

Clinical Communications

Half of systemic reactions to allergen immunotherapy are delayed, majority require treatment with epinephrine

Kevin A. Cook, MD^a, Carolyn M. Ford, RN^a,
Elizabeth A. Leyvas, LVN^a, Jill Waalen, MD, MPH^b, and
Andrew A. White, MD^a

Clinical Implications

- The Allergen Immunotherapy Practice Parameter recommends that patients wait in the physician's office for 30 minutes following each injection. Roughly half of the systemic reactions may occur after the wait period, warranting consideration of universal prescribing of epinephrine autoinjectors.

TO THE EDITOR:

Allergen immunotherapy has been used for more than a century with proven benefits in the management of allergic rhinitis, asthma, and hymenoptera sensitivity.¹ The safety profile of subcutaneous immunotherapy is well studied, with a low rate of systemic reactions per injection given.² However, when systemic reactions occur they may be severe, in rare cases leading to hypotension and death. To mitigate the risk and allow for early intervention, the Joint Task Force Allergen Immunotherapy Practice Parameter recommends that patients wait in the physician's office for 30 minutes following each injection.¹ *Delayed systemic reactions*, defined as reactions occurring more than 30

minutes after an injection, encompass 14% to 50% of all systemic reactions.³⁻⁶ Severe reactions have rarely been reported with delayed onset,³ supporting the recommended 30-minute waiting period. Much of the data regarding the distribution of early and delayed systemic reactions is now 5 or more years old. In light of changes in the way our clinic administers immunotherapy, including increasing use of cluster and rush dosing protocols and premedications, it is helpful to periodically survey data related to the timing of systemic reactions.

We retrospectively reviewed 10 years of records of systemic reactions to subcutaneous immunotherapy at a single clinic site in Southern California. All patients had been checked for signs of local and systemic reactions before leaving the clinic. *Systemic reactions* were defined as signs or symptoms of an allergic reaction extending beyond the site of injection. This may include relatively minor symptoms such as rhinitis and/or generalized urticaria to severe reactions such as hypotension. Systemic reaction data were recorded on a standardized form at the time a reaction was reported. This included reactions that occurred at the clinic, patient-reported reactions after leaving the clinic, and those reported at the time of the next injection. Form data included time from injection to reaction, a brief narrative description of patients' signs and symptoms, and treatment rendered. Location of treatment and grade of reaction were not explicitly recorded for all patients. Shot records were analyzed to determine patients' demographic characteristics, content of allergen extracts, and dosing protocol. Systemic reactions were divided into early onset (≤ 30 minutes) and delayed onset (>30 minutes). Characteristics of these 2 groups were compared by *t* test for continuous variables and chi-square or Fisher exact test for categorical variables. The total number of patients and injections given over the study

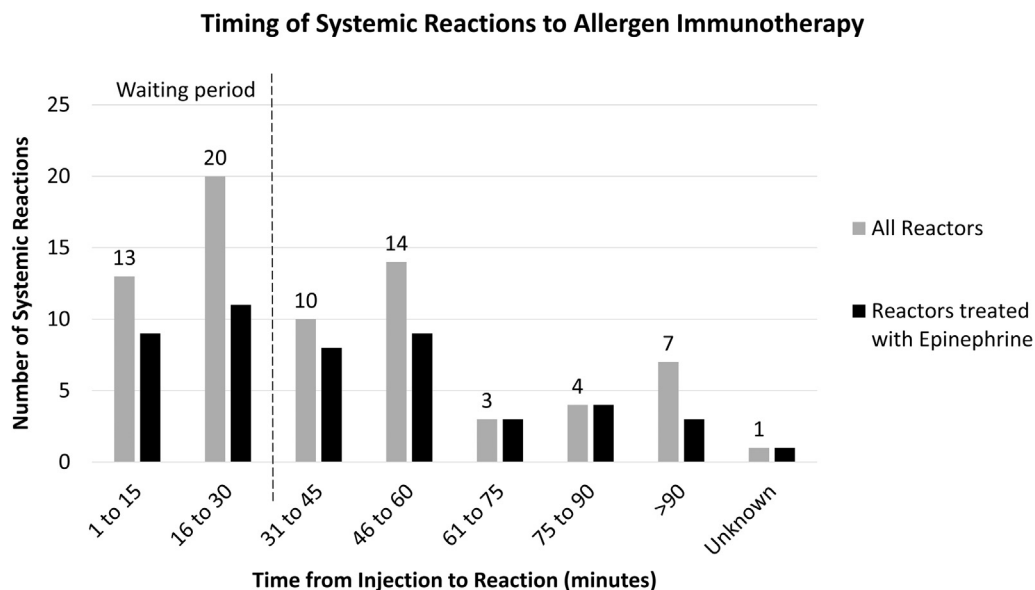


FIGURE 1. Distribution of 72 total systemic reactions is depicted by time from injection to reaction, demonstrating more than half of the reactions occurring after the 30-minute wait period.

