
Successful administration of a 1-day imported fire ant rash immunotherapy protocol

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Background: Young children with a history of systemic reactions to imported fire ant (IFA) stings are at substantial risk of recurrent stings because of their maturational inability to practice appropriate avoidance techniques.

Objective: To present 3 cases in which patients 36 months or younger completed a 1-day rush immunotherapy (RIT) protocol with IFA whole-body extract (WBE).

Methods: The 1-day RIT protocol used for these patients was modified from the Wilford Hall 2-day rush protocol previously published. A 1:1 vol/vol maintenance vial consisted of 1 mL of IFA WBE and 9 mL of human serum albumin diluent in a 10-mL vial.

Results: All 3 patients had positive intradermal skin test results to IFA WBE. No systemic reactions occurred during the 1-day RIT.

Conclusions: This case series provides data with which we can begin to assess the efficacy and safety of a 1-day IFA RIT protocol for the prevention of anaphylaxis in IFA allergic children. Further studies with larger numbers of patients are needed to confirm the findings.

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INTRODUCTION

Young children with a history of systemic reactions to imported fire ant (IFA) stings are at substantial risk of recurrent stings because of their maturational inability to practice appropriate avoidance techniques. The attack rate of IFAs is high in endemic areas, with 38.6% of children ages 1 through 18 years reporting a sting within the previous month and 57.1% of 2- to 5-year-olds already demonstrating specific IgE to IFA venom.¹ Although allergy referral at initial presentation with a systemic sting reaction is low (16.7%), children younger than 16 years are twice as likely (63% vs 32%) to receive an allergy referral compared with those 16 years and older.² IFA stings have been shown to be responsible for the largest proportion of sting-related allergy referrals in endemic areas.³ A recent study demonstrated the inevitability of a re-sting even in those previously treated with immunotherapy for IFA hypersensitivity.⁴ In this study, IFA sensitive patients previously receiving 1.5 to 5.5 years of immunotherapy with IFA whole-body extract (WBE) were contacted 7 years after immunotherapy discontinuation, and 94% of these patients reported being stung again by IFAs. A 2-day rush immunotherapy (RIT) schedule has been demonstrated to be effective for adults in preventing recurrence of anaphylaxis due to IFA

stings, with an efficacy of 98% evaluated by sting challenge.⁵ Susceptible children would also likely benefit from the immediate protection afforded by RIT. We present 3 cases in which patients 36 months or younger completed a 1-day RIT protocol with IFA WBE. To our knowledge, this is the first report in the literature of a 1-day IFA RIT schedule and is unique in that all described patients were 36 months or younger.

REPORT OF CASES

Patient 1 was a 30-month-old boy with a history of moderate persistent asthma who experienced a severe anaphylactic reaction after receiving 2 IFA stings on his foot. Within minutes of being stung, his foot became swollen with 2 pruritic, raised, erythematous lesions. He then developed lip angioedema with perioral cyanosis and respiratory distress, and he lost consciousness for 2 to 3 minutes. The patient was treated with albuterol metered-dose inhaler treatments and oral diphenhydramine before arrival to the emergency department (ED). On arrival to the ED, he was alert and anxious with normal vital signs. On physical examination, he was noted to have bilateral wheezing on auscultation, but he had otherwise normal physical examination results. ED treatment included oral prednisolone and diphenhydramine and intravenous fluids. He was transferred to the general pediatrics inpatient ward for observation. Because of the severity of his reaction and the suspected need for immunotherapy, skin testing (Table 1) was performed 1 day after the sting-induced anaphylaxis.

Patient 2 was a 22-month-old boy with a history of intermittent asthma who developed systemic cutaneous symptoms after being stung 15 to 20 times on his legs. Localized urticaria developed within 10 minutes and then progressed to

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Table 1. Skin Testing Results^a

	Patient 1		Patient 2		Patient 3	
	Prick, mm	Intradermal, mm	Prick, mm	Intradermal, mm	Prick, mm	Intradermal, mm
Diluent						
Wheal	2 × 2	0 × 0	0 × 0	0 × 0	0 × 0	0 × 0
Flare	3 × 3	0 × 0	0 × 0	0 × 0	0 × 0	0 × 0
Histamine						
Wheal	3 × 3	10 × 10	5 × 6	8 × 7	3 × 3	10 × 7
Flare	6 × 6	15 × 15	7 × 10	12 × 13	4 × 4	30 × 25
IFA prick (1:1,000 wt/vol)						
Wheal	2 × 2	ND	2 × 2	ND	2 × 2	ND
Flare	3 × 3		3 × 3		3 × 3	
IFA intradermal (1:1,000,000 wt/vol)						
Wheal	ND	2 × 2	ND	2 × 2	ND	6 × 6
Flare		4 × 4		3 × 3		25 × 30
IFA intradermal (1:100,000 wt/vol)						
Wheal	ND	8 × 8	ND	10 × 11	ND	ND
Flare		9 × 9		20 × 21		

Abbreviations: IFA, imported fire ant; ND, not done.

