

29 Adverse Effects and Fatalities Associated with Subcutaneous Allergen Immunotherapy

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INTRODUCTION

Most local and systemic reactions, which develop during subcutaneous allergen immunotherapy (SCIT), occur within 20 to 30 minutes of injection but can occur later than 30 minutes. Subcutaneous nodules at the site of injection are more common with aluminum-adsorbed vaccines, may persist but usually disappear, and do not necessitate an adjustment in the immunotherapy (IT) dose. Patients who develop nodules that persist should be injected with aqueous preparations.

Van Arsdel's and Sherman's (1) comprehensive review in 1957 analyzed retrospectively the incidence of constitutional reactions in a population of 8706 patients who had received a total of 1,250,000 allergen injections during the 20 years between 1935 and 1955. Their patients experienced a total of 1774 constitutional reactions, about 1 in 700 of the 1,250,000 injections given. The reactions occurred in 663 patients, an incidence of 1.9% versus the 3.5% reported in 1916 by Cooke and Vanderveer (2). Of the 663 reacting patients, 635 were pollen sensitive, representing about 15% of the 4215 pollen-sensitive patients, contrasted with a 0.6% incidence in the remaining 4491 patients. Most of the studies on adverse reactions to allergen IT have been concerned with reactions resulting from the injection itself.

Reports of adverse effects from prick-puncture skin tests prompted an analysis of data derived from the Second National Health and Nutrition Examination Survey (NHANES II) (3). This study revealed that the risk of prick-puncture allergy skin testing was low when carried out with eight extracts licensed by the U.S. Food and Drug Administration (FDA) on a randomly selected population.

The incidence of adverse reactions during IT reported in retrospective and prospective studies has varied considerably, depending on several factors, including the type of allergen vaccine preparation, the patients selected, route of administration, and treatment schedule used, with or without pretreatment and/or preventive procedures (4-12). All of these studies carried out between 1980 and 1989 established the safety of IT when performed on selected patients by experienced physicians who exercised caution and provided adequate monitoring and appropriate treatment, when anaphylaxis does occur. The nonfatal adverse reaction rate ran from less than 1% of patients on IT to 36.2% on rush IT, without pretherapy.

These data have been obtained in studies using the subcutaneous route of injection of allergen vaccines obtained by aqueous extraction of allergens. An "Immunotherapy Coalition" consisting of the American Academy of Allergy Asthma and Immunology (AAAAI), the American College of Allergy Asthma and Immunology (ACAAI), and allergy extract manufacturers supported the benefits of IT and pretreatment to reduce adverse effects associated with the therapy (13-24).

Other allergen molecules and techniques of IT have also been explored to decrease the potential for adverse reactions and to increase efficacy (25-33). These have included oral administration (34,35), nasal administration (36,37), and sublingual-swallow immunotherapy (SLIT) (38-42). A review of the available literature by the World Health Organization (WHO) in 1998 concluded that oral IT was ineffective, whereas SLIT is a viable alternative to the subcutaneous injection route (see chap. 30). These conclusions were also made in a position paper of the European Academy of Allergy and Clinical Immunology. This is reviewed in the paper by Passalacqua et al. (42). Cox et al. have reviewed the literature regarding SLIT from the AAAAI and ACAAI Task Force and report evidence of clinical efficacy and a favorable safety profile (43). SLIT is also well tolerated in children as young as two years (44).

However, in the United States, such therapy is not routinely used because it has not been approved by the U.S. FDA, and the effective dose, treatment schedules, and overall duration of treatment are not yet determined (43).

The traditionally protein-based IT has a limited scope of efficacy. A number of reagents, however, termed "DNA-based immunotherapeutics," have been effective in prevention and reversal of TH-2-mediated hypersensitivity states in mouse models of allergic disease (45,46). The four basic DNA-based IT modalities used include immunization with gene vaccines, allergen mixed with immunostimulating oligodeoxynucleotides (ISS-ODN), and physical allergen-ISS-ODN conjugates as well as immunomodulation with ISS-ODN alone. As the Horner et al. review concludes, "If these reagents prove as effective in humans, as they have proven to be in rodents and nonhuman primates, then DNA-based immunotherapeutics are likely to revolutionize the standard of care for the treatment of allergic disease." Creticos et al. randomized, double-blind, placebo-controlled phase 2 trial of a vaccine consisting of ragweed-pollen antigen, conjugated to a phosphorothioate oligodeoxyribonucleotide immunostimulatory sequence of DNA (AIC), resulted in long-term clinical efficacy in the treatment of ragweed allergic rhinitis. In this study, 25 adults allergic to ragweed received six weekly injections of the AIC or placebo vaccine. The AIC group had significantly better rhinitis scores on the visual-analog scale and nasal symptom diary scores than the placebo group during the first and second ragweed seasons (47). However, for the time being, SCIT remains the standard of care throughout the United States and most other parts of the world.