TABLE I. Characteristics of patients—All reactions

Characteristic	Overall (n = 72)	≤30 min (n = 33 [45.8%])	>30 min (n = 38 [52.8%])	P*
Age (y), mean ± SD	36.8 ± 18.7	34.3 ± 20.0	38.8 ± 17.8	.33
Sex: male, n (%)	29 (40.3)	17 (51.5)	11 (29.0)	.05
No. of shot visits, mean ± SD	59.0 ± 104.8	70.8 ± 125.5	49.9 ± 86.1	.44
Cluster, n (%)	20 (27.8)	6 (18.2)	14 (36.8)	.11
Reaction after cluster	2/20	0/6	2/14	.99
Rush, n (%)	11 (15.3)	5 (15.1)	6 (15.8)	.94
Reaction after rush	1/11	1/5	0/6	.28
Allergens, n (%)				
Molds	26 (36.1)	13 (39.4)	13 (34.2)	.65
Cat	44 (61.1)	19 (57.8)	25 (65.8)	.48
Dog	40 (55.6)	17 (51.5)	22 (57.9)	.59
Horse	10 (14.1)	2 (6.1)	8 (21.6)	.09
Grasses	63 (87.5)	27 (81.8)	35 (92.1)	.29
Weeds	53 (73.6)	24 (72.7)	28 (73.7)	.93
Trees	50 (69.4)	21 (63.6)	28 (73.7)	.36
Feather	8 (11.1)	3 (9.1)	4 (10.5)	.99
Dust mite	43 (59.7)	16 (48.5)	26 (68.4)	.09
Cockroach	6 (8.3)	5 (15.2)	1 (2.6)	.09
Venom(s)	2 (2.8)	1 (3.0)	1 (2.6)	.99
Treatment, n (%)				
ER or UC	5 (6.9)	2 (6.1)	3 (7.9)	.99
Intramuscular epinephrine				
Any	48 (66.7)	20 (60.6)	27 (71.1)	.34
1 injection	43 (59.7)	16 (48.5)	26 (68.4)	.08
2+ injections	5 (6.9)	4 (12.1)	1 (2.6)	.12
Bronchodilator	15 (20.8)	9 (27.3)	6 (15.8)	.26
Antihistamine	59 (81.9)	29 (87.9)	29 (76.3)	.21
Systemic steroid	5 (6.9)	1 (3.0)	3 (7.9)	.38
Symptoms, n (%)				
Skin	50 (69.4)	21 (63.6)	28 (73.7)	.36
Ears	7 (9.7)	1 (3.0)	6 (15.8)	.11
Eyes	18 (25.0)	8 (24.2)	9 (23.7)	.99
Nose	22 (30.6)	10 (30.3)	11 (29.0)	.90
Throat	23 (31.9)	13 (39.4)	10 (26.3)	.24
Lungs	36 (50.0)	15 (45.5)	20 (52.6)	.55
CV	6 (8.3)	3 (9.1)	3 (7.9)	.99

CV, Cardiovascular; ER, emergency room; UC, urgent care.

*Comparing nondelayed vs delayed by *t* test (continuous), χ^2 , or Fisher exact test (categorical).

period was estimated from billing codes. Our estimate assumed that 80% of the patients billed for multiple injections received 2 injections, whereas 20% received 3 injections.

There were 72 systemic reactions reported among 50 patients over the 10-year study period, with an estimated 57,102 injections given to 671 patients (0.13% per injection, 7.5% per patient). Data related to reaction timing were available for all but 1 patient. More than half of the systemic reactions (52.8%) were reported to have begun at least 30 minutes after an injection. Thirty-one (43.1%) occurred 31 to 90 minutes after an injection, whereas 7 (9.7%) occurred after more than 90 minutes (Figure 1). The median time from injection to reaction was 35 minutes, whereas the most delayed reaction occurred after 6 hours.

Twenty (60.6%) of early-onset systemic reactions were treated with intramuscular epinephrine versus 27 (71.1%) of delayed reactions, with no statistically significant difference. Similarly,

there was no difference in treatment with bronchodilators, antihistamines, or systemic steroids between early and delayed reactions. Two early reactors were treated in an emergency department or urgent care clinic versus 3 delayed reactors ($P > .05$). There were no statistically significant differences between early and late reactors with regard to age, sex, dosing protocol (traditional, cluster, or rush), and allergen extract composition although the study was not powered to assess these factors (Table I).

Despite declining rates of severe and fatal systemic reactions in recent years,⁷ delayed reactions outside the clinic continue to encompass a significant portion of observed systemic reactions. In fact, our study suggests that current rates of delayed systemic reactions may be higher than previously reported. One possible explanation for this finding is increasing use of pre- or concurrent medications including antihistamines and leukotriene modifier drugs. One study found reduced rates of pruritus, urticaria, and

angioedema with antihistamine use in patients undergoing allergen immunotherapy, but failed to demonstrate a reduction in systemic reactions as a whole.⁸ Medication use may blunt several early cutaneous signs, leading to delayed recognition of a systemic reaction. However, use of antihistamines, particularly during cluster and rush dosing protocols, may reduce the frequency and severity of systemic reactions,⁹ suggesting that their benefits outweigh apparent drawbacks.

