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Specific Immunotherapy (L Cox, Section Editor)

Optimizing Allergen Immunotherapy Safety: What Do We Know and What Are the Unmet Needs

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Opinion Statement

Subcutaneous immunotherapy (SCIT) is generally safe yet there remains a small risk of fatal and near-fatal injections. Factors that should be considered in the initial risk assessment for systemic reactions to SCIT include poorly controlled asthma, high degree of allergen sensitivity, history of prior systemic reactions, comorbid illness, and building up injections during the height of pollen season. Future studies should evaluate the aforementioned risk factors and also assess protocol modifications including antihistamine pretreatment, lower or higher starting doses (silver [1:10,000 *v/v*] vs red [1:1000 *v/v*]) and different buildup regimens with different dose increases (0.05 vs 0.1 mL). Finally, risk management after systemic reactions (SR) needs to be further investigated, including when to discontinue SCIT, how far to decrease the dose after SR, optimal pretreatment regimens, when to increase wait times, and when to prescribe epinephrine autoinjectors. Sublingual immunotherapy (SLIT) is generally felt to be safer, though anaphylaxis has been reported. Local side effects (oral and gastrointestinal) represent the majority of all reported SLIT adverse reactions and affect up to 75 % of patients. There are a multitude of unanswered questions related to SLIT safety, including the safety of using multiple allergens, using SCIT + SLIT simultaneously, dosage adjustments for missed doses, how long to hold a dose (after infections, dental work, asthma), and identifying SR risk factors.

Subcutaneous immunotherapy

Local reactions from subcutaneous immunotherapy

Local reactions (LR) and large local reactions (LLR) occur frequently during the course of subcutaneous immunotherapy (SCIT). LR is defined as swelling and redness that occur in the immediate vicinity of the injection site [1–3]. LR can cause pain, localized edema, and erythema and are graded according to size. LLR has variable definitions in the literature, from greater than 20–25 mm to larger than the palm of the patient's hand or greater than 10 cm [4–7]. LR are common, ranging from 26 to 82 % of patients and 0.7 to 16 % of injections [2]. Allergists commonly dose adjust for LLR (91.9 % in a survey); the reasons given were because of concerns of patient non-compliance (88.9 %), that LLR predict LLR (45.7 %) and that LLR predict systemic reactions (SR) (29.2 %) [8]. However, in a patient survey, 82 % of IT patients reported their LR were not or were only slightly bothersome, with 5 % reporting them very bothersome; 96 % reported they would not stop SCIT due to LLR [3].

Furthermore, despite patient and allergists' concerns, LLR do not appear to predict LLR at least at the next immunotherapy injection. These data were discovered retrospectively in a 12-month study of 360 patients receiving 9678 injections [2]. Glycerin (in concentrations up to 50 %), a common preservative in SCIT extracts, was not associated with significantly higher LLR rate or size [9]. Several retrospective articles also demonstrate LLR are not predictive of future systemic reactions (SR) at the next injection. Nelson et al. analyzed LLR and SR of 416 immunotherapy patients receiving 25,508 pollen extract injections [1]. LLR were not helpful in predicting which patients would develop SR. Similarly, a double-blind, placebo-controlled trial of 22 children undergoing inhalant rush immunotherapy (RIT) concluded LLR were not associated with subsequent SR. [10].

Several studies have also evaluated whether LLR dose adjustments were associated with lower SR rates. Tankersley et al. analyzed 12,926 SCIT injections and 114 SR over an 18-month period (9-month period of LLR dose adjustments was compared with a 9-month period of no-dose adjustments). He concluded LLR is not a good predictor of a subsequent SR at the next dose and SR rates were similar in each period [11]. He later evaluated 10,636 immunotherapy injections with 89 SR over a 3-year period and concluded again that LLR did not increase SR rates [12]. Kelso evaluated the rate of SR to SCIT over a 2-year period [13]. The first period of 3250 visits included LLR dose adjustments, while during the second period (4692 visits), no dose adjustments were made. SR rates were not statistically different between the two periods.

Some retrospective data associate frequent LLR and SR. Roy et al. found the LLR (defined as >25 mm) rate was four times higher among the 258 SR patients when compared with those SCIT patients who never had SR in practices using routine LLR dose adjustments [7]. In an academic practice not dose adjusting for LLR, it was demonstrated that LLR patients were more likely to have SR (1.3 % of injections and 2 % of visits) compared to non-LLR patients (SR 0.4 % of injections, 0.7 % of visits); similar systemic reactors had a higher frequency of LLR [14]. Therefore, this association between LLR and SR occurs irrespective of whether LLR dose adjustments are made. A case cohort study of fire ant

immunotherapy patients showed that LLR were associated to an increased frequency of SR. [15].

