
Review article

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Hypersensitivity to fire ant venom

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Learning Objectives: Reading this article will reinforce the reader's knowledge of the taxonomy, origin, and distribution of fire ants and will increase his ability to diagnose and manage reactions caused by the two imported species, *Solenopsis invicta* and *richteri*. This review will also enhance the reader's knowledge of the available diagnostic methods and therapeutic measures, including the role of fire ant venom versus whole body extract in the management of fire ant allergy.

Data Sources: Information for this review was obtained primarily from abstracts and articles written by investigators recognized for their expertise in fire ant venom research.

Study Selection: References were selected based on their clinical applicability and relevance to the epidemiology and pathophysiology of imported fire ant hypersensitivity.

Conclusions: The imported fire ant represents a significant health hazard for persons living in fire ant endemic areas in the southern United States. Sting reactions range from local pustules and large, late-phase responses to life-threatening anaphylaxis. Fire ant allergen-specific immunotherapy can reduce the risk of subsequent systemic reactions. Four important Sol i venom allergens have been isolated and characterized. Clinical studies have been designed to compare the safety and efficacy of fire ant venom with whole body extract for diagnosis and treatment of fire ant allergy.

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INTRODUCTION

Imported fire ants now infest large areas of the southern United States where they have adapted well to environmental conditions and have become a considerable agricultural pest and a significant public health problem.¹⁻⁴

TAXONOMY

Fire ants are classified in the order Hymenoptera, superfamily Vespoidea, family Formicidae, subfamily Myrmicinae, tribe Solenopsidini, and genus *Solenopsis*. Native species include *S. xyloni*, the southern fire ant, *S. geminata*, the tropical fire ant, and *S. aurea*, the desert fire ant. The two imported

species, *S. richteri* and *S. invicta*, are of major economic and medical importance.

DISTRIBUTION

The black imported fire ant, *S. richteri*, is originally from Uruguay and eastern Argentina. The red imported fire ant, *S. invicta*, is native to the Mato Grosso region of Brazil where its range extends northward along the Guapore river and southward along the Paraguay river basin into northern Argentina.⁵ Both species were probably imported into the US on produce shipped through the port of Mobile, *S. richteri* in about 1918 and *S. invicta* in about 1939.² *S. richteri* is presently limited to a small area along the northern border between Mississippi and Alabama.

Solenopsis invicta, the most aggressive species, now infests 13 southern states where it has become a consider-

able agricultural pest and a significant health hazard. The present area of infestation is shown in Figure 1. The 10 °F isotherm has long been considered to be the thermal boundary for fire ant infestation, but *S. invicta-richteri* hybrids appear to be adapting to cooler climates as they continue to migrate northward. Imported fire ants have already advanced up the east coast as far north as Richmond, Virginia.⁶ Over the next decade, *S. invicta* is expected to spread westward to California and up the Pacific coast as far north as the Canadian border.

Although not endemic for other regions, the fire ant may still impact on allergy practice in many areas of the country. Many patients who have moved beyond the boundaries of known fire ant infestation continue to receive fire ant immunotherapy for protection when traveling to endemic areas.⁷

Over 260 million acres in the southern US are infested with fire ants. In heavily infested areas, the mound density of single queen colonies may range from 40 to 150 mounds per acre, while multiple queen colonies may exceed 200 to 600 mounds per acre. Tunnels between the mounds may extend over 40 meters. Fire ant mounds measure up to a meter in diameter and a half meter in height. Each single queen colony may be teeming with as many as 100,000 to 250,000 worker ants. Multiple-queen colonies may sustain 20 to 60 egg-laying queens and accommodate as many as 100,000 to 500,000 workers.^{8,9}

CHARACTERISTIC FEATURES

Fire ant workers range in size from 1.8 to 6 mm in length, averaging 3 to 4

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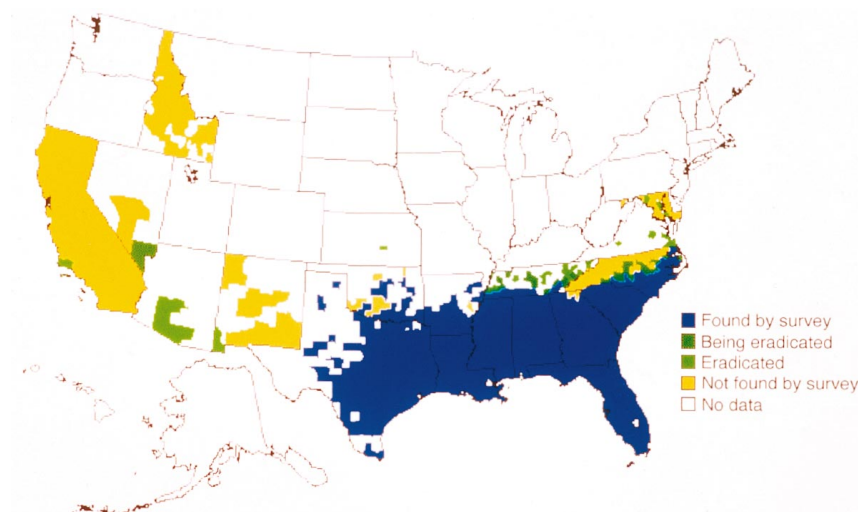


