

Letters

IMPORTED FIRE ANT HYPERSENSITIVITY: A 1-DAY RUSH IMMUNOTHERAPY SCHEDULE WITHOUT PREMEDICATION

Imported fire ants (IFAs), which now reside in much of the southern part of the United States, are a frequent cause of hypersensitivity reactions, being the reason for 42% to 54%^{1,2} of insect hypersensitivity evaluations performed in these endemic areas. Conventional IFA immunotherapy (IT) schedules, given in the insect hypersensitivity practice parameter, comprise 25 to 28 injections to reach the maintenance dose, which could take more than 3 to 6 months.³ Unique to IFAs is the difficulty with practicing effective avoidance measures,⁴ with annual sting rates up to 58% in people residing in endemic areas.⁵ Patients sensitive to IFAs are, therefore, at considerable risk of continued systemic reactions to stings during the months of IT buildup by conventional schedules. We believe these issues, which are unique to IFAs, make rush IT schedules an important option to consider for those patients allergic to IFA stings.

In the only published trial of IFA rush IT, Tankersley et al⁶ reported on a highly successful and safe 2-day IFA rush IT regimen. After continuing to experience ongoing success with this 2-day regimen, we attempted to shorten the rush period to a single day. We believed this could lessen patient inconvenience and time away from work, reduce costs, and make it a more attractive option for more patients. Because a significant benefit to medication pretreatment was not found using the prior 2-day IFA rush protocol, it was not used in the current protocol.

The inclusion criteria for enrollment into the study were patients aged 18 to 65 years, those with a history consistent with a systemic reaction to an IFA sting, and either a positive result to an IFA skin test or an IFA ImmunoCAP (Phadia AB, Uppsala, Sweden) specific IgE test. The protocol was approved by the Wilford Hall Medical Center (San Antonio, Texas) institutional review board.

The rush protocol consisted of 10 injections being given during the course of 8 hours on the rush day (Table 1). The dosing schedule began with an initial dose of 0.30 mL of a 1:1,000 vol/vol (1:100,000 wt/vol equivalent) *Solenopsis invicta*/*Solenopsis richteri* whole body extract (Hollister-Stier, Spokane, Washington). The final dose of the day was 0.30 mL of a 1:1 vol/vol (1:100 wt/vol equivalent) maintenance concentrate. The total cumulative dose for day 1 was equal to 0.70 mL of 1:1 vol/vol (1:100 wt/vol) concentrate. Patients returned on day 8 of the protocol for the full maintenance dose of 0.50 mL of 1:1 vol/vol (1:100 wt/vol) concentrate, and then the dosing interval was gradually spaced out to once monthly injections. The entire protocol was performed in the allergy clinic. If it was believed the patient was having a systemic reaction, then the rush protocol was terminated, the patient was medically treated as needed, and the remainder of the IT buildup was done by a conventional schedule.

The protocol included a sting challenge performed in our clinic on day 22 to ensure efficacy of the IT. The species of ant was later confirmed by an entomologist.

There were 37 patients who underwent the 1-day rush protocol between May 1, 2004, and January 31, 2008. The age range of the patients was from 18 to 49 years (mean age, 30.1 years). There were 13 women (35%) and 24 men (65%).

Overall, 28 (76%) of the 37 patients completed the entire rush protocol without any reaction. Of these 37 patients, 9 (24%) (95% confidence interval, 10%–38%) experienced some type of reaction during the rush protocol. All of these reactions were on the initial rush protocol day, and there were no reactions during the subsequent fol-

Table 1. Imported Fire Ant 1-Day Rush Protocol^a

Day	Dose, mL	Concentration, vol/vol
1		
8:00 AM	0.30	1:1,000
8:30 AM	0.10	1:100
9:00 AM	0.30	1:100
9:30 AM	0.05	1:10
10:00 AM	0.15	1:10
10:30 AM	0.30	1:10
11:00 AM	0.05	1:1
12:00 PM	0.10	1:1
1:00 PM	0.20	1:1
2:00 PM	0.30	1:1
4:00 PM	End of office observation	NA
8	0.50 (split in left and right arms)	1:1
15	0.50	1:1
22	IFA sting challenge	NA
29	0.50	1:1
50	0.50	1:1
Monthly	0.50	1:1

Abbreviations: IFA, imported fire ant; NA, not applicable.

