

Anaphylactic Reactions During Immunotherapy

Maziar Rezvani, MD, David I. Bernstein, MD*

*Division of Allergy/Immunology, University of Cincinnati College of Medicine,
231 Albert Sabin Way, Cincinnati, OH 45267–0563, USA*

In the past 4 decades, the incidence of atopic disorders has expanded in developed countries [1,2]. Subcutaneous immunotherapy (IT) with aeroallergen extracts has been a venerable treatment modality for nearly 100 years [3,4]. Controlled clinical studies have confirmed the efficacy of IT in reducing symptoms and medication requirements in patients with allergic rhinitis (AR) caused by seasonal pollens and standardized house dust mite extract (HDM) [5,6]. Placebo-controlled trials have also established the efficacy of subcutaneous IT in treating allergic asthma associated with exposure to grass pollen, cat, and house dust mite allergen [7]. The unequivocal effectiveness of subcutaneous IT with purified venoms in prevention of insect sting anaphylaxis has been demonstrated in patients with anaphylactic sensitivity to *Hymenoptera* venoms [8–10].

As with any treatment, anticipated benefits attributed to IT must be weighed against its potential risks. It is clear that the major risk associated with IT with commercial aeroallergen extracts is the uncommon occurrence of severe near-fatal or fatal anaphylaxis after injections.

The major objectives of this article are to (1) review the reported incidences of severe anaphylaxis (near-fatal reactions [NFRs] and fatal reactions [FRs]), (2) define factors contributing to these events, and (3) identify preventive measures that are likely to reduce or eliminate future fatal and near-fatal anaphylactic events.

Historical background

In 1910, Noon was the first to develop IT in England with pollen extracts administered subcutaneously [3]. In 1916, Cooke and Vander Veer [11]

* Corresponding author.

E-mail address: david.i.bernstein@uc.edu (D.I. Bernstein).

reported their experience in treating 621 patients, and they identified a 3.5% overall incidence of systemic reactions to subcutaneous grass pollen injections. Six years later, Cooke [12] reported the first known death of a 3-year-old asthmatic child during intracutaneous skin testing. In 1919, Boughton [13] reported fatal anaphylaxis in a 29-year-old asthmatic patient during attempted intravenous desensitization with horse serum. The two later cases were cited in Lamson's 1924 account [14] of another fatality immediately after application of multiple intracutaneous skin tests with oat, milk, rice, and egg in a 5-month-old child with eczema. Aggressive resuscitative measures, including epinephrine and atropine, were of no avail. In a 1932 report of 9 patients who succumbed to fatal anaphylactic shock from various agents, 1 was a 40-year-old "hay fever" patient who died from anaphylaxis after receiving a subcutaneous ragweed extract injection, failing to respond to epinephrine [15].

In 1957, Van Arsdel and Sherman [16] published a larger 20-year survey of systemic allergic reactions (1933–1953) associated with intracutaneous testing and IT in 8706 allergy clinic patients treated at Roosevelt Hospital in New York City. They reported the occurrence of one (0.1%) constitutional reaction per 700 injections in 663 patients (7% incidence). It was noteworthy that only 114 (0.01%) injections resulted in systemic reactions of sufficient severity to warrant epinephrine administration and that only six (0.0005%) reactions led to shock. No fatal events occurred. In a review of systemic anaphylaxis published in 1964, James and Austen [17] reported a delayed FR in a 56-year-old man undergoing "hayfever desensitization" manifested initially by dyspnea 45 minutes after an injection.

In 1986, the Committee on the Safety of Medicines (CSM) in the United Kingdom reported details of 26 IT-related deaths that had occurred between 1957 and 1986 resulting from anaphylaxis or bronchospasm after administration of allergen injections. All fatal reactors were receiving IT for allergic asthma, and it seemed that asthmatic patients were at greatest risk for FRs [18]. This initial report resulted in a mandated 2-hour postinjection waiting period for patients receiving IT, which practically eliminated the use of this modality in the United Kingdom for years until a 1-hour standard was adopted [19].