Figure 1. Reported distribution of *Solenopsis invicta* and *richteri* as of March, 1996. Data retrieved from National Agricultural Pest Information System. Note that green areas being eradicated include the tip of Nevada, almost all of North Carolina and parts of Tennessee. Other green areas indicate places where the fire ant has been eradicated.

mm. The queen is larger, measuring approximately 1 centimeter in length; she also has wings used during her nuptial flight. Multiple egg-laying queens (up to 300 per mound) have been discovered in recent years.² Characteristically, fire ants have two humps on the petiole which connects the thorax and abdomen (Fig 2), an antenna scape that extends more than two-thirds the distance to the back of the head, and prominent mandibles with four teeth.

NATURAL HISTORY

The annual fire ant sting attack rate has been reported to range from 13% to 58%.¹⁰⁻¹³ Even brief exposure to imported fire ant endemic areas can result in elevated sting rates and development of imported fire ant-specific IgE. In a study of medical students temporarily assigned to San Antonio, Texas, field stings resulted in a sting attack rate of 51% and skin test and RAST conversion occurred in 13%.¹⁴

REACTIONS

Named for the fierce burning pain inflicted by its sting, the imported fire ant attacks with little warning. Firmly grasping the skin with its powerful

mandibles, the fire ant arches its back, inserts its stinger into the flesh, and injects venom from the attached venom sac. It then pivots at the head and inflicts an average of seven to eight stings in a circular pattern. Sting reactions range from immediate localized wheal and flare responses to large local or systemic reactions, including fatal anaphylaxis.

Localized Hive Reaction

The usual response to fire ant stings is the development of an immediate 25- to 50-mm dermal flare with formation of a wheal within one minute and papules within two hours. Vesicles develop within four hours, at first filled with clear fluid that becomes cloudy within eight hours and develops into sterile pustules by 24 hours.

Pustule Formation

The fire ant pustule results from tissue inflammation caused by the venom alkaloid which consists of water insoluble cis and trans isomers of 2-methyl, 6-n-alkyl piperidine compounds. The superficial pustule is infiltrated with activated neutrophils and platelets with necrosis at the base at 24 hours.¹⁵ Pustules associated with the development

of late-phase reactions contain eosinophils.¹³

Large Local Reactions

Seventeen percent to 56% of patients develop large localized, erythematous, edematous reactions to imported fire ant stings. These large local lesions are extremely pruritic and painful and may persist for 24 to 72 hours. Histologically, such lesions resemble mast cell-dependent, late-phase reactions consisting of a cellular infiltrate of neutrophils and eosinophils with fibrin deposition in a gel structure.¹³

Anaphylaxis

A well known cause of significant morbidity due to large local reactions and secondary infections, imported fire ant stings also have been reported to cause life-threatening, and even fatal, anaphylaxis.² Anaphylaxis usually occurs in persons sensitized by a previous sting. It may be manifested by flushing, generalized urticaria, angioedema, laryngeal edema, bronchospasm, or loss of consciousness.

A 3-state survey conducted in 1971 found that approximately 16% of patients treated for fire ant stings had systemic allergic reactions and 0.6% had anaphylactic shock.¹⁶ In a more recent study, physicians in 13 southern states were surveyed to assess the magnitude of medical problems caused by imported fire ant stings.¹⁷ Of the 29,205 physicians surveyed, 2,022 (7%) reported treating approximately 20,755 patients annually for fire ant sting reactions. Most patients were treated for local reactions, but 2% required treatment for life-threatening anaphylaxis.

Fatal anaphylactic reactions to imported fire ant stings also have been reported. A physician questionnaire survey disclosed 83 fatal and two nearly fatal anaphylactic reactions caused by imported fire ant stings.¹⁸ Most anaphylactic deaths were reported from Florida (22) and Texas (19). After excluding duplicate reports, 32 anaphylactic deaths were documented to fire ant stings: 14 in Texas, 10 in Florida, 4 in Alabama, and 2 each



Figure 2. *Solenopsis invicta* worker. Note two humps on the petiole and prominent mandibles. Sting apparatus is contained in the terminal abdominal segment.



Figure 3. SDS-PAGE of fire ant venom with known molecular weight standards. Bands are identified at the molecular weights of the four allergens isolated from fire ant venom (Sol i 1, 2, 3 & 4).

in Louisiana and Georgia. Victims ranged in age from 16 months to 65 years of age. Additional reports of fatal fire ant sting reactions are documented each year.

