

Should Epinephrine Autoinjectors Be Prescribed to All Patients on Subcutaneous Immunotherapy?



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Subcutaneous allergen immunotherapy (SCIT) clearly benefits appropriately selected patients with allergic rhinitis, asthma and anaphylaxis to stinging insects. Since inception of SCIT, systemic allergic reactions (SRs) and severe anaphylaxis have been risk management challenges facing the practicing allergist. Recently it has estimated that 14% of reported SRs begin at least 30 minutes after injection administration or after the 30 minute recommended clinic observation period. Faced with the possibility that SRs could occur after the patient leaves the clinic, some practicing allergists routinely prescribe epinephrine auto-injectors to all injection patients. This article summarizes the key arguments for and against routine prescription of epinephrine auto-injectors for all allergen injection patients, discussed in a PRO/CON debate at the 2015 AAAAI meeting. Currently, there is insufficient clinical evidence to make a strong recommendation for or against this practice. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:862-7)

Subcutaneous immunotherapy (SCIT) with aqueous allergen extracts has been practiced for more than 100 years.^{1,2} In the last 4 decades, controlled clinical trials have demonstrated the efficacy of this modality in the treatment of patients with allergic rhinitis, asthma, and Hymenoptera allergy. Since its inception, the potential risk of severe systemic reactions (SRs) and rare fatal anaphylaxis associated with SCIT has been recognized. During the last 4 decades in the United States, retrospective surveys of the experience

of practicing allergists and, more recently, annual surveillance studies have helped to define the frequency of rare fatal reactions (FRs) after administration of SCIT injections as well as factors that might increase their risk.³⁻⁶ A recent annual surveillance study of clinical allergy practice in the United States indicates that SRs after SCIT injection reactions occur at 0.1% of all injection visits.⁶ A retrospective study of SCIT FRs estimated that from 1990 to 2001, one fatal injection reaction occurred in every 2.5 million injection visits.⁷ Investigation of potential risk factors in this and other surveys among practitioners revealed that uncontrolled asthma appeared to be the most commonly cited factor noted at the time of SCIT-related fatal events. Heightened awareness from discussions of severe SCIT reactions described in the aforementioned studies has led to the development of practice guidelines recommending routine preinjection screening of all asthmatic patients for asthma control and observing patients for a minimum of 30 minutes after SCIT injections.⁸ Since 2008, it appears that the number of fatal SCIT reactions have declined.⁶ In the annual surveillance study conducted in 2009-2010, only 3.4% of all reported SCIT-associated SRs would be classified as anaphylaxis and only 0.4% of these as delayed-onset anaphylaxis beginning after 30 minutes.⁹ The available evidence suggests that most SRs occur within 30 minutes after injections but a minority of SRs (14%) begin after more than 30 minutes.⁹ For this and other reasons, a minority of allergists have begun to routinely prescribe epinephrine autoinjectors to all patients receiving SCIT and provide training on self-administration in the event of a late-onset SR. A survey conducted among 273 practicing allergists in North America found a wide variation in this practice with 33% responding that self-injectable epinephrine was routinely prescribed to all their patients receiving SCIT injections; 53% of respondents indicated that they risk-stratify patients in arriving at a clinical decision to prescribe. It is noteworthy that 25% of survey participants were uncertain if epinephrine prescriptions had actually been filled and the majority of these physicians administered SCIT injections regardless of whether patients carried self-injectable epinephrine devices with them to their injection visits.¹⁰ Arguments for and against this practice were recently debated in a Pro-Con Debate at the 2015 annual American Academy of Allergy, Asthma & Immunology (AAAAI) meeting. A summary of the debate favoring and opposing this practice is listed in Table I and detailed arguments are presented below.

PRO POSITION: EPINEPHRINE AUTOINJECTORS SHOULD BE PRESCRIBED FOR ALL PATIENTS RECEIVING SCIT

SCIT is unique as a medical therapy in that a known precipitant of anaphylaxis is being intentionally delivered. Although a highly efficacious option for atopic disease, rare but significant SRs including life-threatening anaphylaxis do occur. Any

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Abbreviations used

FR- Fatal reaction

NFR- Near-fatal reaction

SCIT- Subcutaneous immunotherapy

SLIT- Sublingual

SR- Systemic reaction

clinician administering SCIT must be prepared to treat such reactions in the office. Safety can be maximized by making self-injectable epinephrine routinely available to all SCIT patients in the event of a delayed reaction outside the office. Although severe SRs occurring after the customary in-office 30-minute period are quite infrequent, systemic injection with epinephrine is nevertheless the only appropriate therapy for such reactions, which is the same as for any anaphylactic event.

