman notes that sera from patients allergic to bees and vespids react primarily with *Sol I* and suggests that this is a cross-reactive allergen.

Diagnosis

Imported fire ant whole body extract (WBE) is the only com-

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Rogaine® minoxidil 2% TOPICAL SOLUTION

INDICATIONS AND USAGE

Male pattern baldness (alopecia androgenetica) of the vertex of the scalp. No effect has been seen on frontal baldness. At least four months of treatment are generally required before evidence of hair growth can be expected; further growth continues through one year. The new growth is not permanent; cessation of treatment will lead to its loss in a few months.

CONTRAINDICATIONS

Hypersensitivity to minoxidil, propylene glycol or ethanol.

WARNINGS

1. *Need for normal scalp:* Before starting treatment, make sure that the patient has a normal, healthy scalp. Local abrasion or dermatitis may increase absorption and hence the risk of side effects.

2. *Potential adverse effects:* Although extensive use of topical minoxidil has not revealed evidence that enough minoxidil is absorbed to have systemic effects, greater absorption due to misuse, individual variability or unusual sensitivity could, at least theoretically, produce a systemic effect.

Experience with oral minoxidil has shown the following major cardiovascular effects (Review the package insert for LONITEN® Tablets for details):

—salt and water retention, generalized and local edema

—pericardial effusion, pericarditis, tamponade

—tachycardia

—increased incidence of angina or new onset of angina

Patients with underlying heart disease, including coronary artery disease and congestive heart failure, would be at particular risk of these potential effects. Additive effects could also emerge in patients being treated for hypertension.

Potential patients should have a history and physical, should be advised of potential risks and a risk/benefit decision should be made. Heart patients should realize that adverse effects may be especially serious. Alert patients to the possibility of tachycardia and fluid retention, and monitor for increased heart rate, weight gain or other systemic effects.

PRECAUTIONS

General Precautions: Monitor patients one month after starting ROGAINE and at least every six months afterward. Discontinue ROGAINE if systemic effects occur. The alcohol base will burn and irritate the eye. If ROGAINE reaches sensitive surfaces (eg, eye, abraded skin and mucous membranes) bathe with copious cool water.

Avoid inhaling the spray.

Do not use in conjunction with other topical agents such as corticosteroids, retinoids and petrolatum or agents that enhance percutaneous absorption. ROGAINE is for topical use only. Each mL contains 20 mg minoxidil and accidental ingestion could cause adverse systemic effects.

Decreased integrity of the epidermal barrier caused by inflammation or disease of the skin, eg, excoriations, psoriasis or severe sunburn, may increase minoxidil absorption.

Patient Information: A patient information leaflet is included with each package and in the full product information.

Drug Interactions: No drug interactions are known. Theoretically, absorbed minoxidil may potentiate orthostatic hypotension in patients taking guanethidine.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No carcinogenicity was found with topical application. Oral administration may be associated with an increased incidence of malignant lymphomas in female mice and hepatic nodules in male mice. In rats, there was a dose-dependent reduction in conception rate.

Pregnancy Category C: ROGAINE should not be used by pregnant women.

Labor and Delivery: The effects are not known.

Nursing Mothers: ROGAINE should not be administered.

Pediatric Use: Safety and effectiveness have not been established under age 18.

ADVERSE REACTIONS

ROGAINE was used by 3510 patients in placebo-controlled trials. Except for dermatologic events, no individual reaction or reactions grouped by body systems appeared to be increased in the minoxidil-treated patients.

Respiratory (bronchitis, upper respiratory infection, sinusitis) 5.95%; **Dermatologic** (irritant or allergic contact dermatitis) 5.27%; **Gastrointestinal** (diarrhea, nausea, vomiting) 3.42%; **Neurology** (headache, dizziness, faintness, light-headedness) 2.56%; **Musculoskeletal** (fractures, back pain, tendinitis) 2.17%;

Cardiovascular (edema, chest pain, blood pressure increases/decreases, palpitation, pulse rate increases/decreases) 1.28%; **Allergy** (non-specific allergic reactions, hives, allergic rhinitis, facial swelling and sensitivity) 1.03%; **Special Senses** (conjunctivitis, ear infections, vertigo) 0.94%; **Metabolic-Nutritional** (edema, weight gain) 0.60%; **Urinary Tract** (urinary tract infections, renal calculi, urethritis) 0.46%; **Genital Tract** (prostatitis, epididymitis) 0.46%; **Psychiatric** (anxiety, depression, fatigue) 0.28%; **Hematology** (lymphadenopathy, thrombocytopenia) 0.23%; **Endocrine** 0.09%.