Unusual Reactions

Rare reports of neuropathy and nephropathy have also appeared as a consequence of imported fire ant stings. Neurologic reactions have ranged from mononeuropathy to grand mal seizures. Some patients have experienced anaphylaxis before the onset of seizure

activity.¹⁹ Minimal change nephrotic syndrome was reported in a 3-year-old child who experienced edema of the face and extremities 2 weeks after fire ant stings on the legs and genitalia.²⁰ The condition responded to steroid therapy without further sequelae. As the geographic range of the imported fire ant increases and more patients are stung, unusual reactions may be seen with greater frequency.

While most reactions have been caused by stings encountered outdoors,

several massive indoor sting episodes have been reported recently.²¹ Individuals with cognitive dysfunction seem to be especially at risk for attacks by fire ants.

DIAGNOSIS

Useful clinical clues to the diagnosis of fire ant allergy include (1) the development of a typical pustule at the sting site after 24 hours; (2) species identification of the culprit insect, and (3) the description of a typical fire ant mound in the vicinity of the sting incident. The diagnosis, however, of fire ant allergy is determined by correlation of the clinical manifestations of fire ant sting reactions with imported fire ant-specific IgE determined by skin testing or RAST.

Imported fire ant whole body extract is the only reagent presently available for diagnostic testing and immunotherapy for fire ant sting allergy. After screening prick tests, usually at 10^{-3} wt/vol, intradermal skin tests are performed with 0.02 to 0.03 mL of 10^{-6} wt/vol and 10-fold increments in concentration to 10^{-3} wt/vol or until a positive reaction is obtained.¹ Skin tests are considered positive if a wheal at least 6×6 mm and erythema at least 11×11 mm develop within 15 minutes and the reaction is at least 3 mm greater than the negative control.

IMPORTED FIRE ANT WHOLE BODY EXTRACT

Fire ant whole body extract has been shown to contain relevant venom allergens and appears to be protective. While most imported fire ant whole body extracts appear to be useful for diagnosis and treatment, some preparations appear to contain variable concentrations of venom allergens.^{22,23,24} Investigators have expressed concern about the clinical efficacy of imported fire ant whole body extracts compared to imported fire ant venom. A possible explanation for variability among imported fire ant whole body extract preparations may be seasonal variation in antigenic activity. A more than 100-fold difference in phospholipase activity has been reported in extracts pre-

Proportion of Protein

μg/mL

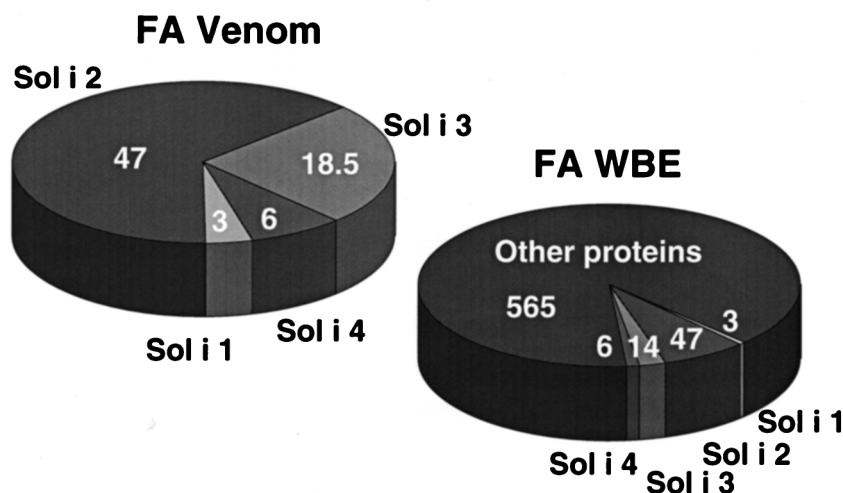


Figure 4. Left: Concentration Sol i allergens in fire ant venom. Right: Sol i allergen concentration compared to relatively large amount of extraneous body protein in fire ant whole body extract.

pared from ants collected in early summer compared with winter.²³

FIRE ANT VENOM

Fire ant venom is available only for investigational research. Until recently, fire ant venom could only be obtained by tediously hand-milking venom into microcapillary pipettes under a dissecting microscope. Relatively large amounts of fire ant venom can be produced now by more efficient technical methods.

Immunochemical Studies

Fire ant venom is unique because of its low protein content and high concentration of piperidine toxins consisting of 90% to 95% water insoluble n-alkyl and n-alkenyl piperidine alkaloids. The venom of the red imported fire ant, *S. invicta*, has been studied extensively. *S. invicta* venom contains about 0.04 to 0.11 μL of venom per sting and 10 to 100 ng of protein per sting. Four major protein allergens have been isolated and characterized from Sol i venom^{2,6,25,26,27} (Fig 3). Monoclonal antibody assays have been developed for all four antigens. The largest molecular weight protein, Sol i 1, is present in the smallest amount (2% to 5%). It ap-

pears to be a phospholipase of the vespid venom type that cross-reacts with sera from many vespid allergic patients. This may explain reactions reported by some vespid-sensitive individuals to their initial fire ant sting.²⁸ Sol i 2, the largest fraction (67%), is a disulfide-bonded dimeric protein of 26,224 molecular weight, which has been protein sequenced and cloned. Sol i 3 comprises about 20% of the venom protein and contains 212 amino acid residues, giving a molecular weight of 24,040 daltons. It is not related by sequence to other known proteins. It is a member of the antigen 5 family of wasp venom proteins. Despite this high degree of sequence homology, it does not appear to exhibit immunologic cross-reactivity. Sol i 4 comprises about 9% of the venom protein and has 117 amino acid residues and a molecular weight of 13,340 daltons.