Incidence of systemic, fatal, and near-fatal immunotherapy reactions

Because of manufacturing differences in allergen extracts, it is difficult to compare incidence data in Europe and North America with regard to IT-related anaphylactic reactions. Currently, nearly all products used in Europe are aluminum absorbed or modified, whereas pure aqueous extracts are used exclusively in the United States. Severe and potentially life-threatening reactions represent a small percentage of all injection-related systemic allergic reactions. One clinic in the United Kingdom reported that 0.2% of 919

injections with alum-absorbed grass pollen extract resulted in severe systemic reactions compared with 2% that led to mild systemic reactions (hives, rhinitis, and mild wheeze) [20]. In the United States, Greenberg and colleagues [21] reported systemic reactions in 7% of patients receiving IT with mixed allergen extracts and an injection reaction rate of 0.25%. Ewan and colleagues [22] evaluated systemic reactions in patients receiving injections with aqueous *Dermatophagoides pteronyssinus* in a clinical trial using a rapid build-up protocol and reported an injection reaction rate of 23%, although only 8% of these reactions were serious and required epinephrine. Bousquet and colleagues [23] assessed systemic reactions in a prospective study of 125 patients receiving IT with house dust mite extract (*D pteronyssinus*). Systemic reactions were reported in 47 (38%) of patients during the rush protocol, of whom 4 experienced mild urticaria, 35 had asthma exacerbations, and 8 experienced anaphylactic shock. No reactions occurred later than 45 minutes after the last injection. Based on the aforementioned studies, rush or cluster dosing regimens seem to be associated with increased systemic reaction rates compared with conventional and slower induction protocols [24].

FRs associated with IT injections have appropriately received much attention and scrutiny. During the past 20 years, the Immunotherapy Committee of the American Academy of Allergy, Asthma, and Clinical Immunology (AAAAI) has sponsored a series of retrospective surveys of fatalities associated with allergen injections and skin testing. In the first survey reported in 1987, Lockey and colleagues [25] summarized information obtained from responses to long questionnaires provided voluntarily by physicians who had experienced IT and skin test FRs in their clinics or were aware of others in their region. These investigators estimated that 1 FR occurred in every 2.8 million injections based on an estimated 47 million annual doses of IT administered in the United States. In a follow-up survey of fatal events between 1985 and 1989, Reid and colleagues [26] identified a similar rate of 1 FR per 2 million injections based on 33 million administered doses, or an incidence of four cases per year. In the most recent AAAAI physician survey of FRs of events from 1990 through 2001, Bernstein and colleagues [27] identified 41 confirmed FRs, which translated to an annual case incidence of 3.4 deaths per year and 1 fatal event in 2.5 million injections. The methods used in the latest survey differed from those of the two former studies in that a brief survey was initially sent to all physician members of the AAAAI, resulting in 646 respondents, or 27% of 2404 physicians contacted [27]. Physicians were queried about NFRs and FRs in their clinic or other practices in their geographic regions and were asked to estimate annual allergen injections administered based on billing codes during the preceding 1 and 3 years. These data allowed direct estimation of FR and NFR rates relative to the number of injections administered. Despite the fact that the initial two AAAAI surveys used a different data source to estimate injection numbers, actual estimated fatal injection

reaction rates in all AAAAI surveys seem to remain consistent over time (approximately 1 case in 2,000,000) [25–27].

NFRs were evaluated in the most recent AAAAI survey spanning 1990 through 2001. NFRs were defined as anaphylactic events involving signs of cardiovascular collapse or severe bronchospasm necessitating epinephrine administration [28], equivalent to grade IV anaphylactic events [29]. The injection reaction rate was estimated at 1.0 event per 1 million injections on the basis of confirmed NFRs (68 cases) [28], and this rate was approximately 2.5 times greater than that for confirmed FRs. Based on all 273 confirmed and unconfirmed events reported by 646 respondents in the brief survey, however, 5.4 near-fatal events were estimated per every 1 million injections. The average incidence of confirmed NFRs was 4.7 events per year and 23 cases per year for all reported NFRs (confirmed and unconfirmed). In a separate prospective survey conducted in North America, 20 grade IV anaphylactic events manifested by hypotension and respiratory symptoms occurred in every 1 million aqueous IT injections administered in a large allergy clinic population [30]. In an Italian survey of AR and asthmatic patients on standardized HDM, tree and grass pollen IT with alum-absorbed extracts, a grade IV anaphylactic reaction rate of 82 per 1 million injections was documented [31]. Thus, in this study, use of alum-absorbed extracts did not seem to diminish the risk of severe IT-related anaphylaxis.