A number of questions must be considered before issuing a recommendation to routinely prescribe self-injectable epinephrine to all SCIT patients:

1. What is the frequency of delayed SRs, and of these, how many are severe?
2. What is the efficacy of epinephrine for delayed SRs?
3. What is the cost of the intervention?
4. Can patients at elevated risk for delayed SRs be identified?

Severe delayed SRs to SCIT are overall rare. Using data from the prospective AAAAI/American College of Allergy, Asthma & Immunology (ACAAI) Immunotherapy Surveillance study, delayed SRs occurred at an incidence of 1 per 14,000 injection visits.⁹ Of these, 12.5% were classified as severe (grade 3). Thus, the calculated incidence of severe, delayed SRs after SCIT is approximately 1 per 112,000 injection visits. Although such events are indeed infrequent, all patients receiving SCIT require an anaphylaxis preparedness plan for such an out-of-office event. Certainly, one strategy for managing a delayed SR could be for the patient to return to the administering physician's office or a nearby emergency facility. Although these strategies are not unreasonable, medical attention is not always readily available and anaphylaxis continues to evolve during any delay in receiving medical care. Having self-injectable epinephrine available to all SCIT patients ensures immediate access to potentially life-saving therapy in the event of a delayed SR to an SCIT injection.

Regarding efficacy epinephrine for delayed SRs, there is extensive, high-quality evidence that prompt administration of intramuscular epinephrine on recognition of anaphylaxis is the therapy of choice and all other therapies are essentially adjunctive.¹¹ Delayed administration of epinephrine is a contributing factor for some FRs to immunotherapy.⁸ No study has been designed to compare outcomes of delayed SRs among patients who did or did not receive self-administered epinephrine. There is no reason to believe that the physiologic mechanism of anaphylaxis in delayed SRs operates differently than, say, food anaphylaxis and that administration of epinephrine should be any less efficacious. Indeed, in the AAAAI/ACAAI surveillance study, all of 9 patients with late-onset, severe SRs required and *eventually* received epinephrine. However, unfortunately, only a minority of these patients (4 of 9) had epinephrine autoinjectors previously prescribed and only 2 of these 4 actually self-administered epinephrine.⁹

Although the cost of autoinjectable epinephrine cannot be discounted, cost should not be a deterrent to prescribing the only accepted first-line treatment for anaphylaxis. Unfortunately, the average wholesale price of epinephrine autoinjectors continues to climb in the United States. The average wholesale price of autoinjectors was near \$100 in 2011, whereas the retail price varies dramatically but can approach \$300 per device.¹² However, cost defrayment mechanisms are available in the form of copay cards and patient assistance programs from all major manufacturers of autoinjectors.¹² The cost dilemma of providing epinephrine for SCIT patients is unfortunately no different than that faced by other patients who are at risk for anaphylaxis due to food or venom allergy. Finally, it is worth noting that if a recommendation for all SCIT patients to have epinephrine autoinjectors were implemented in the Allergen Immunotherapy (AIT) Practice Parameters, this would likely be covered as a no-cost preventative service to patients under the Affordable Care Act, irrespective of deductible or copay/coinsurance obligations.

Because delayed SRs to immunotherapy are overall rare, it would be highly desirable to establish which patients are at elevated risk for such reactions. This question is really the central axis about which the question to prescribe epinephrine autoinjectors to SCIT patients revolves: *are there any clear risk-stratification criteria to identify patients at increased risk for delayed SRs to immunotherapy who might benefit most from having self-injectable epinephrine available?* There are a number of risk factors that may predispose patients to SR, delayed or otherwise, most notably labile asthma or a history of prior SR.¹³ The most recent update of the Immunotherapy Practice Parameter supports such a risk-stratification scheme, stating: "Some physicians might request that patients considered at increased risk of a serious systemic reaction outside of the office/medical clinic carry injectable epinephrine. These patients should be instructed in the use of epinephrine to treat a systemic reaction that occurs after they have left the physician's office or other location where the injection was given."⁸

The essence of this decision dilemma in assigning future risk to patients is that there are no reliable patient characteristics that predict which patients might experience a future delayed SR. Interestingly, in the AAAAI/ACAAI surveillance study, "among patients experiencing severe delayed-onset SRs for whom complete reaction details were available, *none had ever had a SR in the past.*"⁹ Selectively prescribing self-injectable epinephrine only to patients deemed to be at higher risk, while commendable, ignores the fact that many SRs, including delayed SRs, occur without obvious risk factors.