The allergens of the black imported fire ant, *Solenopsis richteri*, have also been isolated and studied.⁶ Sol r 2 shows 78% sequence identity with Sol i 2; Sol r 3 is much more closely related to Sol i 3. There is no molecule analogous to Sol i 4 in the venom. Sera

from allergic patients from both endemic areas show a very high degree of cross-reactivity. Venom of *S. invicta-richteri* hybrid ants contains allergens from both species. Sera from patients sensitized by the native fire ant species, *Solenopsis xyloni* and *aurora*, show a high degree of reactivity with imported fire ant venom allergens.

The relative amounts of Sol i allergens in *S. invicta* fire ant venom are shown in the left diagram in Figure 4. All four Sol i proteins are important allergens. Most patients react to all four allergens, while some react almost exclusively to a single allergen.²

Unlike honey bee and vespid whole body extracts, imported fire ant whole body extracts contain significant amounts of immunoreactive allergens. The concentrations of Sol i allergens in fire ant whole body extract is shown in the right diagram in Figure 4. While most fire ant whole body extracts appear to contain relevant Sol i allergens, the concentrations are reduced by the relatively large amount of extraneous body proteins. While some commercial extracts have been found to contain sufficient amounts of venom allergens to provide protection from stings, other commercial extracts have been shown to be deficient in one or more components, including Sol i 2. Currently available fire ant extracts are not standardized, but it has been suggested that they should be assayed for protein concentration and the content of Sol i allergens.

DIAGNOSTIC METHODS

Several investigators have compared skin testing and RAST with fire ant whole body extracts and with venom in the diagnosis of fire ant sting allergy.^{22-24,29-36} James et al first studied imported fire ant venom and found it to be a sensitive skin test reagent.³⁵ Strom et al reported venom skin test reactivity in 91% of patients tested with fire ant venom compared to 82% with whole body extract, but noted marked variability in the degree of responsiveness with different extract preparations.²² Paull et al demonstrated cross-

Fire Ant Skin Test Reactivity

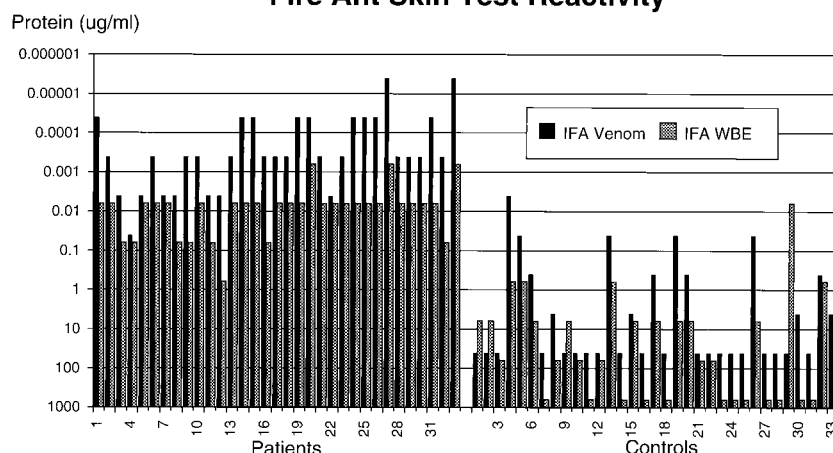


Figure 5. Bar graph showing the results of skin test reactivity based on protein concentration in µg/mL shown in a log₁₀ scale on the y axis.

reactivity between fire ant venom and whole body extract by RAST inhibition, but found the allergenic potency of venom to be approximately ten times that of whole body extract.³⁴ Bahna et al performed skin testing with fire ant whole body extract, and RAST with whole body extract and venom in young children with systemic reactions to fire ant stings. Whole body extract skin tests were reactive in 94%. Between the two in vitro assays, however, venom RAST was concluded to be superior to whole body extract RAST for diagnosis of fire ant sting allergy in children.³⁵

Investigators at the Medical College of Georgia have completed an investigational new drug (IND) study of the safety and efficacy of fire ant venom (*Vespa*) in the diagnosis of fire ant allergy.³⁶ The study design included the following criteria for study patients: (1) history of a systemic reaction to fire ant sting within the past year and (2) no history of a systemic or large local reaction to other insect stings. Thirty-three patients and 33 control subjects were enrolled in the study and were skin tested with fire ant venom and two commercial fire ant whole body extracts. All extracts were analyzed for protein and Sol i 3 content. Fire ant venom and fire ant whole body extract RASTs were performed on sera from all study subjects.