Clinical manifestations

Severe anaphylaxis is characterized by bronchospasm, respiratory failure, or hemodynamic compromise manifested by profound hypotension and cardiovascular shock. In the most recent AAAAI surveys of fatal (2004) and near-fatal IT reactions (2006), hypotension was reported by 81% and 88% of respondents, respectively [27,28]. In the initial AAAAI survey (Lockey and colleagues [25]) shock, syncope, or cardiac dysrhythmia was reported in 69% of 17 reported fatal events.

In a recent AAAAI study, Amin and colleagues [28] evaluated data comparing clinical manifestations of near-fatal and fatal anaphylactic reactions in detail (Fig. 1). Cutaneous manifestations, including urticaria, angioedema, and pruritus, were reported at much greater frequency with NFRs (70%) versus FRs (29%). The absence of cutaneous signs in most fatal reactors was noteworthy and would suggest that the absence of cutaneous signs may have delayed prompt recognition and treatment of fatal anaphylaxis in some cases.

Although upper airway obstruction and bronchospasm were reported with similar frequencies in fatal and near-fatal reactors, acute respiratory failure was identified in 94% of FRs compared with 10% of NFRs. All fatal and near-fatal reactors who developed respiratory failure and required intubation had been previously diagnosed with asthma. It was noteworthy that

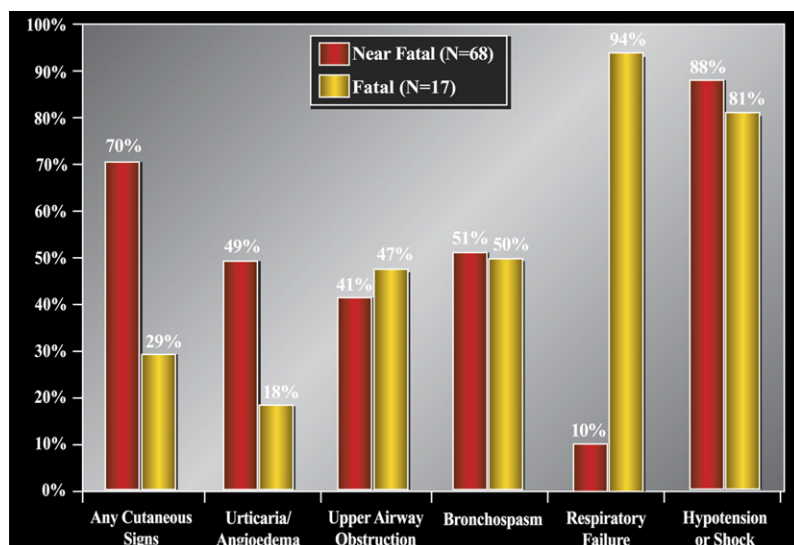


Fig. 1. Clinical manifestations reported by treating physicians during FRs and NFRs to IT injections. (From Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. *J Allergy Clin Immunol* 2006;117:172; with permission.)

four (57%) of seven patients with NFRs requiring intubation had pretreatment forced expiratory volume in 1 second (FEV₁) values of less than 70% predicted [28].