^a The cumulative day 1 dose was 0.7 mL of 1:1 vol/vol, where 1:1 vol/vol equals 1:100 wt/vol. The postinjection wait time from day 8 on was 30 minutes.

low-up injections. Specifically, there were 4 patients who complained of generalized pruritis; 3 who complained of urticaria; 1 who complained of nausea, chest tightness, and tachycardia; and 1 who complained of dyspnea and throat scratchiness. There were 2 reactions after the 0.15 mL 1:10 vol/vol dose, 1 reaction after the 0.05 mL 1:1 vol/vol dose, 1 reaction after the 0.20 mL 1:1 vol/vol dose, and 5 reactions after the final 0.30 mL 1:1 vol/vol dose. No patients withdrew from the study or had their dose adjusted as a result of large local reactions. There were no statistically significant correlations between rush protocol reaction rates and initial IFA sting reaction grade, positive skin test dose, or sex.

Of the 22 sting challenges, 21 did not result in any signs or symptoms of a systemic reaction, giving an efficacy rate of preventing systemic reactions of 95.5% for the rush protocol, consistent with other IFA IT protocols.^{6,7} There have been multiple reports of field stings in this study group of 37 patients after completion of the rush protocol, and none of these has led to a systemic reaction.

This study suggests that a 1-day IFA whole body extract rush IT protocol is effective and safe for use in a general office setting to more rapidly achieve protective doses. However, further work is needed in this area to more completely refine IFA rush IT protocols; this work should include consideration of pretreatment and use of a randomized placebo-controlled design.

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HANDLE WITH CARE ... NITROGLYCERIN ANAPHYLAXIS

Nitroglycerin is a frequently used medication for the treatment of angina. There have been few previously reported cases of reactions to forms of nitroglycerin, other than the transdermal form.^{1–5} There has been a reported case of an allergic reaction to the intravenous (IV) form of nitroglycerin, without anaphylaxis.⁵ Adverse effects associated with nitroglycerin include diaphoresis, facial flushing, hypotension, tachycardia, lightheadedness, syncope, nausea, and emesis. To our knowledge, this is the first reported case of anaphylaxis to IV nitroglycerin.

A 69-year-old woman with chest pain and a questionable history of exposure to sublingual nitroglycerin greater than 5 years prior was transported by ambulance to an emergency department. En route, the patient received 3 doses of sublingual nitroglycerin. On arrival to the emergency department, she received IV nitroglycerin at a rate of 10 $\mu\text{g}/\text{min}$. Fewer than 5 minutes after starting the nitroglycerin infusion, the patient developed raised pruritic blanching and erythematous urticarial lesions on the extensor surface of her mid left forearm. The urticarial lesions continued to evolve as the infusion progressed, resulting in discontinuation of the infusion. IV diphenhydramine, 12.5 mg, and methylprednisolone, 80 mg, were each administered; this therapy improved her symptoms, but the urticaria progressed to a generalized distribution involving most of her body. Approximately 18 hours after receiving IV nitroglycerin, the patient developed angioedema of her upper lip and hoarseness. The patient denied lightheadedness, throat swelling, shortness of breath, emesis, and diarrhea. Her vital signs remained stable, and she was treated with oral hydroxyzine, 25 mg, 3 times per day. All of her symptoms resolved within 4 to 5 days. The patient's medications at the time of admission included aspirin, omeprazole, metoprolol, simvastatin, inhaled budesonide, bandronate sodium, calcium carbonate, and lactase. The patient had a history of a cutaneous pruritic reaction to tetracycline and of feeling faint after taking nitrofurantoin but no history of latex allergy.