Management of bothersome LLR is an important component of an SCIT program. Empirical treatment options include antihistamines, leukotriene antagonists (LTRAs), cold compresses, NSAIDs, and split dosing (in patients on one injection, give half the dose in one arm and half in the other arm); however, none of these has been prospectively studied and shown to prevent LLR in conventional SCIT though antihistamines and LTRAs have shown benefit in accelerated schedules. Oral antihistamines including terfenadine and fexofenadine have been effective in reducing LLR in rush venom immunotherapy (VIT) [16–18]. Montelukast was effective in decreasing LLR size in a small study of 15 patients undergoing rush VIT [19]. LLR should be approached individually in patients and attempts made to prevent recurrence and minimize discomfort.

SR from SCIT

Generally, SCIT is felt to be safe; however, there is the risk of systemic anaphylactic reactions from immunotherapy. There have been differing SR rates after allergen immunotherapy depending on the given method of immunotherapy, the particular study, and the criteria for defining a SR. The World Allergy Organization (WAO) has published an SR grading system to help clinicians and researchers speak the same language (Fig. 1) [20].

Severe SR after immunotherapy range from <1 to 7 % for patients receiving conventional immunotherapy in the buildup and maintenance phase [21–23]. Cox et al. published a comprehensive SCIT safety review over 15 years and discovered the SR rate per injection with conventional schedules is approximately 0.2 % [20]. In contrast, the SR rate for patients receiving RIT has been reported as high as 34 % [24, 25]. Life-threatening and fatal reactions have occurred. In 2006, a survey of near-fatal and fatal reactions was completed by 273 allergists that covered the time period of 1990–2001. A near-fatal reaction was defined as respiratory compromise, hypotension, or both requiring epinephrine. There were 17 fatal reactions and 68 near-fatal reactions. The mean near-fatal reaction rate was 1 per million injections and the estimated fatality rate was 1 per 2.5 million injections [26]. A subsequent surveillance study of 806 physicians evaluated SCIT SR. No fatal reactions were reported; however, six fatal reactions were reported retrospectively from 2001 to 2007 [25].

Risk factors for SCIT SR include the administration of immunotherapy during the height of the pollen season, dosing errors, patients with asthma, and delayed administration of epinephrine [26]. Fatal anaphylaxis from immunotherapy is also seen in patients with severe or poorly controlled asthma [27, 28]. Other factors contributing to SCIT SR are cardiovascular disease, beta blocker use among patients, injections given during the buildup phase, and injections not administered in a medical facility [26–30]. Some authors have raised concern about the concomitant use of angiotensin-converting enzyme (ACE) inhibitors in patients receiving immunotherapy. There have been a few cases of anaphylaxis from immunotherapy in patient receiving ACE inhibitors, but the relative risk has not

World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (see text)				
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Symptom(s)/ sign(s) of one organ system present [i] **Cutaneous** Generalized pruritus, urticaria, flushing or sensation of heat or warmth[ii] **or** Angioedema (not laryngeal, tongue or uvular) **or** **Upper respiratory** Rhinitis (e.g., sneezing, rhinorrhea, nasal pruritus and/or nasal congestion) **or** Throat-clearing (itchy throat) **or** Cough perceived to come from the upper airway, not the lung, larynx, or trachea **or** **Conjunctival** Conjunctival erythema, pruritus or tearing **Other** Nausea, metallic taste, or headache	***Symptom(s)/ sign(s) of more than one organ system present*** **or** **Lower respiratory** Asthma: cough, wheezing, shortness of breath (e.g., less than 40% PEF or FEV1 drop, responding to an inhaled bronchodilator) **or** **Gastrointestinal** Abdominal cramps, vomiting, or diarrhea or **Other** Uterine cramps	**Lower respiratory** Asthma (e.g., 40% PEF or FEV1 drop, NOT responding to an inhaled bronchodilator) **or** **Upper respiratory** Laryngeal, uvula or tongue edema with or without stridor	**Lower or Upper respiratory** Respiratory failure with or without loss of consciousness **or** **Cardiovascular** Hypotension with or without loss of consciousness	Death
Patients may also have a feeling of impending doom, especially in grades 2, 3, or 4. **Note:** children with anaphylaxis seldom convey a sense of impending doom and their behavior changes may be a sign of anaphylaxis, e.g., becoming very quiet or irritable and cranky.				
Scoring includes a suffix that denotes if and when epinephrine is or is not administered in relationship to symptom(s)/sign(s) of the SR: a, ≤ 5 minutes; b, >5 minutes to ≤10 minutes; c, >10 to ≤ 20 minutes; d, >20 minutes; z, epinephrine not administered.				
The final grade of the reaction will not be determined until the event is over, regardless of the medication administered. The final report should include the first symptom(s)/sign(s) and the time of onset after the subcutaneous allergen immunotherapy injection [iii] and a suffix reflecting if and when epinephrine was or was not administered, **e.g., Grade 2a; rhinitis:10 minutes.**				
Final report: Grade a-d,or z _____First symptom _____ Time of onset of first symptom _____				
Comments[iv]				