^a For the skin prick test, a positive result is a wheal of 3 mm or greater with flare; for the intradermal test, a positive result is a 5-mm or greater wheal with flare.

generalized urticaria within 1 hour. He also had angioedema of his ears and eyes but no respiratory complaints. He was taken to the ED where he had wheezing on auscultation. His ED treatment consisted of nebulized albuterol and intramuscular dexamethasone. He was discharged home with oral prednisolone, hydroxyzine, and 0.15 mg of self-injectable epinephrine. Skin testing was completed 10 days after the stings occurred (Table 1).

Patient 3 was a 36-month-old boy with a history of 2 previous systemic reactions after IFA stings. His initial episode consisted only of diffuse urticaria with no further systemic involvement. Three months later, he was stung by 2 IFAs and developed eyelid angioedema and pruritic diffuse urticaria within 10 minutes followed by difficulty breathing. He was given oral hydroxyzine and diphenhydramine by the mother and taken to the ED. By the time he reached the ED, he had normal vital signs and normal physical examination results with no wheezing on auscultation. He was given corticosteroids and discharged home on a 5-day course of oral prednisolone. Given the history of respiratory complaints after the second sting attack, skin testing was completed 2 months later when he was seen in our clinic (Table 1).

METHODS

The 1-day RIT protocol used for these patients was modified from the Wilford Hall 2-day IFA WBE RIT protocol previously published by Tankersley et al.⁵ Written informed consent for each patient was obtained from a parent before initiation of RIT. Pediatric resuscitation equipment and medications were available during the administration of RIT in all 3 cases. Preinjection vital signs, physical examination, and intravenous access were obtained for all 3 patients. Measurement of vital signs and chest auscultation were performed

again before each injection. Patient 1, who underwent RIT 2 days after anaphylaxis, was premedicated with oral cetirizine and prednisolone. Patient 2, who underwent RIT 11 days after being stung, was not premedicated. Patient 3 was also not premedicated and underwent RIT 4 months after his last sting reaction. The RIT protocol is outlined in Table 2. The patients were observed for 2 hours after the highest dose of the 1-day RIT protocol. A 1:1 vol/vol maintenance vial consisted of 1 mL of IFA WBE (1:10 wt/vol stock bottle of *Solenopsis invicta* and *Solenopsis richtera* mix; Hollister-Stier, Spokane, Washington) and 9 mL of human serum albumin diluent in a 10-mL vial. The 0.5-mL 1:1 vol/vol (ie, 1:100 wt/vol) maintenance dose (Table 3) is consistent with the practice parameter recommendation.⁶ Table 3 maintenance injections were all followed by a 30-minute observation. IFA WBE is a nonstandardized extract. Antigenic activity of the IFA WBE

Table 2. Wilford Hall 1-Day Rush Protocol

Amount, mL	Concentration, vol/vol ^a
0.3 ^b	1:1,000
0.1 ^b	1:100
0.3 ^b	1:100
0.05 ^b	1:10
0.15 ^c	1:10
0.3 ^c	1:10
0.05 ^c	1:1
0.1 ^c	1:1
0.2 ^c	1:1
0.3 ^c	1:1

^a 1:1 vol/vol = 1:100 wt/vol.

^b Injections given every 30 minutes.

^c Injections given every 60 minutes.

Table 3. Maintenance Schedule

	Amount, mL	Concentration, vol/vol
Day 8 ^a	0.25/0.25	1:1/1:1
Day 15	0.5	1:1
Day 29	0.5	1:1
Day 50	0.5	1:1
Monthly	0.5	1:1

^a Simultaneous injections split between both arms; 1:1 vol/vol = 1:100 wt/vol.

used in these 3 patients was not assayed in our laboratory. Maintenance vials (ie, 1:1 vol/vol = 1:100 wt/vol) had a 1-year expiration date.

RESULTS

All 3 patients had positive intradermal skin test results to IFA WBE (Table 1). Of note, patient 1 had positive skin test results 1 day after his anaphylactic reaction despite also receiving an antihistamine as part of the treatment for that reaction. No systemic reactions occurred during the 1-day RIT (Table 2), although all 3 patients experienced mild local reactions at the injection sites. Local reactions were not measured. No modifications of the 1-day RIT protocol schedule were required. Each patient was then started on a schedule for appropriate buildup to monthly maintenance immunotherapy as detailed in Table 3.

