

The stinging impact of the imported fire ant

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Purpose of review

Imported fire ants pose a real and present danger to allergic individuals living in endemic areas. This overview examines the impact of their presence, specifics of their venom and approach to the treatment of the hypersensitive individuals.

Recent findings

Imported fire ant sting attack rates are high in endemic areas with sensitization occurring early in life among those dwelling in these locations. Once considered an outdoor pest, sting attacks are now known to occur indoors with the very young and the very old being especially susceptible due to the decreased mobility of these age extremes. Immunotherapy with whole body extract appears efficacious with both traditional and rush schedules finding utility among allergists. Both the mobility of the populace and the portability of imported fire ants have broadened the presence of both allergic patients and the ant itself among allergists previously unfamiliar with hypersensitive patients or the imported fire ant.

Summary

Recent work has focused on achieving more rapid protection in hypersensitive patients given the high sting attack rates in endemic area with sensitization occurring early in life among those exposed to the imported fire ant.

Keywords

anaphylaxis, immunotherapy, imported fire ant

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Introduction

Since their introduction into the United States in the 1920s, imported fire ants (IFA) have slowly spread at a rate of about 100 miles per year throughout the southern United States. Although IFA hypersensitivity principally remains a concern for those in endemic areas, it potentially impacts allergists worldwide in our mobile society as patients with known hypersensitivity move out of endemic areas into other parts of the nation and world, and as IFA are also imported to other regions of the world [1•]. Since 1950 when the US Department of Agriculture declared the IFA to be a problem, numerous lay publications, including newspapers, musicians (cdfa.ca.gov/exec/Public_Affairs/PSAs/Lalo-EnglishRIFA.mp3), magazines, fictional books (The Fire Ants, Wernick 1976) and even Hollywood movies (Empire of the Ants, American International Pictures 1977) have featured these crawling critters and commented, sometimes in hysterical terms, on their stinging impact upon the geographical areas they invade [2]. In endemic areas, IFA is the most frequent cause of Hymenoptera hypersensitivity accounting for both the majority of referrals to a venom clinic and the majority of Hymenoptera immunotherapy offered. In an IFA endemic area in San Antonio, Texas, IFA (42% of individuals seeking evaluation) were the most frequently implicated

insect as causing systemic anaphylaxis, followed by wasp (29%) and yellow jacket (15%) [3]. Among the patients with Hymenoptera hypersensitivity, the majority of them offered immunotherapy had a history and skin testing consistent with IFA hypersensitivity (59% of the total immunotherapy offered).

Approximately 5% of those stung have required physician management [4], and current criteria for immunotherapy for IFA allergy are similar to those for flying Hymenoptera [5]. The majority of those who seek medical attention do so for nonsystemic reactions but up to 16% may be for generalized reactions [6]. During a 6-month period on an IFA endemic Army installation in Georgia, an estimated 208 outpatient visits and five hospitalization days were due to IFA stings [7].

History and background

It is commonly accepted that around the 1920s, *Solenopsis invicta* (red imported fire ant) and *Solenopsis richteri* (black imported fire ant) were introduced into the United States at the port of Mobile, Alabama, through ships from the Paraguay River drainage area of northern Argentina, southern Brazil and Uruguay [2,8]. Although it is not known exactly, it is generally believed that they arrived

in the soil used as ballast for the ships coming over from South America [2]. *S. invicta* has the broadest geographical spread with *S. richteri* formerly limited to northeastern Mississippi and northwestern Alabama until its recent near extinction in the United States. The IFA occupies more than 300 million acres predominately in the southern United States and Puerto Rico. An overview of the order Hymenoptera is listed below. The *Solenopsis* genus is in the Formicidae family, Myrmicinae subfamily and Solenopsidini tribe.