FREQUENCY OF IgE SYSTEMIC REACTIONS

The risk of death after the injection of a foreign substance has been known since Lamson's report in 1929 (48). No other cited studies had reported fatalities; however in 1942, Vance and Strassman (49) reported seven cases of sudden death following injection of foreign protein, and James and Austin (50) published an analysis of six instances of fatal anaphylaxis in humans, following parenteral administration of antigen (penicillin, guinea pig hemoglobin, bee venom, and ragweed vaccine), citing several single case reports by Sheppe (51) and Blanton and Sutphin (52), as well as the seven cases of Vance and Strassman by Rosenthal (53), following penicillin injection.

Rands, a general practitioner in the United Kingdom, published a report of a single fatality of a 19-year-old female due to nonresponsive bronchoconstriction developing within five minutes following the injection of her usual maintenance dose of Pollinex (a commercial pollen vaccine manufactured in Toronto, Canada) given five weeks after the same dose had been administered without effect (54). This was followed by a report of 26 fatalities due to IT and the recommendations of the Committee on Safety of Medicine in the United Kingdom (55), which established preconditions for IT, which resulted in the virtual temporary abandonment of SCIT in the United Kingdom.

A major objective of this chapter is to compare the retrospective reviews of fatalities occurring during skin testing and IT made by the Committee on Allergen Standardization of the AAAAI and by the Paul Ehrlich Institute, the German Federal Agency for Sera and Vaccines (56). These studies analyzed the factors contributing to fatalities occurring during skin tests or IT, with a view to diminishing and, hopefully, eliminating them.

NON-IgE-MEDIATED ADVERSE REACTIONS

It is appropriate to review reports of some aspects of adverse reactions to IT that are controversial. The possible role of precipitins, as responsible for adverse reactions, was addressed by Busse et al. in a study correlating *alternaria* IgG precipitins and adverse reactions (57). Their prospective study revealed that 5 of 23 *alternaria*-sensitive persons had IgG precipitins before IT and another six developed precipitins during therapy. Only 1 of the 23 experienced a reaction to *alternaria* four to six hours after an injection of *alternaria* vaccine. They conclude that precipitins to *alternaria* are common and do not seem to be the basis for late reactions and their presence is not a contraindication to IT. A contrasting report by Kaad and Ostergaard suggests that IT of asthmatic children with mold vaccines might be hazardous

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by provoking immune complex reactions (58). Of 38 children with bronchial asthma who were immunized with mold vaccines, seven (19%) were withdrawn from SCIT because of "serious" side effects that were considered clinically consistent with an immune complex reaction. These seven children exhibited a two- to fourfold increase in circulating precipitating antibodies to the injected vaccines. Of the remaining 31 patients also treated with mold vaccines, 14, who were without side effects, did not develop precipitating antibodies. The sera of these patients were not examined for immune complexes, and the authors quote the contradictory findings of the Kemler and Stein (59,60) groups as well as apparently supportive reports by Cano et al., EI-Hefny et al., Kuukiala et al., Moore and Fink, and Stendardi et al. (61-65).

Relevant to these studies is the report by Clausen and Yanari that immune complex-mediated disease is not a factor in patients on maintenance venom IT (66). They evaluated the problem in 30 adults and 15 pediatric patients receiving regular monthly doses of venom (100 µg of antigen), all for between 9 and 12 months. A serum sickness-like presentation had been reported as a sequela of Hymenoptera stings, but the possible role of immune complexes had not been addressed.

No patients developed clinical manifestations suggestive of immune complex pathology; all urinalyses were negative for gross and microscopic hematuria, no sera showed an elevation of Clq, and only 4 of the 45 patients had significantly elevated Raji cell assays. Prospective reevaluation showed the presence of immune complexes before venom administration with no change in acute phase reactants or Raji cell titers 12 hours later. The authors conclude that monthly administration of Hymenoptera venom does not appear to be associated with immune complex disease by either clinical or immunological parameters. A further relevant article was contributed by Umetsu et al. who described an 8-year-old male child with rhinitis and asthma, who developed serum sickness triggered by anaphylaxis-complicating SCIT with multiple inhalant allergens (ragweed, grass, and tree pollens; mold spores; and dust) (67). This child developed puffy eyelids one hour following a half dose of his vaccine and progressed thereafter to an impressive serum sickness syndrome characterized by severe generalized raised annular urticaria, severe asthma, angioedema, severe arthralgias, fever, and episodes of confusion and disorientation. The authors hypothesized that the enhanced vascular permeability that accompanied the anaphylaxis allowed immune complexes that may have persisted in the circulation, to deposit in the blood vessels of the patient. The immune complexes may or may not have been related to the IT itself; tests for these complexes, however, were negative. Clemmensen and Knudsen reported a patient with eczema who apparently developed contact sensitivity to aluminum while receiving IT for hay fever with an aluminum-precipitated allergen (68). Standard patch testing was positive to the aluminum discs used for testing and negative in 53 controls; the eczema disappeared when therapy was discontinued.