Practical considerations involve whether patients prescribed self-injectable epinephrine actually have autoinjectors available in the event of a severe delayed SR or, if they do, whether or not they decide to promptly self-administer the drug. Failure to carry or to self-administer previously prescribed autoinjectable epinephrine is a challenge we commonly face in convincing patients at risk for severe anaphylaxis due to food or venom allergy. The data for timely self-administration of epinephrine are not encouraging. We must continue to educate our patients about the central role of prompt epinephrine delivery in the treatment of severe allergic reactions and ensure that patients, parents, and other caregivers have the confidence and experience to utilize the device when indicated.^{12,13} Although we cannot assure that epinephrine will be delivered in all instances by patients in the field when we might give it in the clinic, it is fairly

TABLE I. Arguments for (Pro) and against (Con) routinely prescribing epinephrine autoinjectors to all patients on subcutaneous immunotherapy

Pro	Con
● Delayed-onset reactions (>30 min) are common ● Patients should have access to lifesaving therapy should delayed-onset severe reactions occur outside the clinic	● Nearly all life-threatening anaphylactic reactions occur within 30 min after administration of injections ● Alternative strategies are available including seeking immediate emergency care. All patients receiving SCIT should be provided with an action plan in the event of a delayed SR ● There is insufficient evidence showing that the routine prescription of epinephrine autoinjectors reduces risk of fatal injection events
● All patients receiving injections should be prescribed self-injectable epinephrine ● There are no reliable risk-stratification criteria by which to predict patients at risk of future late-onset SRs	● Evidence suggests many patients do not carry or use their epinephrine autoinjectors during anaphylaxis in the field ● Instead, patients with clearly defined risk factors for SRs (eg, prior history of SRs) should be prescribed epinephrine autoinjectors
● Cost of universal prescription of self-injectable epinephrine is a consideration, but is not an insurmountable obstacle ● Cost defrayment mechanisms exist in the form of copay cards and manufacturer assistance programs	● Current evidence does not show sufficient clinical benefit to justify this approach ● Secondarily, the cost to treat one severe delayed-onset SR far exceeds current standards for third-party reimbursement

SCIT, Subcutaneous immunotherapy; SR, systemic reaction.

certain that if epinephrine has never been prescribed, it would not be available when truly needed.

It is notable that the prescribing information for all 3 commercially available sublingual immunotherapy (SLIT) products in the United States all contains a boxed warning mandating that self-injectable epinephrine be available for these products, despite the fact that the incidence of severe SRs to SLIT is extraordinarily low and there have been no reported anaphylactic deaths from SLIT administration.¹⁴ Should the same standard be applied to all patients receiving SCIT, considering the low but real risk of delayed-onset SRs?

Simply prescribing epinephrine to SCIT patients, however, is inadequate: it should be the cornerstone of a well-conceived anaphylaxis preparedness plan, which involves patient education to recognize the signs and symptoms of a reaction, prompt medical attention in the event of a reaction, and when appropriate, timely delivery of self-injectable epinephrine.

In summary, routine prescribing of self-injectable epinephrine is a practice that helps ensure maximal safety for patients receiving SCIT. Because there are no predictive criteria that are adequately reliable to identify patients at risk for severe, delayed SRs, the only rational way to ensure timely access to potentially life-saving treatment for severe, delayed immunotherapy reactions is to prescribe epinephrine universally to all SCIT patients.

CON POSITION: EPINEPHRINE AUTOINJECTORS SHOULD NOT BE PRESCRIBED FOR ALL PATIENTS RECEIVING SCIT

SCIT is a highly effective treatment modality for allergic asthma, allergic rhinitis, and prevention of stinging insect anaphylaxis. The major disadvantage of SCIT is the risk of injection-related systemic allergic reactions and life-threatening anaphylaxis.¹⁵ For this reason, current guidelines mandate that allergen injections be administered in a clinic facility prepared to treat anaphylaxis under observation of a physician.⁸ Although

most SRs begin immediately after injections, there is a risk of late-onset systemic allergic reactions that may begin after patients have departed from the health care facility after the recommended observation period (30 minutes).¹⁶ Because late-onset reactions are not uncommon and SRs could occur if patients decide to leave the clinic early against medical advice, a considerable number of allergists in North America routinely prescribe epinephrine autoinjector devices to all patients receiving allergen injections. In this section, the prevalence, severity, and risk of delayed-onset SRs to injections will be discussed as well as strategies to minimize risk of adverse outcomes from delayed reactions. The evidence presented will conclude that there is little evidence that routine prescription of self-injectable epinephrine would improve overall safety of SCIT.