Prick testing with IV nitroglycerin solution, 200 $\mu\text{g}/\text{mL}$, and intradermal dilutions, 20 and 2 $\mu\text{g}/\text{mL}$, was performed on the patient and on 3 control patients with no history of nitroglycerin exposure. Our patient and the controls had a positive prick test result to the 200- $\mu\text{g}/\text{mL}$ nitroglycerin and the histamine and a negative response to the saline control (Fig 1). Intradermal testing was performed on the controls with nitroglycerin dilutions of 1:10 (20 $\mu\text{g}/\text{mL}$) and 1:100 (2 $\mu\text{g}/\text{mL}$), resulting in positive reactions at both dilution concentrations. Although our patient and our controls developed reactions to the IV nitroglycerin on prick testing, our patient's reaction to prick testing was more significant in size (+4) than those of the controls (+3). Because of the lack of a standardized protocol and literature-supported dosing for skin testing, it was surmised that the nitroglycerin likely caused a false-positive result because of an irritant reaction or a local vasodilator effect.

In this case report, the urticarial rash was initially treated with IV diphenhydramine, 12.5 mg, and methylprednisolone, 80 mg,



Figure 1. Skin prick testing performed on the patient: 1, nitroglycerin, 200 $\mu\text{g}/\text{mL}$; 2, positive control (histamine); 3, negative control (saline).

followed by oral hydroxyzine, 25 mg, 3 times per day. Although a preferred treatment plan for the anaphylactic reaction may have included epinephrine, steroids, and hydroxyzine, the patient was treated by the primary medical service with hydroxyzine only.

Allergic responses to forms of nitroglycerin, excluding the transdermal form, rarely occur. Because of the patient's findings of diffuse pruritic urticaria that began and progressed with the administration of the IV nitroglycerin infusion and angioedema in association with signs of upper airway involvement manifesting as a hoarse voice, we concluded that the patient experienced an anaphylactic reaction to nitroglycerin. To our knowledge, this is the first reported case of anaphylaxis to the IV form of nitroglycerin.

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PHENYTOIN-INDUCED DRESS

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe multiorgan system reaction caused by specific drugs, such as aromatic anticonvulsants, sulfonamides, allopurinol, and nevirapine.^{1,2} We describe a 14-year-old girl with a widespread erythematous pruritic maculopapular confluent eruption over the face, trunk, and upper limbs; edema of both hands and the face; fever (temperature, 39°C); and bilateral cervical, postauricular, and suboccipital lymphadenopathy. The oropharynx and oral mucosa showed mild hyperemia. Symptoms first started on day 22 of phenytoin therapy (5 mg/d). She was admitted to the emergency department. Viral exanthema was diagnosed, and antipyretics and antihistaminics were prescribed. The patient's symptoms continued to worsen, and she was again seen 2 days later. Her history was unremarkable. Her mother also had developed a drug-induced reaction to the same drug (phenytoin).

Laboratory results revealed the following: white blood cell count, 9,400/mm³; eosinophils, 7%; lymphocytes, 68% (10% atypical lymphocytes); C-reactive protein, 10.5 mg/dL; aspartate aminotransferase (AST), 104 U/L; alanine aminotransferase (ALT), 84 U/L; lactate dehydrogenase, 518 U/L; and γ -glutamyl transpeptidase, 310 U/L. Blood phenytoin level was 0.79 μ g/mL; serum IgA, 46 mg/dL.

Serologic test results for viral hepatitis (types A, B, and C), mumps, rubella, parvovirus B19, and human immunodeficiency virus were negative. Anticytomegalovirus IgM, IgG antibodies, and Epstein-Barr virus capsid antigen specific IgM and IgG antibodies did not indicate primary infection or reactivation. Human herpesvirus 6 (HHV-6) DNA was positive by polymerase chain reaction (PCR) in peripheral blood mononuclear cells (PBMCs).

Phenytoin administration was immediately stopped, and symptomatic treatment was given. Eruptions became generalized during the next 2 days. On admission day 3, DRESS was diagnosed. Hepatomegaly was not observed. After 6 days, the fever subsided and the eruptions gradually resolved. The patient was discharged with markedly clinical improvement 2 weeks after admission. AST and ALT values were normalized on day 26 after eruption onset. Immunophenotyping of peripheral blood lymphocytes performed on admission and follow-up are summarized in Table 1.