Patients were at least 10-fold more reactive to fire ant venom than whole body extract. (Fig 5) Control subjects were generally much less reactive to both antigens. Several controls did not even react to the highest possible concentration.

Patients and control subjects experienced no adverse reactions to skin testing with the fire ant venom product; however, several control subjects developed large delayed local reactions to higher concentrations of fire ant whole body extract. These reactions were attributed to the relatively large amounts of extraneous body proteins in the fire ant whole body extract preparations. Differences in reactivity between fire ant venom and whole body extract based on Sol i 3 concentration was less striking, but patients again were significantly more reactive than controls. A 2-fold difference in skin test reactivity was noted between the two whole body extract preparations. RAST reactivity was approximately 10-fold greater to fire ant venom than imported fire ant whole body extract among patients. Control subjects had low levels of RAST reactivity to both antigens.

Assessment of sensitivity and specificity based on the results of this study suggests that fire ant venom may be a more sensitive skin test reagent (97%) than fire ant whole body extract (76%)

at a protein concentration of 0.01 µg/mL, which compares favorably with RAST results. Both antigens appear to be equally sensitive by skin testing at 0.1 µg/mL.

Limited conclusions can be drawn from the results of this study but a few observations are apparent. First, fire ant venom is more potent than fire ant whole body extract as determined by protein concentration. Skin testing with fire ant venom is safe; there were no adverse reactions to skin testing with fire ant venom. Nevertheless, fire ant whole body extract contains extraneous body proteins that may cause delayed local reactions at higher concentrations. Fire ant whole body extracts may also vary in Sol i 3 concentration. Finally, fire ant venom RAST was also found to be more sensitive than fire ant whole body extract RAST. These observations suggest that fire ant venom may be superior to fire ant whole body extract for diagnosis of fire ant allergy.

Additional in vitro assays have since been developed. An enzyme-linked immunosorbent assay (ELISA) for in vitro measurement of IgE specific for *S. invicta* venom was developed by Ponder et al.³⁷ The ELISA correlated well with the imported fire ant venom RAST ($r = .87, P < .0001$). Using skin test reactivity as the standard measure of venom-specific IgE, the venom ELISA appeared to be a sensitive in vitro assay comparable to venom RAST. The assay was also less expensive than RAST and did not require licensing or handling of radioisotopes.

A Pharmacia CAP System assay for specific IgE to *S. invicta* whole body extract also is available. Assay results were compared with data from venom skin testing, RAST, and ELISA. It was concluded that the Pharmacia Cap System with fire ant whole body extract appears to be an acceptable alternative in vitro method for determination of fire ant allergen-specific IgE in situations where skin testing is not feasible.³⁸ In a subsequent study, a prototype imported fire ant venom solid phase was evaluated in comparison to fire ant whole body extract in the Phar-

macia Cap System.³⁹ Assay results were compared also with data from venom intradermal skin test titration, venom RAST, and venom ELISA. There was good correlation with fire ant venom RAST and ELISA, as well as with quantitative intradermal skin testing. Analysis of the data suggests that the Pharmacia Cap System fire ant venom solid phase may be more sensitive and specific than the whole body extract solid phase for measurement of fire ant allergen-specific IgE. These results underscore the importance of using fire ant venom for diagnostic testing.

Nonallergic Reactivity

Studies have suggested that fire ant non-allergic persons living in imported fire ant endemic areas may have an increased incidence of reactivity to imported fire ant whole body extract.³⁻⁶ Hoffman et al demonstrated positive fire ant venom RAST reactivity in 57 of 60 patients who had recently experienced systemic reactions to fire ant stings compared with no reactivity among 100 control subjects not exposed to fire ants, and 5 of 21 (24%) control subjects living in a fire ant endemic area.⁴⁰ Skin test reactivity in fire ant nonallergic subjects was confirmed by Rhoades et al who demonstrated intradermal skin test reactivity to fire ant whole body extract at 1:1000 wt/vol in 102 of 450 (23%) of subjects residing in a fire ant endemic area.⁴¹ The prognostic significance of imported fire ant whole body extract skin test reactivity in individuals without a history of insect sting allergy is unknown. These results emphasize the need to correlate the clinical manifestations of fire ant sting reactions with imported fire ant-specific IgE determined by skin testing or in vitro assays.

CURRENT CLINICAL RESEARCH

Fire ant venom has been designated an orphan drug by the US Food and Drug Administration. Previous clinical studies have demonstrated the safety and efficacy of fire ant venom in the diag-

nosis of fire ant allergy.³⁶ Additional studies have been designed to compare the safety and efficacy of fire ant venom with whole body extract for immunotherapy of fire ant sting allergy.