Fig. 1. World Allergy Organization subcutaneous immunotherapy systemic reaction grading system. Reprinted from *Journal of Allergy and Clinical Immunology*, Volume 125, Issue 3, Linda Cox, Desiree Larenas-Linnemann, Richard F. Lockey,Giovanni Passalacqua, Speaking the same language: the World Allergy Organization subcutaneous immunotherapy systemic reaction grading system, 569–574., Copyright (2010), with permission from Elsevier.

been determined [29–32]. Two retrospective cohort studies did not find an association between ACE inhibitors and SR to SCIT [31, 32]. ACE appear to increase risk of severe anaphylaxis to field stings but not to buildup VIT [33, 34].

Most SR including the most severe reactions occur within 30 min after the injection(s) [20, 35]. Because of the timing of these reactions, the allergen immunotherapy practice parameter recommends a 30-min wait in the physician's office after the injection [36]. There are also reports of delayed (range 3–50 %) and biphasic SR but in general, these delayed reactions tend not to be severe [23, 32, 37–41]. However, a surveillance study found 13 % of all severe grade 3 WAO SR were delayed and epinephrine was given for 60 % of delayed SR [42]. Patients should be aware of these delayed reactions and seek emergency care if needed. Allergists should have a delayed SR plan for their patients; many prescribe an epinephrine autoinjector to their patients at higher risk of SR including those with a history of delayed SR.

New findings

Based on data gathered on 28.9 million injection visits from the first 5 years of a national surveillance study (2008–2013) with voluntary reporting from USA and Canadian physicians, SCIT-related SR occur in 82–85 % of practices, and with 0.1 % of injection visits [43••]. This includes on average 6.7 World Allergy Organization (WAO) grade 1 (mild) SR, 2.9 WAO grade 2 (moderate), 0.4 WAO grade 3 (severe) SR, and 0.1 WAO grade 4 (very severe) SR per 10,000 injection visits annually. Preliminary estimates from the most recent year are that 1.9 % of patients on SCIT experience SR, including grade 1 SR in 1.1 %, grade 2 in 0.69 %, grade 3 in 0.08 %, and grade 4 SR in 0.02 % of patients; although these figures may be based on under-reporting [43••]. Four fatalities were reported (two under care of allergists, two under the care of non-allergists). Less SR were seen in practices that did not administer immunotherapy to patients with uncontrolled asthma and in practices that lowered the dose during pollen seasons with highly positive skin tests [43••].

Another recent publication evaluated LR and SR to SCIT in a pediatric clinic. The study evaluated 14,308 injections and found that LR and SR occurred in 11.9 and 4.7 % of patients, respectively. LR were most common in the buildup phase and with dust mite immunotherapy, and interestingly in this study, SR were most frequent in the maintenance phase and in patients undergoing immunotherapy with multiple allergens [44]. Finally, investigators evaluated epinephrine delivery during SCIT SR over a 7-year period (2005–2012) among 1328 patients who received 93,136 injections (aeroallergen and venom immunotherapy). The SR rate was 0.28 %/injection. Prefilled epinephrine syringes were administered in the deltoid muscle vs the vastus lateralis for patients' SR, and there was no difference in time to resolution of symptoms regardless of location [45••].

Unmet needs

Many studies have been published regarding SCIT safety focusing on SR and LLR. Protocol modifications should be evaluated including lower or higher starting doses (silver vs red) and different buildup regimens with different dose increases (0.05 vs 0.1 mL). Anti-histamine pretreatment should be more thoroughly studied. Prospective studies are needed to investigate whether different immunotherapy delivery systems may be safer and more convenient. For example, intra-lymphatic administration

[46••], T cell-based immunotherapy [47] and the use of nanoparticles [48] have recently been reported. Additionally, there should be more research evaluating SCIT in patients with chronic medical problems, pregnancy, and using certain medications such as beta blockers and ACE inhibitors. Prospective studies are needed to evaluate potential SR risk factors such as high skin test reactivity, previous SR (does SR predict SR?), and persistent asthma. Furthermore, studies should focus on whether it is important to decrease immunotherapy dosing during the height of pollen season. Finally, risk management after SR needs to be further investigated, including when to discontinue SCIT, how far to decrease the dose after SR, optimal pretreatment regimens, when to increase wait times, and when to prescribe epinephrine autoinjectors.