DRESS is a serious adverse systemic reaction that usually appears after a 2- to 6-week exposure to certain drugs, such as anticonvulsants.¹ In this patient, phenytoin was responsible for inducing DRESS. Immediate withdrawal of the causative drug is the most important step in treatment of this syndrome. Systemic corticosteroid use is controversial in DRESS but is recommended by some experts.¹ Corticosteroid treatment was not started in this patient.

The exact pathogenesis of this syndrome remains unknown. The metabolism of the parent drug to chemically reactive (or toxic) metabolites is thought to be important to initiate the cascade of events leading to DRESS.¹ The reactive metabolite for phenytoin is arene oxide. Recently, the role of HHV-6 reactivation as a possible etiologic factor in DRESS has been suggested.^{3–5} Reactivation of HHV-6 from latently infected PBMCs requires T-cell activation. Tohyama et al⁴ suggested T-cell activation caused by reactive metabolite as the primary step for the development of DRESS. However, many adverse drug reactions via T-cell activation do not always develop into DRESS. Alternatively,

Table 1. Absolute Numbers of Peripheral Blood Lymphocytes

	Counts, cells/mL		
	Initial	Week 10	Month 8
CD3 ⁺ /CD4 ⁺ (helper T cells)	1,736	855	716
CD3 ⁺ /CD8 ⁺ (cytotoxic T cells)	3,989	841	567
CD19 ⁺ (B cells)	100	368	343
CD3 ⁺ /CD16 ⁺ /CD56 ⁺ (NK cells)	81	69	71
CD4 ⁺ /CD8 ⁺ ratio (T helper/T cytotoxic cell ratio)	0.45	1.02	1.26

Abbreviation: NK, natural killer.

Kano et al⁶ stated that drug (metabolites)-induced hypogammaglobulinemia and B-cell depletion lead to an environment in which HHV-6 reactivates. Recently, Inaoka⁷ proposed that the intrinsic dysfunction of natural killer (NK) cells to express CD122 is primarily responsible for a drug-induced decrease in B cells and subsequently reactivation of HHV-6, thereby causing excessive activation of antiviral CD8 T-cell responses in compensation for dysfunctional NK cells. In this patient, HHV-6 DNA was positive by PCR in PBMCs.

Recent studies^{5,8} have shown that reactivation of other HHVs besides HHV-6 might also be involved in the development of DRESS. However, we could not find reactivation of other viruses in this patient.

This patient presented with low B- and NK cell numbers and a low IgA level. These data are concordant with recent reports suggesting that a decrease in B- and NK cell counts can be associated with HHV-6 reactivation and the subsequent onset of DRESS. As compensation for low NK cell numbers, there is excessive activation of antiviral CD8⁺ T-cell responses. On follow-up, B-cell counts reached the reference range in this patient. We have not evaluated the function of NK cells to express CD122. However, NK cells were still low in number even 8 months after the acute onset of DRESS. Also, the CD4⁺/CD8⁺ ratio still continued to be low. This was related to the high number of CD8⁺ cells rather than to the decreased number of CD4⁺ cells. We suggest that CD8⁺ T cells could be cross-reactive with multiple antigens, causing severe clinical illness involving multiple organs in phenytoin-induced DRESS. We conclude that immunophenotyping of peripheral blood lymphocytes is useful for the early detection of this potentially life-threatening syndrome.

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RAPID ORAL DESENSITIZATION TO FUROSEMIDE

Furosemide is a commonly used loop diuretic that contains a sulfonamide group. Although there are rare reports of hypersensitivity to furosemide, severe reactions, including anaphylaxis, have been reported.¹ Ethacrynic acid, the only loop diuretic without a sulfonamide moiety, is no longer available in oral formulation, thus posing a dilemma in the outpatient treatment of patients with furosemide allergy.²

Published protocols for furosemide desensitization include rapid intravenous administration and oral protocols lasting 3 to 10 days.^{3–5} The oral protocols were performed in patients with non-type I hypersensitivity reactions. We present a rapid, oral protocol for desensitization in a patient with presumed type I furosemide allergy manifesting as urticaria.