Risk of immediate versus delayed-onset allergic SRs

During the last 40 years, rare cases of fatal anaphylaxis have been documented among allergists practicing SCIT in North America.^{2,3,17} Since 1973, there have been 84 confirmed FRs to allergen immunotherapy injections. Between the years 1990 and 2001, in a 12-year retrospective survey of practicing allergists, FRs to SCIT injections were estimated to occur once in every 2.5 million injection visits, translating into 3.4 fatal events per year.⁵ To track severe SRs in North America longitudinally, an annual surveillance study of practices of trained allergist-immunologists was initiated in 2008.¹⁷ Since the retrospective survey spanning 1990-2001, the rate of FRs in North America may have decreased by approximately 6-fold among patients receiving injections under the supervision of board certified allergists.¹⁸ The exact explanations for this reduction cannot be precisely determined but could be related to enhanced awareness among clinicians of factors contributing to fatal SCIT reactions, leading to more careful risk assessment of patients before initiation of SCIT as well as widespread preinjection screening of asthma control.

Three retrospective surveys conducted in North America have resulted in the identification of possible contributing factors to

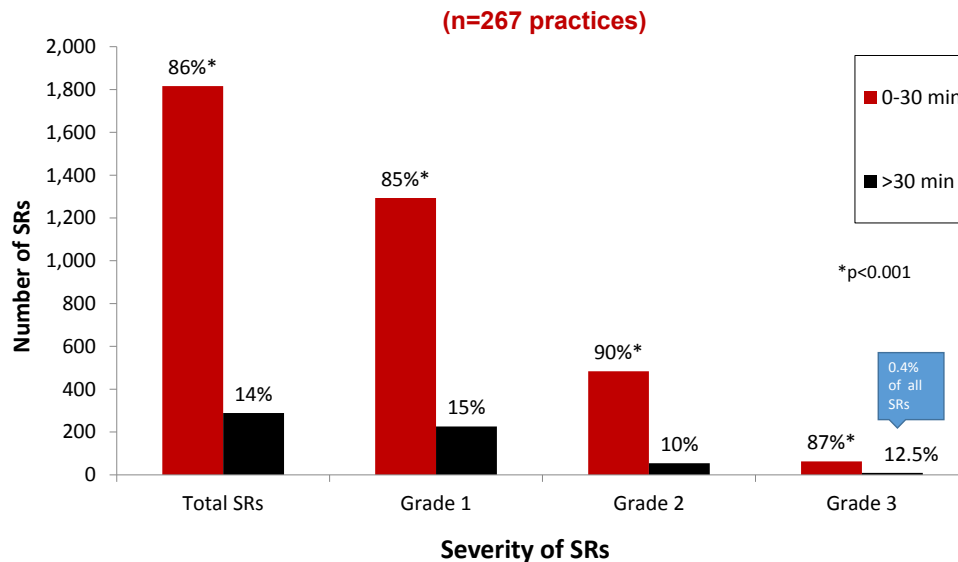


FIGURE 1. Annual AIT surveillance data collected from North American allergists showing numbers and proportions of systemic reactions of varying severity (ie, mild, moderate, and severe) during 2009 beginning within and greater than 30 minutes after administration of allergen injections.⁷

fatal anaphylaxis after SCIT injections.³⁻⁵ In all published surveys, uncontrolled or labile asthma is the most frequent contributing factor to fatal SCIT reactions cited by treating physicians. Other cited factors include a history of prior systemic SCIT reactions; delayed administration of epinephrine; home administration of injections; dose administration errors; and insufficient observation times after injection administration. The vast majority of FRs to SCIT injections begin within the first 30 minutes. In 4 (12%) cases, fatal SCIT reactions were reported to have begun after 30 minutes, although the delay in onset was well documented in only 2 of the 4 cases. Near-fatal reactions (NFRs) were also evaluated in the aforementioned 12-year retrospective study of FRs; 3 of 68 (4%) began after 30 minutes.² Of the 3 patients with late NFRs, 2 returned to clinic 45 minutes after receiving their injection, presenting with pruritus, hives, and bronchospasm. Epinephrine was delayed but administered in 2 patients; the third patient experienced severe hypotension 60 minutes after the injection and was administered epinephrine in the emergency department. Because of rare severe late SRs, some have raised the question whether self-injectable epinephrine should be routinely prescribed to all patients on SCIT injections.