Cluster immunotherapy

As patient inconvenience is one of the most commonly cited reason for the failure to complete the buildup phase of SCIT, efforts to decrease the number of visits required to reach the maintenance phase have existed since the work of Freeman [49]. Conventional weekly buildup injections require approximately 6 months to reach maintenance; however, cluster buildup schedules typically can reduce this time to as little as 4 to 8 weeks. With this acceleration, there is often a perceived increase in SR risk, but many studies report a similar SR rate compared with conventional schedules [50–54] and SR rates appear similar between inhalant and venom allergens. However, one study reported SR rate of 79 % suspected secondary to a 10-fold increase in maintenance dose for timothy grass compared to other studies [55].

Furthermore, a retrospective analysis involving 441 patients undergoing an 8-visit cluster protocol in a large multicenter allergy practice reported a 10.9 % SR rate including five grade 3 WAO SR and one grade 4 WAO SR. [56].

Most of the SR rate data are reported as a safety measure captured within study with a different designed hypothesis or as a retrospective review. However, two prospective, double blinded, placebo controlled studies examined dust mite (DM) allergic patients randomized to a conventional or cluster buildup schedule and neither study found a significant difference in the SR rate [50, 52]. The data regarding cluster SR rates primarily come from single allergen studies with varying experimental designs; therefore, aggregation of data for meta-analysis remains problematic. As such, evidence for the use for multi-allergen extracts remains only supported by extrapolation.

The SR risk while undergoing cluster immunotherapy appears to decrease with antihistamine premedication (loratadine reduced SR from 79 to 33 %) [55] and omalizumab (reduced SR rates from 26 to 14 % in asthmatic patients) [57]. No data regarding the effects of anti-leukotriene medications are available. Only antihistamines have data to support their use in reducing LLR [17]. No deaths have been reported in immunotherapy trials utilizing cluster buildup schedules though one death was recently reported to investigators performing a nationwide surveillance study (T Epstein, personal communication,

March 2016). Finally, a recent review article analyzed 29 cluster immunotherapy studies and summarized ways to attempt to improve safety: pre-medicating with antihistamines, using depot extracts, limiting injections to four at most per visit, utilizing 4–6 cluster appointments, and scheduling these appointments 1–2 times per week [58].

Rush immunotherapy

Rush immunotherapy (RIT) is defined as administering incremental doses of allergens over 1 to 3 days until a therapeutic dose is reached. While cluster buildup schedules are commonly utilized to improve the convenience of immunotherapy, RIT is most commonly used to attempt to prevent anaphylaxis from Hymenoptera. Ultra-rush immunotherapy buildup schedules also exist in which maintenance dose injections are reached in a matter of hours and therefore, theoretically providing protection from anaphylaxis in a single day [59]. Studies also exist using RIT schedules for aeroallergens and come with relative high SR rates. Premedication reduced the risk of SR from 55 to 73 % of patients without premedication to 27–35 % with premedication [10, 60, 61]. Interestingly, RIT with venom extracts do not appear to be associated with a similar SR increase [62, 63]. As SR are low in rush VIT, data are conflicting on the utility of premedication with antihistamines and therefore is not routinely recommended [17, 19, 63]. Omalizumab pretreatment significantly reduced SR to ragweed rush immunotherapy [64] and case reports demonstrate improved tolerance of VIT in patients with prior SR to VIT and indolent systemic mastocytosis after high-dose omalizumab [65, 66]. In summation, venom RIT appears to have comparable risk for SR (with or without premedication) to conventional buildup, but conveys protection from anaphylaxis much more rapidly. The time benefits for RIT to aeroallergens are generally outweighed by increased SR risk.