The maintenance course of patient 1 was complicated by increasingly bothersome large local reactions. In addition, his mother reported 1 delayed systemic reaction that involved respiratory distress that began an hour after an injection. The mother of the patient treated him with self-injectable epinephrine and oral diphenhydramine at home but failed to report this reaction until several months later.

Patient 1 experienced 3 field stings after RIT. Each of these stings resulted in urticaria and respiratory distress. The third sting, which occurred after having missed several months of maintenance immunotherapy injections, resulted in facial flushing, diffuse urticaria, sweating, and respiratory distress. For all of these reactions, the patient's mother treated him with self-injectable epinephrine, oral diphenhydramine, and albuterol metered-dose inhaler treatments. None of the reactions were reported to any medical professional until several months after the reactions occurred. Because the patient had been nonadherent to the maintenance schedule and had field stings with reactions, he underwent another 1-day RIT without complication and completed several more months of maintenance injections. The mother eventually refused further immunotherapy for her son because of our clinic's mandated 1-hour wait time after injections instituted after the patient's first delayed systemic reaction. The patient has subsequently been lost to follow-up.

Twelve months after patient 2 initiated IFA immunotherapy, no field stings and only local reactions to immunotherapy were reported. Immunotherapy was discontinued when

the patient relocated to an IFA nonendemic region of the country.

Patient 3 had a mild reaction to his immunotherapy injection on day 8 of the maintenance schedule. He developed facial flushing with perioral urticaria. He had no respiratory symptoms and no significant change in vital signs. His symptoms resolved quickly after administration of oral cetirizine and intramuscular epinephrine. His injection dose was decreased to 0.05 mL of 1:1 vol/vol at his next scheduled injection, and he progressed on a slower schedule without further reactions. Eight months after his RIT, the family discontinued the immunotherapy because of logistical difficulty. In addition, the father changed jobs and the family lost medical coverage at our institution. The mother stated that just before the discontinuation, he had 5 sting attacks without systemic reaction, and since discontinuing the immunotherapy, he had 5 additional sting attacks with no associated systemic symptoms.

DISCUSSION

The Joint Task Force on Practice Parameters currently recommends immunotherapy as the standard of care for children who experience a systemic reaction and demonstrate IFA antigen specific IgE on skin or serologic testing.⁶ Compared with flying Hymenoptera, the natural history of IFA hypersensitivity and immunotherapy efficacy is not as well described.^{4,7,8} Similar to flying Hymenoptera, children 16 years and younger experiencing cutaneous-only reactions to IFA have not been reported to have more severe stings with subsequent stings.⁸ However, because the natural history of IFA hypersensitivity in children with only cutaneous manifestations has not been clearly defined and there is increased risk of IFA stings in children in endemic areas, immunotherapy might be considered for such children.⁶ None of the 3 children described in this report had signs and symptoms confined solely to the skin.

The management of young children who have life-threatening reactions to IFA stings is complicated by the fact that they lack the cognitive maturity to practice appropriate avoidance measures and may be unable to communicate the early signs of a systemic reaction to an IFA sting. Indoor stings among infants resulting in death have been reported.⁹ Although garments such as cotton socks may provide a temporary barrier to IFA contact,¹⁰ there is still a high risk of future stings for those living in endemic areas. A recent study has shown the effectiveness of a 2-day RIT protocol for the prevention of subsequent anaphylaxis in adults.⁵ A 1-day RIT protocol was used in these 3 patients because of the heightened risk of subsequent stings in this endemic area for these mobile toddlers and to minimize the 16 injections required in the 2-day RIT to the 10 injections used with this 1-day RIT schedule. We suspect that children could benefit from the immediate protection of a 1-day RIT protocol if proven safe and effective. Greater acceptance of the 1-day RIT would be anticipated because a strong parental preference for limiting vaccine injections has been reported.¹¹

All 3 children in this report tolerated the 1-day RIT without systemic reaction, but maintenance courses were complicated for patients 1 and 3. Patient 1 had 3 subsequent field stings with variable reactions. None of these were as severe as his presenting reaction, and 1 occurred during a period of non-adherence to scheduled immunotherapy. Patient 3 tolerated the 1-day RIT but had a systemic reaction on day 8 of his maintenance course. He had 10 additional sting attacks both before and after discontinuation of the immunotherapy with no further systemic reactions.