MANAGEMENT OF STING REACTIONS

Persons allergic to fire ant stings should be educated regarding practical avoidance measures to reduce the likelihood of subsequent stings. Sensitive individuals predisposed to experience serious clinical reactions should be prescribed an emergency kit containing epinephrine and be instructed in its proper use. Patients suffering systemic reactions should be referred to an allergist for definitive diagnosis and consideration for immunotherapy if indicated.

Pustular Lesions

Most fire ant vesicles and pustules resolve with conservative management.⁴² Treatment is aimed at preventing secondary bacterial infection that may occur if the pustule is disrupted. Pustular lesions should be left intact and cleansed with soap and water to prevent secondary infection. While fire ant stings may sometimes be complicated by secondary infection, most reactions do not require antibiotic therapy. Persons at special risk for complications include diabetics and others with circulatory disorders, eg, varicose veins and phlebitis.

Local Reactions

Most fire ant stings cause only localized reactions that are of little serious medical consequence. Localized pain and swelling may be reduced with cold compresses. Pruritus may be relieved by topical steroid ointments or local anesthetic creams; however, no specific treatment is usually necessary. Various medical regimens have been employed but antihistamines, steroids, epinephrine, topical aluminum sulfate and meat tenderizer containing papain appear to be of no therapeutic value.⁴³ Medical attention is recommended if progressive swelling develops or infection is suspected.

Large Local Reactions

Large local reactions manifested by extensive erythematous, painful swelling and pruritus may persist for several days. Medical management consists of elevation of the affected extremity plus treatment with antihistamines and corticosteroids in severe cases. Antibiotics usually are not necessary.

Anaphylaxis

Systemic allergic reactions to fire ant stings may range from mild cutaneous urticaria to life-threatening reactions manifested by bronchospasm, obstructive angioedema of the upper airway, and anaphylactic shock. Anaphylactic reactions should be managed as medical emergencies. If stung, persons at risk should immediately report to a physician. Emergency self-treatment should be administered enroute to the nearest medical facility. Treatment of anaphylaxis due to fire ant stings is essentially the same as that from other causes.

PREVENTION

Preventive measures are recommended for fire ant allergic individuals at risk for subsequent systemic sting reactions. Such patients should (a) be taught practical measures for avoidance of subsequent stings, (b) be prescribed an emergency treatment kit containing epinephrine, and (c) be referred to an allergist for further evaluation and consideration for fire ant allergen testing and immunotherapy.

Avoidance

Fire ant allergic patients should be taught practical avoidance measures to reduce the likelihood of subsequent stings. Precautions should include the following specific recommendations.

1. Avoid going barefoot or wearing sandals.
2. Wear gloves and protective footwear while gardening.
3. Wear long sleeves and other protective clothing.
4. Be cautious along roadways, in picnic areas, and near refuse containers.

5. Have fire ant mounds near the home treated with bait insecticides. Effective methods for insecticide treatment of fire ant mounds involve use of attractant baits consisting of soybean oil, corn grits, and a chemical agent, eg, abamectin (Affirm), fenoxycarb (Logic), hydramethylnon (Amdro), acephate (Orthene), bendiocarb (Rotate), or carbaryl (Sevin). The bait is picked up by the worker ants and taken deep into the mound to the queen.⁴⁴

Epinephrine

Epinephrine (Adrenalin) is the initial drug of choice for treatment of anaphylaxis. Fire ant allergic patients should carry an emergency kit containing epinephrine [eg, EpiPen (Center Laboratories) or AnaKit (Bayer Corp)] for self-administration in case of a sting. EpiPen (0.3 mg of epinephrine) and EpiPen Jr. (0.15 mg of epinephrine) are spring-actuated autoinjectors. AnaKit and Ana-Guard (Center Laboratories) provide a syringe loaded with two doses of 0.3 mg of epinephrine. While these kits require self-injection, they also permit the administration of fractional doses.

Allergy Evaluation

Anyone who has suffered a systemic allergic reaction to a fire ant sting should be referred to a trained allergist for evaluation including diagnostic testing and consideration for immunotherapy.

IMMUNOTHERAPY

Allergen immunotherapy has proved to be an extremely effective form of treatment for individuals at risk of insect sting anaphylaxis, including anaphylactic reactions caused by fire ant stings. Imported fire ant whole body extract is the only reagent presently available for immunotherapy for fire ant venom allergy. Because of high degree of cross-reactivity between the two imported species, skin testing and immunotherapy with *S. invicta* alone is probably sufficient in most cases. The initial dose is determined by skin test titration as previously described. The dosage schedule is similar to that for aeroallergen immunotherapy. Patients

are usually maintained on the maximum tolerated dose up to 0.5 mL of 1:100 wt/vol or 1:10 wt/vol.