Our patient is a 44-year-old woman with hypertension, mild intermittent asthma, and chronic kidney disease with significant volume overload. She had a history of an erythematous, non-urticarial rash while undergoing trimethoprim-sulfamethoxazole therapy. She was initially prescribed a furosemide dose of 20 mg/d, which was increased at more than 4 weeks to 40 mg 3 times daily. At this point, she developed a diffuse, pruritic, urticarial rash. She stopped taking the medication and took 1 dose of cetirizine, 10 mg, with symptom relief. As a result of her inability to tolerate escalating doses of furosemide and prior unresponsiveness to alternative medications (eg, metolazone), she was admitted to the hospital for diuresis with intravenous ethacrynate.

The allergy service was asked to evaluate the patient. Given her presumed furosemide hypersensitivity with the clear description of urticaria, her significant volume overload, and the absence of any contraindications, we chose to proceed with desensitization in the post-anesthesia care unit. We designed a rapid protocol with oral furosemide because a prior report of rapid intravenous desensitization had described no adverse effects⁴ and the patient would ultimately be taking the oral formulation. A negative skin test result to the parent compound would not preclude an allergy because reactions can be to a drug metabolite. Also, no reliable skin test reagents are available for either sulfonamides or furosemide because the immunogen is not known. In fact, the published description of the patient who underwent rapid intravenous desensitization for facial swelling revealed that the patient had a negative intradermal skin test result to 1% furosemide solution. Hence, we did not think that skin testing was warranted.

The patient tolerated the procedure, despite some generalized pruritus after the 1-mg dose. This dose was repeated, but because of continued itching she required diphenhydramine. Although her pruritus persisted, she had no rash or urticaria. She was successfully desensitized to a dose of 100 mg and then started on a maintenance regimen of furosemide, 100 mg 3 times daily, without any problems.

Although sulfonamide allergy is common, IgE-mediated reactions are rare. The most common immune-mediated reaction is a nonurticarial rash.⁶ Reactions appear to be dose related and may be to drug metabolites. This may explain the delayed reaction seen in our patient. There is a reported association between hypersensitivity to sulfonamide antibiotics and a subsequent allergic reaction to nonantibiotic sulfonamide drugs.⁷ However, this is thought to be due to a predisposition to allergic reactions rather than cross-reactivity among sulfonamide-based drugs. Sulfonamide antimicrobial agents have an aromatic amine group at the N4 position and a substituted ring at the N1 position. These groups are not found in nonantibiotic

sulfonamide drugs. Thus, cross-reactivity between these 2 groups of sulfonamides is thought to be unlikely.⁸

Table 1. Rapid Oral Furosemide Desensitization Protocol

Time, min	Solution strength	Dose
0	1 µg/mL	1 mL (1 µg)
20	1 µg/mL	3 mL (3 µg)
40	10 µg/mL	1 mL (10 µg)
60	10 µg/mL	3 mL (30 µg)
80	100 µg/mL	1 mL (100 µg)
100	100 µg/mL	3 mL (300 µg)
120	1 mg/mL	1 mL (1 mg)
140	1 mg/mL	3 mL (3 mg)
160	10 mg/mL	1 mL (10 mg)
180	10 mg/mL	4 mL (40 mg)
200	10 mg/mL	10 mL (100 mg)
220	Oral tablet dose	Lasix (100 mg)

Desensitization to sulfonamide-containing antibiotics has been extensively used, but desensitization to furosemide is uncommon. The oral protocols previously described took 3 to 10 days and were performed in patients with non-type I hypersensitivity reactions, one with pancytopenia and the other with pancreatitis.^{3,5} The patient with a type I hypersensitivity reaction underwent an intravenous desensitization protocol.⁴ Rapid oral desensitization to a loop diuretic has not been previously described. The potential advantages of oral desensitization are that it is probably safer than intravenous desensitization, it may be more cost-effective in terms of monitoring and staff requirements, and it may be possible to perform in an outpatient setting. We propose our protocol as a novel approach to furosemide desensitization therapy for patients with non-life-threatening reactions to furosemide. Further progress in the diagnosis and treatment of hypersensitivity to sulfonamide drugs will require identification of the major antigenic determinant and standardization of skin testing and specific IgE testing.

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