Sensitivity and specificity of 1:1,000 wt/vol vs 1:100 wt/vol vs 1:10 wt/vol skin prick tests with IFA WBE and any associated systemic reaction rates to these 3 skin prick concentrations have not been studied. Our institution has historically performed a single prick test with the 1:1,000 wt/vol concentration before proceeding to intradermal testing. Because we have observed systemic reactions occurring with this 1:1,000 wt/vol prick concentration, because we frequently see positive test results at this prick concentration, and because our IFA skin testing is limited to only a single test at each concentration (compared with up to 5 tests at each concentration with flying Hymenoptera), we continue to use this starting concentration. The practice parameter does not specify a prick concentration but rather gives a maximum concentration of 1:500 wt/vol IFA WBE for intradermal skin testing.⁶ In an effort to avoid intradermal tests, prick tests with a 1:100 wt/vol or 1:10 wt/vol preparation could be considered. Although *S invicta* alone may be sufficient for treatment because of the cross-reactivity between the 2 species, our institution has historically used an *S invicta* and *S richteri* mix. Although *S richteri* has a more limited geographic distribution, *S invicta* and *S richteri* hybrids exist from mating of the 2 species. Either *S invicta* alone or an *S invicta* and *S richteri* WBE mix is acceptable for skin testing and immunotherapy.⁶

The results of studies performed to evaluate the impact of pretreatment on the incidence of adverse effects encountered during venom RIT have been mixed. Double-blinded, placebo-controlled studies of RIT for flying Hymenoptera venoms have shown a significant decrease in local and systemic adverse effects when patients were pretreated with antihistamines.¹²⁻¹³ A separate double-blind, placebo-controlled study that compared terfenadine, 120 mg twice daily, to placebo as pretreatment to honeybee venom RIT showed no influence on systemic adverse effects consisting of respiratory or cardiovascular symptoms.¹⁴ One study comparing pretreatment with terfenadine or placebo during rush immunotherapy with honeybee venom demonstrated an enhanced efficacy of venom immunotherapy in the terfenadine group when evaluated with sting challenge or field sting during immunotherapy.¹⁵ In the only controlled study performed regarding IFA RIT, neither safety nor efficacy was significantly affected by pretreatment with a combination of terfenadine, ranitidine, and prednisone.⁵ In our series, patient 1 received premedication before RIT because of the shortened interval between the reaction and RIT and the severity of his presenting reaction. The other

2 patients did not receive premedication, and they tolerated all 10 injections on the day of RIT without adverse events. Premedication was not used in these 2 cases because of the absence of benefit demonstrated in the 2-day protocol.⁵

The attack rate and the incidence of IFA specific IgE do not correlate with the incidence of IFA anaphylaxis. Because much is still unknown about the natural history of IFA hypersensitivity, it is still unclear whether the presence of specific IgE in the absence of clinical reactivity represents asymptomatic sensitization as is commonly discussed with aeroallergen skin testing or whether it represents a false-positive result as is commonly discussed with food skin testing. In the recent article by Partridge et al,¹ they speculate in their discussion that this high sensitivity and low clinical reactivity discrepancy may be secondary to a natural desensitization that occurs because of the frequent exposure to IFA in endemic areas during childhood. They cite the high and rapid development of IFA venom specific IgG seen in their population as evidence to support their hypothesis. In the only report that evaluated IFA venom specific IgG in IFA hypersensitive patients, Reed and Butcher¹⁶ found that IFA venom specific IgG and IgG4 levels did not differ between IFA allergic patients undergoing WBE immunotherapy vs those with IFA allergy who had declined immunotherapy. However, both the treated and the untreated groups had higher IFA venom specific IgG and IgG4 than the control group. In addition, the IFA venom specific IgG4/IgE level was higher in the treated vs the untreated group but lower in both these groups compared with the control group. Further studies that evaluated IFA WBE and IFA venom specific IgG4/IgE and compared IFA venom and WBE specific IgG, IgG1, and IgG4 responses and the outcome of IFA sting challenges are needed to ascertain whether these antibody responses are adequate or required for protection.

Our case series provides data with which we can begin to evaluate the efficacy and safety of a 1-day IFA RIT protocol for the prevention of anaphylaxis in IFA allergic children. As reported in previous studies that involved adults who underwent RIT for IFA sensitivity, we found no increase in adverse effects or reactions to RIT in the 2 children who were not premedicated. This case series provides promising early information on the safety and utility of a 1-day RIT in a highly susceptible patient population. Clearly, further studies with larger numbers of patients are needed to confirm our findings.

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