Extrapolating from the Sol i 3 content, a good quality 1:10 wt/vol whole body extract has been estimated to contain approximately 30 to 45 mcg/mL of total antigenic venom protein; therefore, a maintenance dose of 0.5 mL should deliver 15 to 22 mcg of venom protein.⁴⁵ Since most patients suffer an average of eight fire ant stings per incident and each sting contains less than 100 ng of venom protein, this dose has been estimated to be sufficient to provide adequate protection.

A survey was conducted to determine the maintenance immunotherapy dose being administered by practicing physicians in an attempt to assess the level of protection provided by imported fire ant whole body extract.⁴⁸ One hundred allergists practicing in the southern United States were surveyed, with a response rate of 42%. Thirty-six physicians reported an average maintenance dose of 5.9 mcg of venom protein administered to 231 patients receiving imported fire ant whole body extract immunotherapy. Only 16% (37/231) of patients were receiving at least 22 mcg and 26% (59/231) were receiving less than 2 mcg. Only 12% (28/231) of patients experienced local reactions, suggesting that many patients may not be receiving the maximum tolerated dose. These data suggest that the dose of imported fire ant whole body extract that some fire ant allergic patients are receiving may not be sufficient to provide adequate protection from the venom dose delivered by the average number of fire ant stings. Based on clinical experience most authorities consider a maintenance dose of 0.5 mL of 1:100 wt/vol to be protective for most patients. It has been suggested that, until fire ant venom is available, the dosage of fire ant whole body extract used for skin testing and immunotherapy should be based on protein or Sol i allergen concentration, which should be specified on the label.

THERAPEUTIC GOALS

The therapeutic goals of fire ant allergen immunotherapy are to (1) prevent life-threatening reactions, (2) reduce allergic morbidity, and (3) alleviate anxiety associated with insect stings.

Immunotherapy with fire ant whole body extract has been evaluated by several investigators. Triplett reported an apparent 100% efficacy in 18 patients on hyposensitization who had no systemic reactions to natural re-stings.²⁹ Rhoades et al reported two systemic reactions in 19 patients who were re-stung while being treated with fire ant whole body extract immunotherapy.³¹ Neither of these reactions was severe; one occurred early in the course of therapy, presumably before protection had been achieved. Paull et al reported two treatment failures,⁴⁷ and Rhoades and Stafford subsequently reported another on maintenance doses of fire ant whole body extract immunotherapy.⁴⁸

The strongest evidence for the efficacy of immunotherapy with fire ant whole body extract is the report by Freeman et al, who treated 65 patients with fire ant whole body extract immunotherapy for anaphylaxis.⁴⁹ Of the 47/65 (72%) patients who sustained field stings, only one suffered anaphylaxis. Of the 30 patients who were stung while on maintenance immunotherapy, none had anaphylaxis. The control group consisted of 11 insect-allergic patients who were not treated. Six of the eleven control patients were stung and all six suffered anaphylaxis.

Imported fire ant whole body extract appears to contain relevant allergens and imported fire ant whole body extract immunotherapy appears to be efficacious for most patients. The degree of protection compared with that which may be achieved with fire ant venom or specific Sol i allergens has not been determined. Double-blind controlled studies, including sting challenges, should be performed to determine the relative efficacy of immunotherapy with fire ant whole body extract, venom, and placebo in the

treatment of imported fire ant sting allergy.

DURATION OF IMMUNOTHERAPY

The natural history of fire ant allergy is unknown and the optimal duration of immunotherapy has not been clearly established. In a recent study, immunotherapy was discontinued in 17 patients after 2 to 19 years of treatment.⁵⁰ All patients were retested and stung 3 months later. Thirteen of 17 (76%) had positive skin tests and 16/17 (94%) had no reaction to re-sting. The investigators concluded that most patients on immunotherapy for at least 2 years can probably tolerate a sting without reaction. Additional studies are warranted to clarify the optimal duration of fire ant immunotherapy.

UNRESOLVED ISSUES

Although important advances have been made in the study of fire ant allergy, important issues remain unresolved. These include the following questions:

1. What is the natural history of fire ant allergy?
2. Do children with only cutaneous reactions to fire ant stings require immunotherapy?
3. When will fire ant venom be available for skin testing and immunotherapy?
4. Would immunotherapy with fire ant venom be superior to that with fire ant whole body extract?
5. Would treatment with specific venom allergens be superior to whole venom?
6. Can higher, more protective doses be achieved with fire ant venom immunotherapy?
7. What is the optimal duration of fire ant immunotherapy?
8. What will be the cost of fire ant venom immunotherapy?

We await answers to these and other questions with hopeful anticipation.

SUMMARY

The imported fire ant, *Solenopsis invicta*, represents a significant health hazard for persons living in fire ant

endemic areas in the southern United States. Sting reactions range from local pustules and large, late-phase responses to life-threatening anaphylaxis. Fire ant allergen-specific immunotherapy can reduce the risk of subsequent reactions. Four important Sol i venom allergens have been isolated and characterized. Clinical studies have been designed to compare the safety and efficacy of fire ant venom with that of whole body extract for treatment of fire ant venom hypersensitivity. Preventive care measures for management of fire ant sting allergy include (1) precautions for sting avoidance, (2) prescription of emergency treatment kits containing epinephrine, and (3) allergy referral for evaluation for immunotherapy. These practical preventive measures should help reduce the health hazards caused by imported fire ant stings.