- (1) Family Apidae (Apids)
 - (a) Genus *Apis* (honeybee)
 - (b) Genus *Bombus*, *Megabombus* and *Pyrobombus* (bumblebee)
 - (c) Genus *Halictus* and *Dialictus* (sweatbee)
- (2) Family Vespidae (Vespids)
 - (a) Genus *Polistes* (wasp)
 - (b) Genus *Vespula* (yellow jacket)
 - (c) Genus *Dolichovespula* (yellow hornet and bald-faced hornet)
 - (d) Genus *Vespa* (true hornet)
- (3) Family Formicidae (Formicids)
 - (a) Genus *Solenopsis* (partial list; over 280 species worldwide)
 - (i) Species *invicta* (red imported fire ant)
 - (ii) Species *richteri* (black imported fire ant)
 - (iii) Species *aurea* (native US desert fire ant)
 - (iv) Species *geminata* (native US tropical fire ant)
 - (v) Species *xyloni* (native US southern fire ant)
 - (vi) Species *molesta* (native US thief ant)
 - (b) Genus *Myrmecia* (bulldog ant)
 - (i) Species *pilosula* (Australian jack jumper ant)
 - (ii) Species *forcicata* (Australian inchman ant)
 - (c) Genus *Pachycondyla*
 - (i) Species *chinensis* (East Asian ant)
 - (ii) Species *sennaarensis* (Samsum ant)
 - (d) Genus *Monomorium*
 - (i) Species *pharaonis* (pharaoh ant)

A bite and a sting!

IFA anchor themselves to their victim by their mandibles and then arch their abdomen (Fig. 1) to inflict the sting (Fig. 2) [9]. They then may pivot in a circular fashion to sting again or they may loosen their mandibular grip, advance, reanchor and sting again. Thus, if allowed the opportunity to sting multiple times, they may leave either a linear or circular design of characteristic pustules. Although the pain of an IFA sting is not as severe as that of the flying Hymenoptera, multiple stings result in a sensation of fire at the sting site, hence, the common name of fire ant. For those who live in IFA endemic areas, the question is not if they will be stung but rather when they will be stung. Of 107 military medical students followed for a brief 3-week period in an IFA endemic

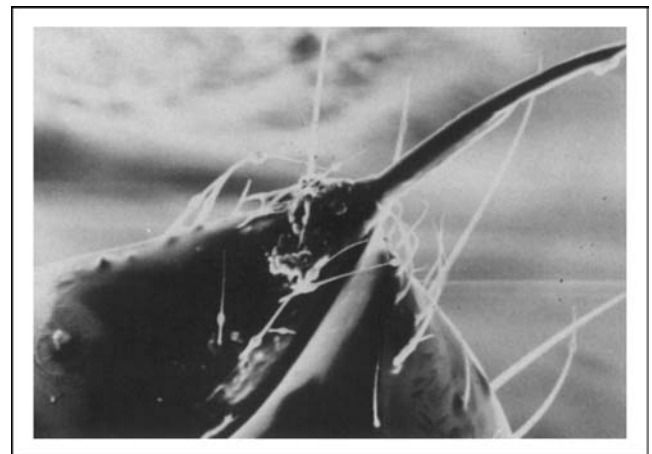
Figure 1 Imported fire ant with body arched, stinging and injecting venom through the stinger



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area in San Antonio, 55 reported an IFA sting during this time, resulting in a sting attack rate of 51% [10]. A similar sting attack rate (55%) was reported in a group of children less than 10 years of age over a 3-month summer period [11]. Among children aged 1–18 years surveyed in a pediatric clinic, 38.6% had been stung in the previous month with 23.9% receiving more than six stings per month [12^{••}]. Utilizing a *S. invicta* venom ImmunoCAP with a blinded survey of discarded serum samples from an endemic IFA area, this same study revealed sensitization rates of 35.7 and 52.5% among 2–5 and 6–10 year olds, respectively, utilizing the standard cutoff of 0.35 kUa/l. Specific immunoglobulin E (IgE) to IFA whole body extract (WBE) is 1.7 times more common among adults residing in an endemic area of Georgia [13]. Reports of sting attacks indoors reveal both the aggressiveness of

Figure 2 Scanning electron micrograph of the stinger (×90)



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IFA and the difficulty in avoiding contact with them in endemic areas [14–18]. A previous history of immunotherapy appears to have no impact upon IFA sting avoidance as 93% of those with some history of IFA immunotherapy had experienced a another sting over the 7 years since discontinuation of their immunotherapy [19**].