Factors associated with severe anaphylaxis

Patient characteristics

Fatal anaphylaxis attributable to various causes has been consistently reported to occur with greater frequency among patients with severe or poorly controlled asthma [25,26,32]. As already mentioned, patients with severe or uncontrolled asthma are at greater risk for FRs after IT injections [27]. In the aforementioned recent AAAAI survey, asthma was present in 15 (88%) of 17 fatal reactors compared with 46% in near-fatal reactors [27]. As shown in Fig. 2, asthma was not optimally controlled before death in most asthmatic patients who went on to have fatal IT reactions but was poorly controlled in only 10% of asthmatics experiencing NFRs [28]. Fatal reactors were more likely to have labile asthma and prior emergency department visits (54% versus 9%, odds ratio [OR] = 12.1, 95% confidence interval [CI]: 2.6–61.1) and hospitalizations for asthma (61.5% versus 4%, OR = 34.7, 95% CI: 5.7–251) relative to near-fatal reactors who survived severe anaphylaxis (see Fig. 2) [28].

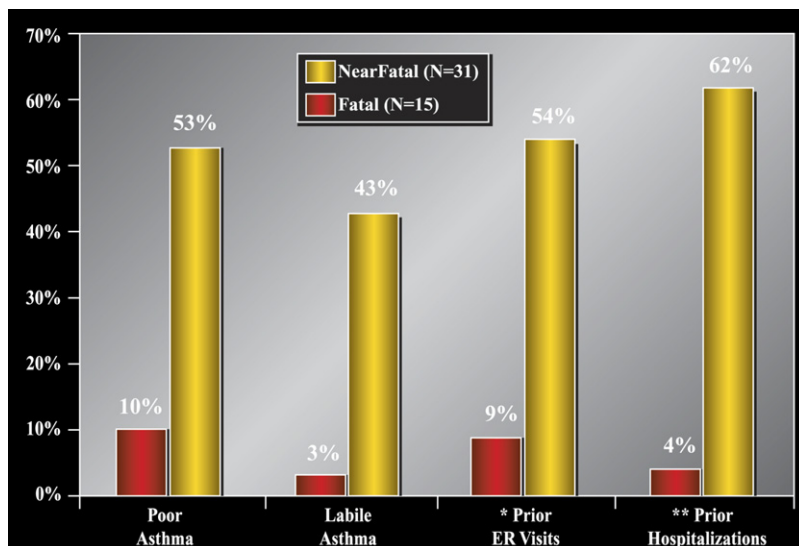


Fig. 2. Comparison of prior indicators of asthma severity in fatal and near-fatal reactors reported by treating physicians. (From Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. *J Allergy Clin Immunol* 2006;117:173; with permission.)

The association of IT fatalities with poorly controlled asthma is consistent with the findings of the 1986 British CSM report [18]. In a 1990 prospective study of rush IT with a standardized *D pteronyssinus* extract, more than 60% of patients with FEV₁ values of less than 70% experienced bronchospasm after IT injections, suggesting that patients with severe airway obstruction are at much greater risk [24]. Bernstein and colleagues [27] reported that FEV₁ values less than 70% predicted were reported in 50% of asthmatics who had FRs in whom spirometry data were available.

Practice guidelines have stated that concomitant medical conditions other than asthma and medications could compromise the ability of patients to tolerate IT-induced anaphylaxis and that these should be considered as relative contraindications for administration of IT [4]. Although 5 of 17 patients with FRs reported by Lockey and colleagues had underlying cardiovascular disease, subsequent surveys have not confirmed this association [25–27]. There is little evidence to suggest that use of beta-blockers increases the incidence of systemic reactions to IT [33,34]. Nevertheless, experimental evidence has been published showing that beta-blockers may enhance hypotensive responses during anaphylaxis and may reduce beneficial adrenergic responses to emergency epinephrine [10,35]. Lockey and colleagues [25] identified that 2 of 17 fatal reactors (1973–1984) were receiving beta-blockers (propranolol and timolol), as was 1 of 17 fatal reactors in the subsequent survey of Reid and colleagues [26]. In the AAAAI near-fatal survey

(1990–2001), Amin and colleagues [28] reported only 1 patient on low-dose atenolol (25 mg qd), who had an excellent response to epinephrine during an NFR and did not require glucagon. Concern has been raised about the theoretic risk of concomitant use of angiotensin-converting enzyme (ACE) inhibitors [36] in patients receiving IT. Eight cases of IT-related anaphylaxis have been reported in patients receiving ACE inhibitors, but the relative risk has not been determined [27,28,36,37].