An association between brachial plexus neuropathy and allergen IT was reported by Wolpow (69). Two patients were described who developed acute, self-limiting, unilateral brachial plexus neuropathy in association with subcutaneous injections of dust and molds. Previous reports of this neurological illness had "in many cases followed injection of foreign substances, but usually of animal rather than vegetable origin."

Schatz et al. call attention to what they termed "nonorganic adverse reactions" to allergen IT (70). They described 10 patients who presented adverse reactions to SCIT, which mimicked immunologically mediated reactions but were believed to be nonorganic in etiology—with a high incidence of coexisting or contributory psychiatric problems.

LONG-TERM SEQUELAE

The possibility that chronic injection of foreign proteins might induce long-term sequelae has been addressed by both experimental animal studies and anecdotal reports in humans. Rabbits hyperimmunized with various vaccines make cryoprecipitating proteins, monoclonal antibody, rheumatoid factor, and anti-DNA antibodies (71-73), and such hyperimmunized animals may develop amyloidosis and myeloma (74,75). There have been anecdotal reports of multiple myeloma and Waldenström's macroglobulinemia in patients on long-term SCIT (76) and a report of a striking incidence of positive rheumatoid factors in atopic children on such therapy (77).

Levinson et al. undertook to determine if long-term allergen IT caused late sequelae, particularly those reflecting abnormal immunological responses (78). Their study, the first systematic investigation of potential adverse effects of long-term IT, examined 41 patients between 18 and 50 years who had received regular IT with three or more allergen vaccines for five or more years at the Walter Reed Army Medical Center Allergy Clinic. Twenty-one age- and gender-matched atopic individuals served as controls prior to initiating such therapy. The treated individuals showed no increased autoimmune, collagen, vascular, or lymphoproliferative disease. Furthermore, long-term allergen IT had no adverse effects on immunological reactivity as assessed by a number of immunological parameters—with a particularly noteworthy absence of immune complexes in the serum of patients undergoing long-term IT. It is true for at least this study of 41 patients, mostly Caucasian females, of an average age of 30, treated for allergic rhinitis and asthma for five or more years in the U.S. Army Allergy Clinic.

Phanuphak and Kohler (79) described in 6 of 20 consecutive patients the onset of polyarteritis nodosa, of vasculitic symptoms that coincided with SCIT for presumptive atopic (IgE-mediated) respiratory disease. Compared with 14 other patients with polyarteritis nodosa, the six on IT had significantly greater skin involvement and peripheral blood eosinophils. There was evidence for circulatory complexes with decreased hemolytic complement, increased cryoglobulins, or increased Clq binding in both groups but no allergen-precipitating antibodies.

A possible association between pemphigus vulgaris and allergen injections with cat pelt vaccine was raised by McCombs et al. (80). Although intriguing, it seems irrelevant since such therapy today is performed with purified cat allergens.

The conflicting results of studies in patients receiving long-term IT might be explained by a nonuniformity of detection methods used. This prompted a group of Australian investigators to examine a population of older patients with documented prolonged IT extending over many years. They examined 35 older patients (mean age 62, range 53–85 years) who received injections of allergen vaccines for between 2 and 30 years (mean of 13 years) and compared them with an age-matched control group (mean age 64.7, range 42–87 years). Treated patients had significantly higher IgG and lower total IgE than controls, but no increased incidence of paraproteins or evidence of immune complex disease such as urinary abnormalities, increased Clq binding levels, cryoglobulins, or rheumatoid (sic) fever (81).

FATALITIES

Fatalities, carefully documented, constitute a less controversial measure of adverse effects related to either skin testing or allergen IT. Since Lamson's first description of death from anaphylaxis associated with SCIT (48), six fatalities have been reported related to or associated with SCIT (49,50,54,82–84). More than 70 deaths (between 1895 and 1964) have been reported after skin testing, the majority of these associated with antigens such as horse serum-derived tetanus or diphtheria antitoxins and pneumococcus antiserum, none of which are currently in use. Nine of these 70 deaths from skin testing were associated with allergens similar to allergens used today. No articles on fatalities associated with IT or skin testing have been published in the United States between 1980 and 1987.

A project defining risk factors for fatalities from skin testing and IT was instituted as a retrospective study by the Committee on Allergen Standardization of the AAAAI in 1983. For this project, Lockey and his coworkers composed a 64-item questionnaire designed to obtain data on fatalities from skin testing and IT. The questionnaire was mailed to the then 3400 members and fellows of the AAAAI and its analysis was published in *The Journal of Allergy and Clinical Immunology* in April, 1987 (85). Although 46 fatalities had been reported from 1945 to 1984, only 30 (6 fatalities from skin testing and 24 from IT) had sufficient data for analysis. Tables 1 and 2 summarize the data on fatalities associated with skin testing and IT, respectively.