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CME Examination

Identification No 016-008

Questions 1–20, Stafford CT. 1996;77:87–99

CME Test Questions

1. Characteristic morphologic features of the imported fire ant include all of the following except:
 - a. distinct clubbed antennae
 - b. two humps on the thorax
 - c. antenna scape extending more than 2/3 to the back of the head
 - d. prominent mandibles with teeth
2. Fire ants:
 - a. bite
 - b. sting
 - c. both
 - d. neither
3. Reactions to fire ant stings include:
 - a. wheal and flare response
 - b. sterile pustule formation
 - c. large, local, mast cell dependent late phase reactions
 - d. systemic allergic reactions
 - e. all of the above
4. Fire ant pustules are caused by:
 - a. Sol i allergens
 - b. piperidine alkaloid allergens
 - c. nonallergenic alkaloid toxins
 - d. none of the above
5. Allergens of the black imported fire ant include all of the following except:
 - a. Sol r 1
 - b. Sol r 2
 - c. Sol r 3
 - d. Sol r 4
6. The amount of venom protein injected from an imported fire ant sting is approximately:
 - a. 1–10ng
 - b. 1–10 μ g
 - c. 10–100ng
 - d. 10–100 μ g
7. Most deaths from fire ant stings occur in:
 - a. Alabama
 - b. Georgia
 - c. Florida
 - d. Texas
8. Useful clinical clues to the diagnosis of fire ant allergy include all of the following except:
 - a. the development of a typical pustule at the sting site after 24 hours
 - b. eschar formation at the sting site
 - c. species identification of the culprit insect
 - d. the description of a typical fire ant mound or nest in the vicinity of the sting incident
9. Which of the following is the least sensitive diagnostic test for determining fire ant specific IgE:
 - a. fire ant venom skin testing
 - b. fire ant whole body extract skin testing
 - c. fire ant venom RAST
 - d. fire ant whole body extract RAST
10. Effective treatment for fire ant pustular lesions includes:
 - a. antihistamines and steroids
 - b. topical aluminum sulfate
 - c. meat tenderizer containing papain
 - d. none of the above
11. Treatment for large local fire ant sting reactions includes all of the following except:
 - a. elevation of the extremity
 - b. antihistamines
 - c. corticosteroids
 - d. antibiotics
12. Preventive care measures recommended for fire ant allergic individuals at risk for subsequent systemic sting reactions include the following except:
 - a. practical sting avoidance measures
 - b. emergency kit containing epinephrine
 - c. referral to an allergist
 - d. venom immunotherapy
13. Immunotherapy with fire ant whole body extract is indicated for which of the following:
 - a. fire ant sting pustule reactions
 - b. large, localized, mast cell dependent late-phase reactions
 - c. anaphylaxis to fire ant stings
 - d. none of the above
14. Until fire ant venom is available, the dosage of fire ant whole body extract used for skin testing and immunotherapy should be based on:
 - a. weight/volume
 - b. protein nitrogen units
 - c. protein concentration
 - d. Sol r allergen concentration
15. Fire ant allergic patients who move beyond fire ant endemic areas:
 - a. need not be concerned about subsequent fire ant stings
 - b. may safely discontinue fire ant allergen immunotherapy
 - c. should consider continuing fire ant immunotherapy
 - d. may require honey bee venom immunotherapy
16. The following statements are correct except:
 - a. imported fire ant venom appears to be more potent than fire ant whole body extract as determined by protein concentration
 - b. skin testing with fire ant venom is safe
 - c. fire ant whole body extracts may contain variable concentrations of venom allergens
 - d. skin testing with fire ant venom causes delayed local reactions

Which lettered item is most closely associated with each of the following numbered items:

- | | |
|-------------|---|
| 17. Sol i 1 | a. Antigen 5 family of wasp venom proteins |
| 18. Sol i 2 | b. 9% of venom protein |
| 19. Sol i 3 | c. Largest antigen fraction |
| 20. Sol i 4 | d. Cross reacts with sera from vespid allergic patients |
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Answers to CME examination—Annals of Allergy, Asthma, & Immunology, July 1996 (Identification No 016-007) Senior BA and DW Kennedy. Management of sinusitis in the asthmatic patient. Ann Allergy, Asthma, Immunol 1996;77:6–19.

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|------|-------|-------|-------|
| 1. E | 6. E | 11. E | 16. B |
| 2. B | 7. E | 12. C | 17. A |
| 3. A | 8. B | 13. A | 18. C |
| 4. C | 9. A | 14. D | 19. B |
| 5. D | 10. C | 15. D | 20. D |