Previous local and systemic reactions

Based on data from the previous surveys as well as the aforementioned AAAAI surveys, large local reactions were not found to predict the subsequent occurrence of severe systemic reactions reliably [27,28,38,39]. Bernstein and colleagues [27] reported that 28.6% (4 of 14) of patients with FRs reported prior injection-related systemic reactions, and Reid and colleagues [26] noted that 36% of IT fatal reactors had experienced prior systemic reactions. Prior systemic reactions were identified in only 9% of those with NFRs [28]. Thus, these data suggest that patients with FRs are likely to have experienced IT-related systemic reactions previously.

The tendency for the numbers of observed systemic IT reactions to increase during peak allergen seasons was noted in 1957 by Van Arsdel and Sherman [16]. In AAAAI surveys, 29% to 56% of physicians reported that FRs and NFRs occurred during their patients' peak allergy seasons [28]. Unfortunately, uncontrolled surveys do not allow estimation of the relative risk of severe anaphylaxis during peak allergen exposure periods.

Other possible contributing factors

The clinic setting in which IT is administered may contribute to fatal anaphylaxis. In the first two AAAAI surveys, 47% to 48% of FRs occurred outside of the prescribing allergist's office [25,26], and 41% in the most recent survey did so. Bernstein and colleagues [27] noted that 3 (18%) of 17 FRs occurred outside of a medical clinic or at home, whereas 63 (93%) of 68 NFRs occurred in the prescribing allergist's facility and the remainder occurred in supervised clinic settings [28]. Delay in onset of injection-related anaphylaxis could delay prompt initiation of life-saving treatment with epinephrine. In the most recent AAAAI survey (1990–2001), 3 of 17 FRs began more than 30 to 45 minutes after allergen injections [27]. In previous separate surveys, 8% to 13% of FRs to IT began 30 minutes or more after injections. Due to similar infrequent delayed reactions observed in the United Kingdom, a 60-minute postinjection observation period was been established [40].

In the last AAAAI survey of FRs and NFRs, the mean number of injections administered by allergy clinics reporting NFRs was 51% greater than that of clinics reporting no life-threatening IT reactions ($P < .02$). The

reduced likelihood of severe reactions in clinics administering fewer IT injections could be related to more careful selection and exclusion of high-risk patients (eg, poorly controlled asthmatics).

Serious allergic reactions to IT injections have been linked to errors in dosing and administration [41]. In the aforementioned NFR survey, dosing errors were implicated in contributing to 25% of anaphylactic reactions [28]. In a prospective French study, errors related to allergen extract vials or doses accounted for 10% of all systemic reactions [42]. Lockey and colleagues [25] reported three “errors” of administration in 14 patients with FRs. Reid and colleagues [26] reported one FR associated with a dosing error and another FR after intramuscular IT administration. Thus, dosing and administrative errors seem to contribute significantly to injection-related anaphylactic events.

In an earlier survey, life-threatening anaphylactic reactions were considered to occur more frequently during the build-up phase of IT [26]. According to the most recent AAAAI surveys, however, most FRs and NFRs occurred after injections from maintenance allergen extract vials [27,28]. In a recent prospective multicenter Danish study of 1038 patients receiving alum-absorbed pollen and indoor allergen extracts, timothy allergen was implicated in all eight severe grade 4 injection-related anaphylactic reactions [43]. This suggests that pollen extracts are more likely to cause severe anaphylactic reactions.