SLIT safety overview

There is little question that Sublingual immunotherapy (SLIT) is safer than SCIT in terms of systemic allergic reactions (SR) and the potential for life-threatening events. Although fatality rates from SCIT have been declining, there have been 84 confirmed fatalities attributed to SCIT in the USA since 1973, including at least 2 fatalities since 2007 [27–30, 43••, 67]. No fatalities from SLIT have ever been reported in the USA or abroad [68••, 69]. Local side effects (LARs) (oral and gastrointestinal) represent the majority (80–90 %) of all reported SLIT adverse reactions and affect up to 75 % of patients. SR to SLIT are defined as systemic side effects such as rhinitis, asthma, urticaria, angioedema, and/or hypotension that do not consist of oropharyngeal or gastrointestinal LR alone [70].

Local reactions to SLIT

The most common SLIT side effects include oral pruritus, ear pruritus, throat irritation, tongue pruritus and mouth edema. These LR can be severe and bothersome enough to discontinue treatment in approximately 3 % of patients [68••]. They often occur in the first 10 days, occur quickly after administration, and usually occur less often with subsequent administration. In a study involving 834 patients receiving house dust mite (HDM) SLIT tablets, the median

onset of LARs was within 1–2 days, and within 1–2 min of SLIT tablet administration [71••]. Resolution of LR, such that they no longer occurred with repeated administration was a median of 4.5 days for oral pruritus, 7 days for throat irritation, and 23 days for mouth edema [71••]. Another HDM SLIT tablet trial found that the median duration of individual LR ranged from 1 to 43 min on day 1 [72]. A grading system for SLIT LR recommends using grade 1 for mild LR (troublesome and no treatment required), grade 2 for moderate LR (troublesome or symptomatic treatment required), and grade 3 for severe LR (grade 2 and SLIT discontinued due to the LR) [70].

SLIT systemic reactions

In a review of 66 SLIT studies conducted outside of the USA, including 4378 patients, 14 probable treatment-related serious adverse events were described, including 7 asthma exacerbations, abdominal pain and vomiting, severe uvular edema, and urticaria [68••]. In those studies, SR only occurred with 0.056 % of doses. Very low SR rates have also been reported from trials of SLIT liquid and tablet monotherapies in the USA. Most US SLIT studies have reported no SR, although at least two have reported SR to SLIT [73–80]. In a recent summary of 29 SLIT-tablet trials, epinephrine was administered in 35 subjects; 25 were receiving active SLIT treatment, and 16 administrations were for SLIT treatment-related events (TRAEs) [81]. The authors calculated that 0.2 % of subjects (16/8152) received epinephrine for SLIT-related events, and no events were considered serious or resulted in airway compromise.

There are case reports from outside the USA of at least 11 severe SR and/or anaphylactic events from liquid SLIT and SLIT tablets [82–90]. Risk factors identified in these reports included the following: overdose, newly started SLIT, multi-allergen SLIT, previous SR to SCIT, or asthma exacerbations with SCIT. Surveillance data for off-label liquid SLIT in the USA, which is non-standardized and generally multi-allergen, identified 45 SR in 3343 patients (1.4 % of patients) between 2012 and 2013, including nine grade 2 (0.3 % of patients) and one grade 3 SR (0.03 % of patients) [43••]. It is important to note that *uncontrolled* asthmatics are likely at higher risk for severe adverse reactions from SLIT, as this has been a risk factor for severe reactions to SCIT. Retrospective surveys found that uncontrolled asthma was implicated in 62 % of fatal reactions and 10 % of near-fatal reactions to SCIT [26, 28–30]. SLIT studies on asthmatics have shown variable results. In a study involving 43 patients on HDM liquid SLIT, which included 63 % asthmatics, seven SR occurred in 23,154 doses and 11.6 % of patients, all of which were grade 2 or 3 SR. [87] In contrast, a recent study of HDM SLIT tablets in 834 adults with asthma not well controlled by ICS or ICS-long acting beta agonist combination inhalers did not report any SR, and only reported one possible treatment related moderate asthmatic exacerbation [71••].

Recognizing SLIT LR and SR

Patients should be educated to recognize and manage their LR appropriately, and should know they occur commonly during the beginning of treatment. For mild to moderate oral symptoms, and for mild abdominal pain and nausea, an antihistamine may be helpful. Antihistamines have been utilized in SCIT with benefit to help with LLR, mainly during accelerated inhalant and Hymenoptera immunotherapy [10, 16–18, 55]. A single trial for conventional SCIT showed

antihistamine pretreatment reduced the occurrence of severe SR using a conventional buildup schedule [91]. Patients who experience severe or recurrent LR should be instructed to contact the prescribing physician and consider stopping SLIT. It is important to remember that even with LR, patients should be counseled to monitor for signs of rapidly progressing reactions, such as worsening laryngeal edema, urticaria, or shortness of breath that could necessitate epinephrine treatment.