Early studies of single practices estimated a surprisingly high incidence of late-onset SRs (beginning more than 30 minutes after injections) ranging from 27% to 50% of patients receiving injections.⁸ Such initial estimates of late-onset SRs appeared higher than what is generally encountered in clinical practice and, if confirmed, could support an argument for routine prescription of self-injectable epinephrine. To address this question, the incidence and severity of late-onset SRs was evaluated in the clinical practices of a large cross section of board certified American allergists, participating in the AAAAI/ACAAI Immunotherapy Surveillance Study.⁹ During 2000-2009, 227 of 630 allergist respondents reported that late-onset SRs (beginning after 30 minutes) accounted for 14% of all 1816 SRs, with 86%

beginning within 30 minutes. Thus, one delayed-onset SR occurred in every 14,286 injection visits (0.007%). Seventy-eight percent of all late-onset SRs were grade 1 mild SRs (ie, generalized cutaneous and/or upper respiratory symptoms); 19% were grade 2 moderate SRs (ie, asthmatic symptoms with reduction in lung function with or without cutaneous, upper respiratory, or gastrointestinal symptoms); and 3% of reported severe SRs (ie, life-threatening anaphylaxis with severe lower upper airway compromise or hypotension) were delayed in onset (Figure 1). The administration of epinephrine was compared for early- and delayed-onset (>30 minutes) SRs of varying severity. Whereas more than 90% of patients experiencing early-onset grade 2 and 3 reactions received epinephrine, only 67% delayed-onset grade 2 SRs were treated with emergency epinephrine (Figure 2). It is noteworthy that all 9 patients who experienced delayed grade 3 SRs eventually received epinephrine and none resulted in hospitalization; 4 of the 9 patients with grade 3 SRs had been previously prescribed an epinephrine autoinjector, but only 2 self-administered epinephrine at the time of the SR as they sought acute medical care. Thus, most delayed SRs were mild or moderate and would not be characterized as anaphylaxis. Late-onset severe grade 3 SRs represented 1 in every 250 SR events (0.4%).⁹

The North American Surveillance Study data examining the frequencies of late reactions of different severity grades support the AIT Practice Parameter (third update), stating that delayed SRs occur after a 30-minute wait period but, in general, are not severe.⁸ It is noteworthy that based on surveillance data derived from 630 allergy practices widely distributed across North America, late-onset SRs are not uncommon but less common than previously reported. Although fewer patients experiencing mild and moderate late-onset SRs received epinephrine, no FRs were reported in this group and late-onset severe and potentially life-threatening SRs were managed successfully.⁹

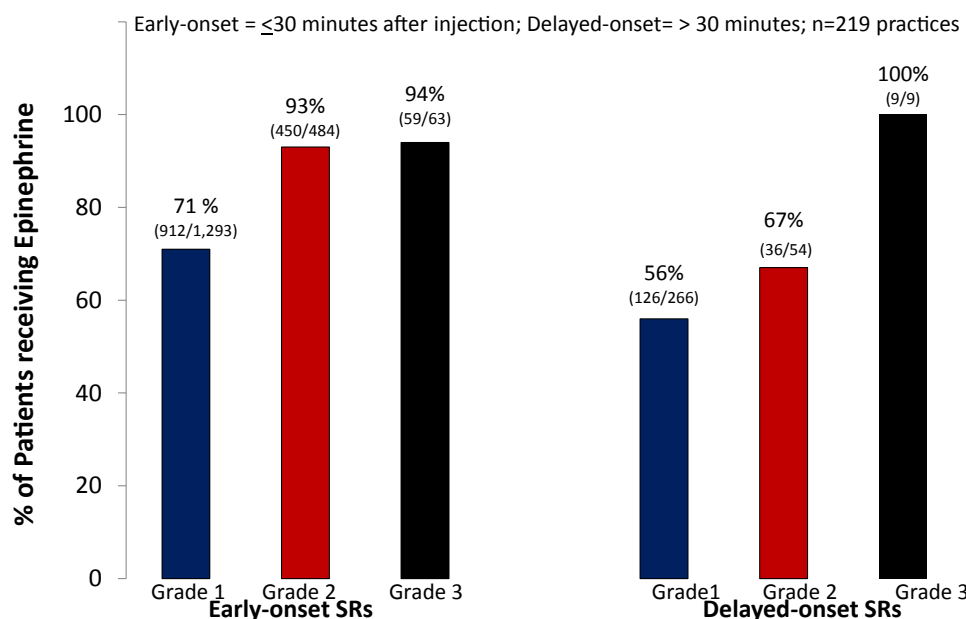


FIGURE 2. Annual AIT surveillance data collected from North American allergists showing numbers and proportions of patients' administered epinephrine for systemic reactions of varying severity (ie, mild, moderate, and severe) during 2009 beginning within and greater than 30 minutes after administration of allergen injections.⁷