Regardless of the cause of delayed reactions, our study reiterates a need for strategies to address reactions outside the clinic. Although the Practice Parameter outlines the need to educate patients regarding symptoms of a systemic reaction, the Joint Task Force declined to universally recommend prescribing epinephrine autoinjectors to all patients undergoing allergen immunotherapy. The significant proportion of delayed systemic reactions beyond the 30-minute wait period, found in this study and others,^{3,6} highlights the utility of considering a policy of prescribing epinephrine autoinjectors to all or most patients. It is our practice to prescribe autoinjectors to all patients on allergen immunotherapy.

Limitations of this data set include a lack of consistent objective markers of reaction (spirometry, vital signs) or use of a reaction grading system as many reactions occurred outside the clinic. Documentation of urgent care and emergency department visits was not universally available and thus the necessity of these visits could not be determined. Severity of reactions is difficult to retrospectively assess. Treatment with epinephrine is a useful but imprecise surrogate for reaction severity. Epinephrine use may be overused or underused outside the clinic because of patient decision making with or without physician input. Single-site studies may also introduce bias with clinician patterns of epinephrine use, which may not reflect national and international trends of use. Regarding reaction rates, this study may underestimate the number of systemic reactions if mild and unreported by the patient. This study may overestimate the proportion of delayed systemic reactions if early signs went unrecognized by the patient or nursing staff within the 30-minute waiting period. Other limitations of the study include a relatively small sample size, incomplete documentation of reaction severity, and absence of outcome data. A larger sample size, standardized grading system, and full information regarding patient outcomes with and without treatment with epinephrine is needed to adequately determine if universal prescribing of epinephrine autoinjectors is indicated.

In conclusion, this 10-year retrospective study found that more than half of systemic reactions from allergen

immunotherapy occurred after the recommended 30-minute waiting period, with most delayed reactors treated with epinephrine. Because roughly 10% occurred after 90 minutes, it is impractical to extend the wait time to ensure all systemic reactions occur within the clinic. Instead, there is a clear need to continue to educate our patients on the risks and symptoms of systemic reactions. Prescribing of epinephrine autoinjectors should also be considered to ensure timely administration.

^aScripps Clinic, Division of Allergy, Asthma and Immunology, San Diego, Calif

^bScripps Translational Science Institute, La Jolla, Calif

Conflicts of interest: J. Waalen has received research support from the National Institutes of Health (Clinical and Translational Science Award grant UL54 AI108353 [PI: Topol]). The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication January 11, 2017; revised February 22, 2017; accepted for publication March 21, 2017.

Available online ■■

Corresponding author: Kevin A. Cook, MD, 3811 Valley Centre Dr, S99, San Diego, CA 92130. E-mail: cook.kevin@scrippshealth.org.
2213-2198

© 2017 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2017.03.025>

REFERENCES

1. Cox L, Nelson H, Lockett R, Calabria C, Finegold I, Nelson M, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011; 127:S1-S5.
2. Cox L, Larenas-Linnemann D, Lockett RF, Passalacqua G. Speaking the same language: the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. *J Allergy Clin Immunol* 2010;125:569-74. 574.e1-574.e7.
3. Lin MS, Tanner E, Lynn J, Friday GA Jr. Nonfatal systemic allergic reactions induced by skin testing and immunotherapy. *Ann Allergy* 1993;71:557-62.
4. Tinkelman DG, Cole WQ III, Tunno J. Immunotherapy: a one-year prospective study to evaluate risk factors of systemic reactions. *J Allergy Clin Immunol* 1995; 95:8-14.
5. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. Immediate and delayed-onset systemic reactions after subcutaneous immunotherapy injections: ACAAI/AAAAI surveillance study of subcutaneous immunotherapy: year 2. *Ann Allergy Asthma Immunol* 2011;107:426-431.e421.
6. Matloff SM, Bailit IW, Parks P, Madden N, Greineder DK. Systemic reactions to immunotherapy. *Allergy Proc* 1993;14:347-50.
7. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. ACAAI and ACAAI surveillance study of subcutaneous immunotherapy, year 3: what practices modify the risk of systemic reactions? *Ann Allergy Asthma Immunol* 2013;110: 274-8. 278.e1.
8. Reimers A, Hari Y, Muller U. Reduction of side-effects from ultrarush immunotherapy with honeybee venom by pretreatment with fexofenadine: a double-blind, placebo-controlled trial. *Allergy* 2000;55:484-8.
9. Nielsen L, Johnsen CR, Mosbech H, Poulsen LK, Malling HJ. Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. *J Allergy Clin Immunol* 1996;97:1207-13.