Patients should also be instructed how to identify SR to SLIT and educated on when and how to use epinephrine. Patients should have their epinephrine autoinjector available at all times. The American Academy of Allergy, Asthma and Immunology (AAAAI) has developed an action plan (Fig. 2) for LR and SR and consent form (Fig. 3) that can be utilized as a template and discussed with patients. Epinephrine should be given for severe local throat swelling (even if it is a result of a LR) causing difficulty speaking, breathing, or swallowing and for severe GI symptoms such as severe abdominal pain, vomiting, diarrhea, and cramping. Epinephrine should also be given for the systemic symptoms of hives, flushing, angioedema, cough, dyspnea, wheezing, severe lightheadedness, and dizziness.

Contraindications

Contraindications for initiating SLIT listed in the package inserts for all commercially available SLIT products include severe or uncontrolled asthma, history of eosinophilic esophagitis (EoE), history of severe local reaction to SLIT, or history of any severe SR. [92–94] In addition, caution should be used when administering SLIT to individuals at risk of not surviving anaphylaxis. Medications that may interfere with epinephrine, such as beta-blockers, should be changed.

When to hold a dose?

Patients on SLIT should hold their dose for any increased asthma symptoms in the previous 24 h, any worsening heartburn or dysphagia, any recent dental or oral procedures/surgery or lesions, increased viral upper respiratory tract infection symptoms, urticaria or angioedema (regardless of etiology), or fever. They should also hold their dose and notify their allergist for any new blood pressure medications, if newly pregnant, or if diagnosed with a new medical condition. A form developed by the AAAAI to assist patients in determining when to hold a dose of SLIT can be found on their website (Fig. 4).

What about missed doses?

In clinical trials of US FDA-approved tablets, treatment interruptions for up to 7 days were allowed [93, 94]. Data regarding the safety of missed doses are limited. One would expect that missed doses would not be a major safety issue for most patients, as there is no buildup regimen needed for commercially available tablets other than for Oralair® in patients age 10–17 years. It is important to remind patients that they should not take extra doses if they miss any doses, and they should take the next dose at their normal scheduled time on the following day. Patients are advised to contact their healthcare provider before restarting SLIT if they miss more than one dose [92–94]. Information regarding the safety of the first dose of subsequent seasons (2nd, 3rd years) are not published in package inserts.

SLIT Local Reaction and Systemic Reaction Emergency Plan

Patient name: _____ Age: _____
Allergies: _____
_____
Additional health problems: _____
_____
Concurrent medications: _____
_____ _____

FOR MILD TO MODERATE LOCAL REACTION

MOUTH: bothersome itching, and/or mild swelling of lips and/or tongue
THROAT: bothersome itching, irritation, and/or mild tightness
EAR: bothersome itching
GASTROINTESTINAL: mild abdominal pain, nausea, and/or cramps

ACTION→ Use antihistamine: _____ mg or mL

FOR SEVERE LOCAL REACTION*

MOUTH/THROAT: swelling that causes hoarseness and/or throat closing

OR FOR SYSTEMIC REACTION*

SKIN: hives all over body and/or redness all over body
LUNG: shortness of breath, cough, and/or wheezing
HEART: weak pulse, dizziness, and/or passing out
GASTROINTESTINAL: severe abdominal pain, vomiting, diarrhea, and/or cramping

*You may only have a few symptoms. Symptoms can be life-threatening.

ACTION→Inject epinephrine in thigh using (circle one):

Adrenaclick (0.3 mg)	Adrenaclick (0.15 mg)
Auvi-Q (0.3 mg)	Auvi-Q (0.15 mg)
EpiPen (0.3 mg)	EpiPen Jr. (0.15 mg)

- Call 911 (before calling contact)

Emergency contact #1: home_____work_____cell_____
Emergency contact #2: home_____ work_____ cell_____
Emergency contact #3: home_____ work_____ cell_____

Comments_____
Doctor's Signature/Date/Phone Number _____

Fig. 2. SLIT local reaction and systemic reaction emergency plan. This form as well as other related forms and documentation are available to American Academy of Allergy, Asthma and Immunology (AAAAI) members at aaaai.org.