Management of severe reactions

It is recognized that FRs are unpredictable and can occur in patients without any of the aforementioned underlying risk profiles [44]. Therefore, prompt recognition and administration of parenteral epinephrine are critical to successful management of severe anaphylaxis [32,45]. In the most recent AAAAI survey of 17 patients with FRs, Bernstein and colleagues [27] reported that administration of epinephrine was delayed (≥ 10 minutes) or not administered in 31% of cases. In those patients with NFRs, 82% of NFRs were treated within 3 minutes of onset of reactions and 94% of patients received epinephrine within the first 20 minutes [28]. In earlier surveys, epinephrine had been knowingly administered to only 18 (75%) of 24 and 12 (70%) of 17 patients with fatal IT reactions [25,40]. Similarly, fatal outcomes related to severe food-induced anaphylaxis have been associated with significant delays in administration of epinephrine [32]. It is likely that epinephrine was administered by means of the subcutaneous route in early surveys. Interestingly, in the most recent AAAAI survey of NFRs, 31% of patients who experienced NFRs received epinephrine by means of the preferred and recommended intramuscular route, which achieves higher plasma epinephrine levels more rapidly compared with the subcutaneous route [45]. The initial epinephrine dose was adequate (≥ 0.3 mg) in 88% of NFRs. Antihistamines and systemic corticosteroids were administered

along with epinephrine in 63% of NFRs but were not administered to 37% of patients, suggesting that these interventions were much less critical than epinephrine. Optimal epinephrine treatment for NFRs was likely assured by administration of IT injections in medically supervised clinic settings in 93% of cases [28].

In the most recent AAAAI survey of FRs and NFRs, intubation was required for respiratory failure in 88% of FRs compared with only 9% of NFRs [28]. Among the recently reported cases of severe anaphylaxis after IT with fatal outcomes, intubation was attempted in 15 patients. In 6 (40%) patients, the establishment of an airway was delayed or unsuccessful. This experience suggests that clinics administering IT must have procedures in place that enable timely establishment of a functioning airway during life-threatening anaphylaxis. Because many practicing allergists are inexperienced in performing emergency endotracheal intubation, alternative approaches, such as laryngeal mask airways (LMAs) or cricothyroidotomy, may be required to maintain oxygenation.

Preventative measures to reduce immunotherapy-induced life-threatening anaphylaxis

Recommendations have been proposed in the Joint Council of Allergy, Asthma, and Immunology practice parameters (PPs) (2003) aimed at preventing severe IT-related anaphylactic reactions and to ensure optimal management of such reactions [4]. These and other PP recommendations to reduce the risk of systemic anaphylactic reactions to IT injections are listed in **Box 1**. It should be emphasized that these recommendations are largely based on expert opinion and that scientific evidence is often lacking. The most recent PPs state that “Medical conditions that reduce the patient’s ability to survive a systemic reaction are relative contraindications for allergen immunotherapy” [4]. Examples include severe asthma uncontrolled by pharmacotherapy and significant cardiovascular disease (summary statement 15). This document also acknowledges that there is reasonable evidence (category C) to indicate that patients with severe poorly controlled asthma are at greater risk for systemic reactions to allergen IT injections (summary statement 18). In patients with previous systemic reaction(s) to an injection, the PPs state that “the dose of vaccine should be appropriately reduced” (summary statement 38). Patients who previously experienced a systemic reaction that begin more than 30 minutes after an injection may need to be observed for longer than 30 minutes in the physician’s office and trained on the use of self-injectable epinephrine.

According to the practice parameter on IT, allergen IT should be administered “in a setting where procedures that can reduce the risk of anaphylaxis are in place and where the prompt recognition and treatment of anaphylaxis is assured.” The PPs recommend that the office of the physician

Box 1. Actions to reduce the risk of anaphylaxis

1. Assess a patient's general medical condition at the time of injection (eg, asthma exacerbation).
2. Adjust vaccine dose or injection frequency if symptoms of anaphylaxis occur and IT is continued.
3. Use appropriately diluted initial vaccines in patients who seem to have increased sensitivity on the basis of history or tests for specific IgE antibodies.
4. Instruct patients to wait in the physician's office for 20 to 30 minutes after an IT injection. Patients at greater risk of reaction from allergen IT (eg, patients with increased allergen sensitivity or those who have previously had a systemic reaction) may need to wait longer.
5. Carefully evaluate any patient with a late reaction (ie, local or systemic reaction more than 30 minutes after the IT injection).
6. Institute procedures to avoid clerical or nursing errors (eg, careful checking of patient identification).
7. Recognize that dosage adjustments are usually necessary with a newly prepared vaccine or a patient who has had a significant interruption in the IT schedule.
8. Ensure that adequate equipment and medications are immediately available to treat anaphylaxis, including (1) a stethoscope, (2) a sphygmomanometer, (3) tourniquets, (4) syringes, (5) hypodermic needles, (6) large-bore (14-gauge) needles, (7) epinephrine at a ratio of 1:1000, (8) oxygen, (9) equipment for administering intravenous fluids, (10) equipment for establishing an airway, (11) antihistamine for injection, (12) corticosteroid for intravenous injection, and (13) vasopressor.