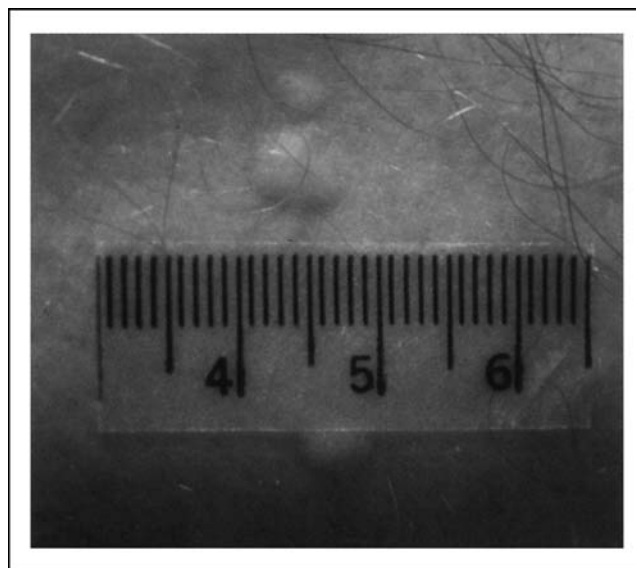
Venom characteristics

Although some individuals have sustained thousands of stings without systemic toxic or immunologic reactions, a single sting has the potential of inducing life-threatening anaphylaxis in the hypersensitive individual. It is estimated that each IFA sting delivers about 100 ng of protein compared with 50 000 ng (50 µg) of protein delivered by flying Hymenoptera. IFA venom differs from that of the other Hymenoptera (70% protein content) in that only 2–5% of its content is protein [20]. The majority (90–95%) of IFA venom is composed of piperidine alkaloids [21]. Although this component is not allergenic, it is responsible for the characteristic pustule seen after an IFA sting. Four distinct proteins (Sol i I–IV) have been identified to be the important venom allergens [22]. Sol i I is a phospholipase and appears to cross-react with yellow jacket and honeybee venom [23–25]. Sol i II makes up two thirds of the venom protein and Sol i III has been found to be a member of the antigen 5 family of wasp venom proteins, but does not appear to be cross-reactive with vespid venom antigen 5 [23]. Significant cross-reactivity has also been demonstrated between the common striped scorpion, *Centruroides vittatus*, and IFA [26]. A considerable degree of overlap exists between the endemic areas in which *C. vittatus* and IFA are found. In massive fire ant attacks (>500 stings), cardiorespiratory failure may result from two alkaloid venom components, which possess significant cardiorespiratory depressant activity and have elicited seizures in mammal models [27].

Sting reactions

Three different reactions may be elicited by a sting: a local, a large local, or a systemic (anaphylaxis). A local reaction consists of an immediate wheal and flare (Fig. 3) followed by the development of a characteristic pustule after 24 h. An IFA sting leaves a pustule at the sting site 88–96% of the time [7,10]. A large local reaction is also confined to the sting site but consists of an erythematous, edematous and indurated region extending beyond the pustule and sometimes lasting several days. Large local reactions may be debilitating with swelling of an entire extremity when a sting occurs on the hand or foot. Both local and large local reactions can be intensely pruritic. Serious systemic reactions occur in about 2% of IFA sting patients who seek medical care. In a retrospective survey to evaluate the occurrence of fatal anaphylactic reactions to IFA stings, 84 fatalities

Figure 3 Wheal-and-flare response that occurred 10 min after envenomation



The scale is in millimeters. Reproduced from [9]. Copyright ©1993 Massachusetts Medical Society.

were reported [28], and a recent fatality from a native *Solenopsis* fire ant was reported in a 3-month-old infant [29*].

Unfortunately, allergic patients often do not receive appropriate management and counseling and, therefore, remain at high risk for another potentially life-threatening anaphylactic event. In a survey among physicians in urgent care centers and emergency departments regarding the management of Hymenoptera sting anaphylaxis in the adult patient, 53% did not prescribe anaphylaxis identification bracelets, 24% did not feel urticaria warranted referral to an allergist, a paltry 38% referred all patients to an allergist, 63% prescribed epinephrine for future initial outpatient self-treatment to all patients and only 19% provided written information on how to avoid insect stings [30]. A recent review of systemic reactions within an emergency department and primary care clinic substantiated this previous physician survey [31]. In this retrospective chart review, 39% of patients were referred to an allergist, 55% were discharged with autoinjectable epinephrine and 12% were provided information on insect avoidance. As can be seen, much needs to be done to better educate primary care physicians on the management and follow-up of patients presenting with IFA hypersensitivity.