SLIT safety in asthmatics

Asthmatic patients in the clinical trials for FDA-approved SLIT tablets were at most on a low-dose ICS and the great majority were only using as needed beta-agonists [92–94]. Caution should therefore be utilized when initiating SLIT in moderate to severe persistent and high-risk asthmatics, and SLIT should not be

American Academy of Allergy Asthma & Immunology

SUBLINGUAL ALLERGEN IMMUNOTHERAPY PATIENT CONSENT FORM

Sublingual immunotherapy (SLIT) is an allergy tablet given under the tongue. SLIT should be taken under the care of a physician who is trained to prescribe the medication and to treat any possible reactions. The first dose is given at the medical office and, as long as this initial dosing is well tolerated, subsequent daily doses are taken at home. For the first week or so, it is not uncommon for you to experience some local reactions in your mouth consisting of minor itchiness or discomfort. These symptoms, should they occur, are typically brief and go away without any special treatment. Some individuals experience mild abdominal discomfort in the first days of treatment. Occasional serious reactions have been reported that may require immediate treatment. These reactions may consist of any or all of the following symptoms: itchy eyes, nose, ears or throat; stuffy nose; sneezing; runny nose; mouth, nose or abdominal discomfort; coughing; swelling of the lips, tongue or throat; difficulty breathing; nausea and vomiting; hives; itching all over your body; and very rarely, a life-threatening systemic reaction known as anaphylaxis. Severe reactions, even though very unusual, may rarely occur at any time during the course of SLIT therapy. Because of the risk of a severe reaction, **you must agree to have self-injectable epinephrine on hand with each dose of SLIT therapy.**

For the initial dosing, you are required to wait in the prescribing doctor's office for at least 30 minutes after using the tablet. If you are 17 years of age or younger, a parent or legal guardian must be present during the waiting period.

I have read (if new patient) or re-read (if established patient) the patient information sheet on sublingual immunotherapy and understand it. The opportunity has been provided for me to ask questions regarding the potential side effects of sublingual immunotherapy and these questions have been answered to my satisfaction. I understand that every precaution consistent with the best medical practice will be carried out to protect me against possible reactions associated with this treatment. I also agree that if I have an allergic reaction to the sublingual medication, I will follow the action plan I was given.

I acknowledge that I am aware of the risks/benefits/alternatives to sublingual immunotherapy and consent/agree to starting this treatment.

PATIENT_____ **DATE** _____

PARENT or LEGAL GUARDIAN_____ **DATE** _____

As parent or legal guardian, I understand that I must accompany my child throughout the entire 30-minute wait.

WITNESS_____ **DATE**_____

Additional SLIT and traditional immunotherapy forms and documentation are available to AAAAI members at www.aaaai.org

Fig. 3. Sublingual allergen immunotherapy patient consent form. This form as well as other related forms and documentation are available to American Academy of Allergy, Asthma and Immunology (AAAAI) members at aaaai.org.

initiated in uncontrolled asthmatics. It is important that proper steps are taken for diagnosis and management of asthma, including spirometry with reversibility testing, adjustment of medications to achieve control, instruction on avoidance of triggers, and possibly reporting exposures to relevant allergens before SLIT dosing. On the day of the first dose, consideration should be given to performing standardized questionnaires to verify asthma control, such as the Asthma Control Test (ACT) and spirometry or peak flow measurement before and after SLIT dosing.

Sublingual Immunotherapy Pre-Dose Checklist

Patient Name:_____Date:_____

This checklist is to help you safely administer your sublingual (under the tongue) immunotherapy (SLIT) at home. If there are **ANY YES** responses, please contact the doctor who prescribed your SLIT **BEFORE** you take your dose. **If you are newly pregnant, have started any new prescription medications for blood pressure or headache, or have been diagnosed with a new medical condition, please notify your doctor immediately.**

Answer these questions: IF YOU ANSWER **YES** TO ANY QUESTION, DO NOT TAKE YOUR SLIT TABLET AND CONTACT YOUR DOCTOR IMMEDIATELY.

After your last SLIT dose, did you have:

YES	NO	
☐	☐	Any increased allergy or asthma symptoms, hives (welts), or itching all over?
☐	☐	Any new heartburn, severe abdominal discomfort, nausea, cramping, diarrhea, trouble swallowing or chest pain?
☐	☐	Any new mouth symptoms (such as itching, tingling, swelling, or burning) not previously discussed with your doctor?

Since your last SLIT dose, have you:

☐	☐	Had any dental procedures?
☐	☐	Had any new mouth sores, cuts, lesions or breaks in the skin inside your mouth?
☐	☐	Started taking any new blood pressure or headache medications (for example, beta-blocker or alpha-blocker)?

In the last 24 hours, have you had:

☐	☐	Any asthma symptoms (chest tightness, cough, wheezing, or shortness of breath)?
☐	☐	Worsened allergy symptoms (itchy eyes or nose, sneezing, runny nose, post-nasal drip, or throat-clearing)?
☐	☐	A cold, respiratory tract infection, flu-like symptoms, or fever?