Patients have been followed for up to 5 years and there has been no change in incidence or severity of reported reactions. Additional events reported since marketing include: eczema, hypertrichosis, local erythema, pruritus, dry skin/scalp flaking, sexual dysfunction, visual disturbances including decreased visual acuity, exacerbation of hair loss, alopecia.

DOSAGE AND ADMINISTRATION

Hair and scalp should be dry before application. 1 mL should be applied to the total affected areas twice daily. Total daily dose should not exceed 2 mL. If the fingertips are used to facilitate drug application, wash the hands afterwards.

HOW SUPPLIED

60 mL bottle with multiple applicators NDC 0009-3367-05

Caution: Federal law prohibits dispensing without a prescription.

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FIRE ANT (continued)

mercial reagent available for diagnosis of and immunotherapy for persons who are hypersensitive to the insect. A commercial venom extract is available for experimental purposes only and has not been approved by the FDA for use in humans. Moreover, it remains to be seen whether commercial suppliers can provide enough venom to treat all hypersensitive patients.

WBE from hymenoptera other than the imported fire ant is not effective for diagnosis and therapy, unlike venom extract, probably because bee and vespid body enzymes biodegrade the venom proteins. This phenomenon does not appear to occur with imported fire ant WBE, which, when properly prepared, contains most clinically important allergens. A number of studies have compared the efficacy of skin testing and RAST with imported fire ant WBE and venom (Figure 7). Variability in responsiveness to WBE can be attributed largely to the different preparations used in these studies.

We and other investigators have concluded that imported fire ant WBE and venom are both valid for skin testing and RAST diagnosis of fire ant hypersensitivity. Venom RAST is more sensitive, but not more specific, than WBE RAST. Both extracts can produce false-positive skin tests and RASTs in nonallergic subjects.

We usually wait 30 days after a systemic reaction to perform the diagnostic workup. Patients first undergo a scratch test with imported fire ant WBE. If they do not respond, serial dilution subcutaneous testing with WBE is performed, beginning with a 1:1,000,000 weight-to-volume dilution. Almost 90% of clinically sensitive patients will produce a wheal-flare reaction before the dilution reaches 1:500.

Immunotherapy

Uncontrolled studies have shown immunotherapy with imported fire ant WBE to be effective for most hypersensitive patients. A progressive increase in venom-specific IgG₄ (blocking antibody) is seen in patients receiving immunotherapy, and the increase is associated with a decrease in venom-specific IgE. Immunotherapy probably does reduce mortality, although death often occurs in patients who have not had a previous systemic reaction.

As early as 1973, Triplett reported that patients receiving desensitization therapy with WBE did

(continues)

PAMELOR® (nortriptyline HCl)

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Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor® (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher AUC, and lower clearance of nortriptyline.

Use in Pregnancy: Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children: Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

Adverse Reactions: **Cardiovascular:** Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. **Psychiatric:** Confusional states (especially in the elderly) with hallucinations, disorientation, delusions, anxiety, restlessness, agitation; insomnia, panic, nightmares, hypomania; exacerbation of psychosis. **Neurologic:** Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy, extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus. **Anticholinergic:** Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract. **Allergic:** Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs. **Hematologic:** Bone marrow depression, including agranulocytosis, eosinophilia; purpura; thrombocytopenia. **Gastrointestinal:** Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black tongue. **Endocrine:** Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion. **Other:** Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia. **Withdrawal Symptoms:** Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage.

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FIRE ANT (continued)

not have a systemic reaction when they were stung again. Rhoades reported two mild systemic reactions in 19 patients who were stung while being treated with WBE immunotherapy. One reaction occurred early in the course of therapy, presumably before protection had been achieved. Barry R. Paull and T. H. Coghlan recently reported two treatment failures in patients receiving maintenance doses of WBE immunotherapy.

A multicenter, double-blind controlled study that uses sting challenges is now being conducted to compare the relative efficacy of immunotherapy with WBE, venom, and placebo. It will then remain to be determined whether treatment with

a specific venom antigen (i.e., Sol I I, II, III, or IV) will be superior to whole venom.

Patients who have had a systemic reaction to an imported fire ant sting are candidates for immunotherapy. Most suitable are those with severe reactions and positive skin testing or RAST, those who are geographically or occupationally susceptible to repeated exposure, and those who exhibit unreasonable anxiety and extreme life-style changes to avoid another exposure. Patients can be advised that immunotherapy dramatically reduces the risk of anaphylaxis. Even if anaphylaxis occurs in the course of maintenance therapy, it is almost always less severe than the one before therapy.