Immunotherapy

The allergist's role in the patient with IFA hypersensitivity is of utmost importance. Hence, continued diligence must be pursued in educating the lay public, those with intimate

contact with IFA (field workers, foresters, etc.) and other physicians. Evidence of the prevalence of misinformation is seen in an entomology periodical in which it is stated as a fact that less than 15% of patients on Hymenoptera immunotherapy will receive protection from further sting reactions [32]. Since the discovery of IFA in southern California in 1998, the California Department of Food and Agriculture has instituted a Web site with information on IFA and includes a toll-free number for the reporting of sighted IFA mounds (www.cdffa.ca.gov/PHPPS/pdep/rifa).

Currently, WBE is a compromise from what would be considered the ideal extract for diagnostic and therapeutic purposes. Both species-specific and mixed species (*S. invicta* and *S. richteri*) nonstandardized IFA WBE are available for the diagnosis and treatment of sensitive individuals. This is in contrast to flying Hymenoptera in which venoms have proved superior to WBE for diagnosis and therapy [33]. The utility of WBE for the diagnosis and treatment of sensitive patients was initially reported in 1973, and several studies since then have supported its efficacy.

In a retrospective evaluation of 53 patients with histories of anaphylaxis to IFA stings and a subsequent field sting by IFA, 2.1% (1/47) of patients on WBE immunotherapy had a repeat anaphylactic event compared with 100% (6/6) of those who had declined immunotherapy [34]. In this same study, sting challenges conducted on 30 patients on immunotherapy resulted in only local reactions. Long-term efficacy after immunotherapy discontinuation has been evaluated. Upon follow-up after a mean of 18 and 57 months off immunotherapy, 13% (2/15, mild subjective cutaneous symptoms) and 0% (0/9) of patients, respectively, had systemic reactions upon sting challenge [35]. The authors concluded that long-term clinical efficacy persists after discontinuation of IFA WBE immunotherapy. Comparing a reduced course group (1.5-year average immunotherapy duration) and a complete course group (5.5-year average immunotherapy duration), there was no difference in systemic reaction rates (6 and 7%, respectively) with field stings occurring after immunotherapy discontinuation [19^{••}]. No prospective, placebo-controlled study has been done for WBE immunotherapy, and no studies on IFA venom immunotherapy have been conducted to date. Thus, much remains to be answered regarding indications, utilization and efficacy of immunotherapy.

Immunotherapy for IFA account for the majority of the total Hymenoptera immunotherapy administered in an IFA endemic area, and patient age extremes of those offered IFA immunotherapy has ranged from 18 months to 80 years [3]. In contrast with the current practice of only children 16 years and older with cutaneous reactions

receiving flying Hymenoptera immunotherapy [36], one survey of allergists in IFA endemic areas showed that almost one third recommended immunotherapy to children with only cutaneous reactions [37]. A possible explanation for this practice had been that no study looked at the natural course of people with only cutaneous reactions to IFA stings and the high likelihood of another sting for those in endemic areas [37]. Recently, 12 patients under the age of 17 years were reported who had initial cutaneous only reactions [38]. None of the 12 patients upon subsequent sting had a more severe reaction, with the findings consistent with existing flying Hymenoptera literature.

Although the majority of allergists in endemic areas have evaluated patients for IFA hypersensitivity and use immunotherapy to treat hypersensitive patients, great variability exists in treatment practices. Although over 98% of allergists in IFA endemic areas surveyed recommended immunotherapy for adults and children with cardiorespiratory reactions, variance occurred in the management of reactions limited to the skin, as 77% recommended immunotherapy for adults but only 29% for children with cutaneous reactions [37]. A wide range of maintenance dosages was reported with half of responders using a maintenance vial concentration of 1:100 w/v and one fourth of responders using a 1:10 w/v concentration for maintenance. A lower efficacious dose has been reported upon sting challenge in a patient unable to tolerate the usual maintenance dose due to repeated systemic reactions [38]. A recent practice parameter reported that most experts recommend a maintenance dose of 0.5 ml of a 1:100 w/v IFA WBE [5].