Adapted from Joint Council on Allergy, Asthma, and Immunology. Allergen immunotherapy: a practice parameter. Ann Allergy Asthma Immunol 2003;90: 1–40; with permission.

who prepared the patient's vaccine be the preferred location for the administration of allergen IT (summary statements 48–50), especially in patients considered to be at high risk of systemic reactions, and that injections be administered under the supervision of appropriately trained physicians and personnel. The PPs further recommend that injections “not be administered at home because of the risk of inadequate recognition and treatment of systemic reactions.” A 20- to 30-minute observation period in the physician's office is recommended based on evidence that most severe anaphylactic reactions begin 20 to 30 minutes after injections.

The authors of the most recent AAAAI survey have suggested similar and additional specific measures for preventing IT-related anaphylaxis based on their review of FRs and NFRs (Table 1) [27,28]. Because asthma represents the highest risk determinant, withholding IT injections is suggested in patients with moderate or severe airway obstruction and in those whose asthma is not optimally controlled. Patients should be assessed for worsening asthma by evaluating symptoms and lung function (peak expiratory flow rate [PEFR]) before each injection. Because there is limited benefit and greater risk in asthmatic patients with FEV₁ values less than 70%, risk and benefit must be considered carefully in individual patients before initiation of IT. Because suboptimal epinephrine dosing was a common feature in fatal IT reactions, physicians supervising IT administration must adhere to published anaphylaxis guidelines that recommend adequate and timely dosing with intramuscular epinephrine (see Table 1). As already mentioned, because of difficulties in establishing airways in fatal reactors, clinical staff in a clinic administering IT must be prepared to establish and maintain an

Table 1

Selected findings of immunotherapy surveys with authors' suggested recommendations for reducing anaphylaxis caused by injection immunotherapy

Study findings	Suggested recommendations
Asthma symptoms not optimally controlled and pretreatment FEV ₁ <70% predicted	Consider risk versus benefit before initiating IT Withhold IT if asthma is not well controlled Assess asthma and PEFR before injections
FRs at home or in unsupervised clinics	Administer IT in fully equipped clinic by trained personnel and never at home
Inadequate epinephrine dosing	Administer epinephrine at a ratio of 1:1000 IM at a dose of 0.3–0.5 mg; repeat if needed If no response to IM dosing, give 1:10,000 epinephrine IV infusion
Difficulty in establishing an airway	Clinical staff must be prepared to establish and maintain an airway when necessary
Prior systemic reactions	Reduce subsequent immunotherapy doses Dispense self-injectable emergency epinephrine to all patients who continue IT Consider discontinuation in high-risk patients
Patients depart prematurely from clinic after injections	All patients should be required to wait 30 minutes in a medically supervised setting after IT injections
Dosing errors were implicated in 25% of NFRs	Prevent dosing errors by educating clinic staff Give injections from patient-specific vials Use standardized forms and protocols Routinely check patient identity (eg, name, birth date) before each injection Same staff person that prepares IT injection should administer Allow only one patient at a time in the injection room

Abbreviations: FEV₁, forced expiratory volume in 1 second; FR, fatal reaction; IM, intramuscular; IT, immunotherapy; IV, intravenous; NFR, nonfatal reaction.

Adapted from Refs. [27,28,41].

airway when necessary (eg, cricothyroidotomy). Finally, because of the recently recognized high prevalence of dosing (errors) associated with systemic reactions, several preventative measures are advocated, including education of clinic staff, administration of injections from patient-specific vials, routine checks of patient identifiers (eg, birth date) before each injection, administration by the same staff person who prepares the injection, and allowing only one patient at a time in the injection room [41].

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