YOU MUST HAVE EPINEPHRINE AVAILABLE. IF YOU DO NOT HAVE AN EPINEPHRINE AUTOINJECTOR IMMEDIATELY AVAILABLE, **STOP** AND WAIT TO TAKE YOUR SLIT TABLET UNTIL YOU HAVE EPINEPHRINE AVAILABLE.

ENTER *PRACTICE CONTACT INFORMATION HERE*

Fig. 4. Sublingual allergen immunotherapy pre-dose checklist. This form as well as other related forms and documentation are available to American Academy of Allergy, Asthma and Immunology (AAAAI) members at aaaai.org.

SLIT and EoE

New-onset EoE has been reported after initiation of grass, mixed tree pollen, and HDM SLIT [95–97]. EoE resolved with discontinuation of SLIT in each of

these case reports. There is a wider body of literature regarding the risk of EoE with food SLIT with a meta-analysis suggesting a 2.7 % risk (95 % CI 1.7–4.0 %) [98]. Physicians should be aware of this potential SLIT complication and educate patients to report worsening dysphagia and/or heartburn.

Epinephrine autoinjector prescription

The FDA mandates that patients receiving SLIT tablets in the USA be prescribed an epinephrine autoinjector, and be instructed on use [92–94]. This is based on the premise that although systemic adverse events from SLIT are rare, they do occur [75]. As with SCIT, early treatment of SLIT SARs with epinephrine should lead to improved outcomes [36] particularly because SLIT patients are outside the clinical setting. The question of whether this recommendation translates into improved clinical outcomes is more complicated. There are several issues to consider including autoinjector cost, compliance with carrying it, recognizing appropriate clinical scenarios for administration, and then following through with administration. In the AAAAI/American College of Allergy, Asthma, and Immunology (ACAAI) national surveillance study on SCIT, only half of patients prescribed an epinephrine autoinjector self-administered the drug for severe delayed SR. [42] In addition, compliance with purchasing an epinephrine autoinjector has become more difficult due to rising autoinjector prices and rising insurance deductibles [99]. Moreover, even when patients can afford autoinjectors, compliance with carrying them is historically poor [100]. That said, it is difficult to argue against prescribing a potentially life-saving device, even for very rare outcomes.

Unmet needs

There are a multitude of unanswered questions related to SLIT safety, including the safety of using multiple allergens, using SCIT + SLIT simultaneously, dosage adjustments for missed doses, how long to hold a dose (after URI, AGE, dental work, asthma), and identifying SR risk factors. One of the most challenging obstacles for use of SLIT is that most patients are multi-sensitized. Almost all studies on SLIT have involved single allergens, and most studies on multiple-allergen SLIT involve off-label liquid SLIT preparations derived from SCIT extracts. Questions remain regarding whether adequate doses can be achieved for more than two extracts delivered sublingually simultaneously [88, 101, 102]. Safety data for multi-allergen liquid SLIT (off-label in USA) are not well established, and cases of anaphylaxis have been reported [43••, 83, 84].

A recent study involving Timothy grass and ragweed SLIT tablets administered to 102 adults found that 4-week sequential dosing of tablets followed by simultaneous administration was well tolerated, with no severe LR, SAR, asthma exacerbations, or epinephrine use [103••]. This finding is helpful for practitioners treating co-sensitized grass and ragweed-allergic patients, particularly given that overlapping treatment may be necessary in much of the USA. An investigation of sequential treatment of HDM SCIT buildup × 16 weeks followed by SLIT maintenance found it effective in reducing symptoms [104]. However, studies regarding the safety of co-administration of SLIT and SCIT simultaneously are lacking, and this practice is not routinely recommended.

Reports of SLIT anaphylaxis [82–90] suggest that asthma, prior SCIT SR, and multi-allergen SLIT were potential risk factors in these individual cases.

However, these risk factors have not been studied prospectively. Studies are needed to evaluate SLIT in moderate to severe persistent asthmatics and in patients with prior SR to SCIT. Furthermore, research needs to determine if a high degree of skin test reactivity/sensitization increases SR risk. As best practices on SLIT and SCIT evolve, Allergists can utilize both their clinical experience and evidence-based medicine to provide optimal treatment to their patients.

Compliance with Ethical Standards

Conflict of Interest

Dr. Christopher W. Calabria declares that he has no conflict of interest. Dr. Derek M. Smith declares that he has no conflict of interest. Dr. Christopher A. Coop declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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