The economic impact for routine prescribing of epinephrine autoinjectors could be substantial. On the basis of data from the North American immunotherapy Safety Study, we have determined that 8621 patients would need to be prescribed an epinephrine autoinjector to treat 1 late-onset severe SR. Furthermore, if epinephrine were routinely prescribed to all patients receiving SCIT, it would cost \$2.9 million to treat a single delayed severe SR, assuming that the retail cost of commercial autoinjectors is \$300 and assuming that the patient makes a decision to self-administer epinephrine injection during the SR. It is noteworthy that noncompliance with recommendations to carry and to self-administer epinephrine autoinjectors is common.¹⁹

Universal prescription of epinephrine autoinjectors cannot be considered a substitute for careful risk assessment, education, and monitoring of patients at risk for SRs as described in the AIT Practice Parameter (third update).⁸ All patients receiving immunotherapy should be educated on how to recognize signs and symptoms of an allergic SR after leaving the clinical facility and provided an action plan on when and where to seek emergency medical attention. The recognition of early signs of SRs and seeking prompt treatment may prevent the evolution to severe anaphylaxis. To prevent future reactions, discontinuation of SCIT should be considered in those patients with prior immediate- or delayed-onset SRs who are at greater risk for recurrence, and especially in those with uncontrolled asthma and/or reduced lung function (ie, FEV1 $< 70\%$) or any underlying medical condition reducing the patient's ability to survive anaphylaxis.⁷

As stated in the AIT Practice Parameter, the decision to prescribe epinephrine autoinjectors to patients receiving immunotherapy should be at the physician's discretion based on individual patient circumstances.⁸ If the decision is made to resume SCIT injections in patients with prior late-onset SRs, an epinephrine autoinjector should be prescribed, and the

TABLE II. Managing late-onset systemic reactions in patients on SCIT

- Before starting treatment, educate all patients receiving SCIT on how to recognize the signs and symptoms of SRs should these begin during or after the 30-min observation period.
- All patients should be monitored for a minimum of 30 min after injections and, should they experience a late-onset SR, for 45-120 min after subsequent injections.
- Patients with previous immediate- or late-onset SR events after SCIT injections should be trained on self-administration of an epinephrine autoinjector.
- In the event of a delayed SR outside the clinic, patients should immediately seek medical attention or instructions from the administering facility. If not available, seek emergency care at a medical facility (eg, ED). If prescribed, immediately self-administer an epinephrine autoinjector in the lateral thigh muscle.

ED, Emergency department; SCIT, subcutaneous immunotherapy; SR, systemic reaction.

observation period should be extended (at least 1 hour) at future injection visits. For example, autoinjectors should be considered in those patients living or traveling in areas where there is limited access to emergency care. The concern over biphasic late reactions after an allergen injection would not justify routinely prescribing epinephrine. The second phase of biphasic reactions are less severe than initial reactions and do not seem to require additional epinephrine.²⁰

SUMMARY AND CONCLUSIONS

A plan for managing late SRs is presented in Table II. Severe life-threatening late-onset SRs to SCIT are uncommon and most late-onset SRs are mild in severity. All patients receiving allergen injections should be educated on recognition of SRs should they

begin outside the clinical facility and be given an action plan on when and where to seek medical attention for treatment. The authors agree that such an anaphylaxis preparedness plan and appropriate patient education are essential to ensure patient safety while receiving SCIT. Epinephrine autoinjectors should be considered for all patients at elevated risk for severe or late-onset SRs. Further studies are needed to better define predictive criteria for patients at risk of such delayed SRs; such data would allow greater confidence in selectively prescribing epinephrine autoinjectors only to high-risk patients. There are no data that support decreased morbidity due to delayed SCIT reactions by universal prescribing of epinephrine autoinjectors. In the absence of such supportive evidence, the decision to prescribe epinephrine to all patients on immunotherapy or to selective patients remains an individual physician determination guided by clinician experience and individual patient factors.

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