One survey among patients receiving IFA immunotherapy from a board-certified allergist revealed an average delay of 1.8 years from the time of initial reaction to referral to an allergist [39]. Among patients with a history of a systemic reaction to IFA, accompanying atopic disease has been reported as high as 47% in a pediatric population [40]. These facts serve to remind the allergist to ask all patients in an allergy practice of any history of IFA reactions regardless of the patient's reason for referral.

Various sources within the literature have reported rush protocols for aeroallergen and flying Hymenoptera immunotherapy including one report of a 1-day schedule achieving a dose of 0.1 ml 1:100 w/v for aeroallergen extract in a pediatric population [41]. If this could be done safely, the advantage of a rush schedule is obvious in saved patient and physician time and money. A rush schedule also offers the additional benefit of enhanced compliance, which has been shown to be a problem with traditional schedules in which 22–55% of patients discontinue immunotherapy [42]. A rush schedule could achieve assumed protection in a short period, whereas a

traditional schedule would not achieve maintenance for the patient till several months later. Based on a rush protocol under study within our department, the first reported case of successful rush immunotherapy to IFA was that of an adolescent male [43]. We later published this study, which included 56 patients with IFA hypersensitivity. Only three systemic reactions were associated with the 2-day rush protocol for a reaction rate of only 5.4% [44]. All patients were brought back on day 22 of the rush protocol and stung twice by IFA gathered from active colonies on the hospital grounds and only one patient had a systemic reaction to the sting challenge (efficacy of 98%). These data strongly support both the safety and efficacy of a 2-day rush schedule. We have just completed a 1-day rush schedule with a similar efficacy as the 2-day schedule, though requiring half the time as the previous study [45].

As large local reactions minimally (10%) increase the risk of a future systemic reaction [36], current standards do not support a role for immunotherapy in IFA patients with large local reactions. Although previous practices have been based on extrapolated data from flying Hymenoptera, a recent article by Nguyen and Napoli [46] did not show a progression of severity with further stings in those patients with a history of large local reactions to IFA and appear to substantiate what has been shown in flying Hymenoptera. However, these large local reactions can at times be quite debilitating to the individual and may even cause loss of work time. Because these reactions may occur with alarming frequency in endemic areas, our department has investigated the efficacy of rush immunotherapy in reducing these large local reactions. Clinically significant results were shown in the five individuals enrolled. A 62% reduction ($P < 0.05$) in local induration was reported 24 h after sting challenge at 1-month post-rush immunotherapy [47]. Of interest, three of these individuals were health professionals, two were surgeons and the other was a laboratory technician. IFA stings most frequently occur on the hands and feet and in these three patients any sting on the hand resulting in severe swelling could significantly alter their ability to perform their job.

As IFA allergic patients may also require aeroallergen immunotherapy, studies have already been performed that evaluate the stability of IFA WBE and aeroallergens [48,49]. Ragweed, cat, *D. pteronyssinus* and mountain cedar extract maintained allergen potency at 6 months when mixed with IFA WBE. However, in this same study, Timothy did show a loss of potency, and mixing IFA WBE and other extracts without proof of loss of potency, is not recommended. Although fewer injections may decrease patient discomfort and associated medical costs, clinical efficacy of these combined extracts will need to be assessed. More studies need to be done on this

and other areas and the IFA-sensitive population may offer a unique population to do so.

Conclusion

Future efforts to minimize the effect of IFA upon the environment must center on ways to control their spread through coordinated community control efforts [50], education of the lay public and medical profession of their beneficial and deleterious effects, and further work in the area of diagnosis and management of those individuals with hypersensitivity. Although repellents and chemical substances do not appear to deter IFA from stinging individuals, socks appear to offer some degree of protection [51,52]. With the anticipated continued spread of the stinging impact of IFA, an even greater proportion of the global population will be aware of its presence. Further research and collaboration is necessary as we seek to more effectively manage this unique insect.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 366).

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