Immunotherapy is not recommended (continues)

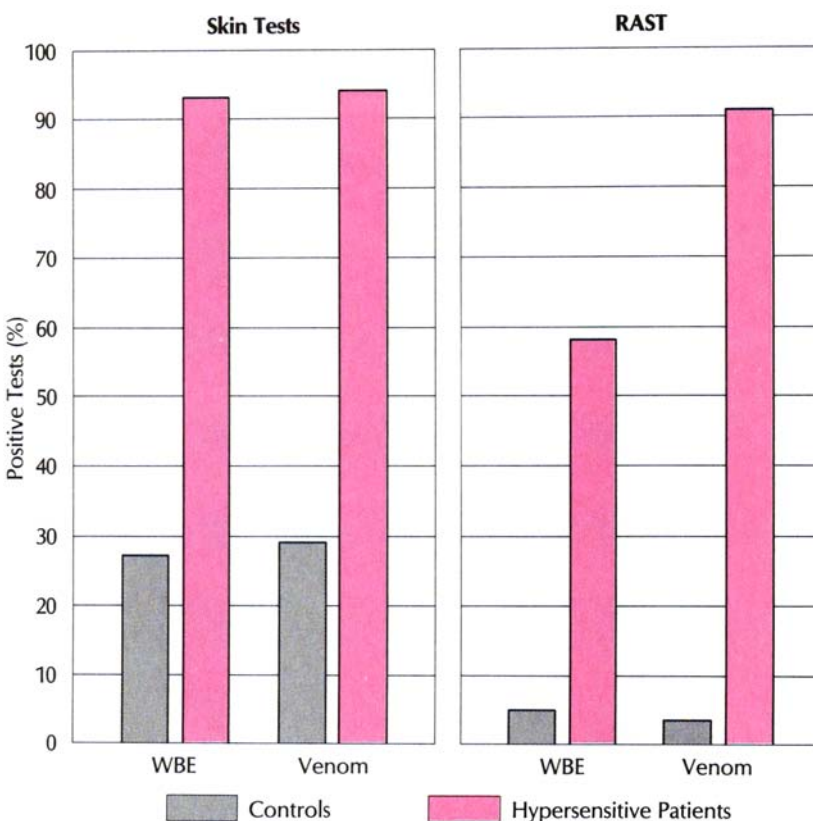


Figure 7. Results of 11 studies involving more than 550 patients indicate that whole body extract of imported fire ants, when properly prepared, is a reliable method for diagnosing hypersensitivity. Both WBE and venom extract produce false-positive skin tests and RASTs in nonallergic patients. Venom RAST is more sensitive than WBE RAST but not more specific.

ommended for patients with severe large local reactions, even though they may be of allergic origin. There is also evidence that children aged three to 16 years who have had only cutaneous manifestations of a systemic reaction—urticaria, angioedema, and generalized pruritus—to other hymenoptera do not have severe systemic reactions when they are stung a second time; therefore, they generally do not need immunotherapy. Whether this is true for children of the same age with fire ant hypersensitivity is unknown.

The initial immunotherapy dose is 0.5 ml of the highest WBE dilution that produces a positive skin test (usually 1:10,000 or 1:100,000 weight-to-volume dilution). Increasing

increments of the extract are administered in a series of weekly or biweekly injections to the maximum tolerated dose (not to exceed 0.5 ml of a 1:10 dilution). That level is usually achieved in six weeks to three months, and this maintenance dose is then administered once every four to six weeks.

Maintenance immunotherapy for hypersensitivity to bees and vespids is usually continued for up to five years. Patients with severe anaphylactic reactions who are continually exposed occupationally to the imported fire ant should be maintained indefinitely until data are obtained demonstrating otherwise. All hypersensitive patients who are not on immunotherapy or have not reached maintenance should carry an emergency insect sting kit contain-

ing aqueous epinephrine in a prefilled syringe. Some hypersensitive patients who are not challenged by another sting and are not placed on immunotherapy apparently lose their sensitivity over time to the imported fire ant.

Systemic reactions can occur during the administration of immunotherapy. It should therefore be performed only by clinicians experienced in the technique, or under the guidance of an allergist-immunologist, and only when adequate means of treating systemic reactions are available. Patients should be informed of the risk and observed closely for 30 minutes after each injection.

Hypersensitivity reactions to the imported fire ant have become an important clinical problem that will continue to grow as the insects spread and the human population encroaches on their habitat. Imported fire ant WBE and venom share allergens, and both are able to identify hypersensitive patients through appropriately performed skin testing or RAST. Although the natural course of imported fire ant hypersensitivity is unknown, immunotherapy with WBE is currently recommended—on the basis of uncontrolled reports of effectiveness, the presence of venom allergens in WBE, and in vitro evidence that WBE contains allergens that react like venom allergens. The continuing characterization of venom allergens will facilitate standardization of imported fire ant venom and whole body extracts and will enable investigators to elucidate the immune response in hypersensitive patients and cross-reactivity between the imported fire ant and other hymenoptera. □

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