Although all ages were affected (range 7–70), the mean ages of the fatalities following skin testing or IT were 30 and 34 years, respectively. There was no gender predilection. Errors of administration appeared to be responsible for three fatalities and questionable for an additional three. Ten patients had died after skin tests or IT during a seasonal exacerbation of the patients' allergic disease, four in patients who had been symptomatic at the time of

Table 1 Case Reports from the Literature, *Fatalities from Skin Test*

Author/year	Age/medical disease	Injected vaccine	Onset of symptoms	Initial symptoms	Cause of death
Baagoe, 1928 (86)	Unknown	Egg white, 0.1 cc	Sudden	Dyspnea	Unknown
Lamson, 1924 (48)	5 mo, eczema	Ovomucoid, 0.05 cc	2 min	Cyanosis	Respiratory arrest
Lamson, 1929 (48)	34 yr, asthma	Buckwheat 1:500, ID	2-3 min	Lacrimation Cyanosis Respiratory difficulty	Anaphylactic shock
Vance and Strassman, 1942 (49)	4 yr	Silkworm, sheep's wool, kapok extracts, IC	5 min	Shock/unconscious	Anaphylactic shock ^a
Wiseman and McCarthy-Brough, 1945 (87)	78 yr, asthma	17 environmental allergens, 0.01 cc, IC	5 min	Cough Asthma	Anaphylactic arrest
Swineford, 1946 (88)	49 yr, asthma	56 food extracts, 8-9 inhalant extracts, IC	3 min	"Not feeling well" Dyspnea	Cardiovascular collapse
Blanton and Sutphin, 1949 (89)	57 yr, asthma	56 skin tests, scratch, and IC	Sudden	Air hunger	Anaphylactic shock ^a
Harris and Shure, 1950 (90)	25 yr, asthma	Environmental substances, ID	1 min	Dyspnea	Respiratory arrest ^a
Dogliotti, 1968 (91)	35 yr	Penicillin scratch	4-5 min	Flush Abdominal pain	Anaphylactic shock
Lockey et al., 1987 (85)	6 subjects, 10-50 yr	Variable	3-20 min	Variable	Asthma, anaphylactic shock Others
Reid et al., 1996 (92)	1 subject	Unknown	Unknown	Unknown	Unknown
Bernstein et al., 2004 (93)	1 young subject, asthma, food allergy	90 food scratch tests	Unknown	Bronchospasm	Respiratory arrest

^aAutopsy confirmed anaphylactic shock.

Source: Adapted from Ref. 85.

injection, two of whom had been receiving β -adrenergic blockers. Of the 24 fatalities associated with IT, 4 had experienced previous reactions, 11 had a high degree of sensitivity, and 4 had been injected with newly prepared vaccines. Fifteen of the total of thirty fatalities had received a pollen vaccine as part of the fatal injection. Five of the six fatalities associated with skin testing had occurred without prior prick-puncture testing. Signs and symptoms of systemic reactions were not reliable predictors of death. The onset of systemic reactions was 30 minutes or less after injection in 23 of 30 patients, more than 30 minutes after injection in two, and had not been reported on five. The cause of death in 14 of 16 patients with asthma was respiratory. Epinephrine had been administered to 18 patients, not given to 3, and was either not recorded or unknown in 9 patients.

A later supplemental survey conducted by Reid et al. on deaths in the United States from SCIT between 1985 and 1989 was reported at the 1990 AAAAI meeting in Baltimore, Maryland (95). There were no deaths from skin testing reported; however, 16 deaths were reported from IT. These deaths were reported in the *Journal of Allergy and Clinical Immunology* and included one additional death for a total of 17 (96). The mean age was 36 years (range 10-77), and there were 5 males and 11 females (gender of one subject not reported) versus 11 males and 13 females in the earlier study. Eighty-seven percent of the subjects had asthma, 1 was on β -blocker therapy, and 10 of 17 were "highly sensitive" by skin testing or the radio-allergosorbent test (RAST). Fourteen of seventeen were on aqueous vaccines, 10 of 17 on increasing doses, and 9 of 17 received epinephrine. The results obtained in this study are very similar to those reported previously.

Reid and Gurka presented an abstract at the 1996 Academy of Allergy, Asthma and Immunology meeting about the continuation of the above-mentioned study that covered

Table 2 Case Reports from the Literature, Fatalities from Immunotherapy

Author	Gender	Age (yr)	Medical disease	Allergen	Status of IT	Onset of symptoms	Symptoms	Cause of death
Lamson, 1929 (48)	M	34	Asthma	Bermuda grass pollen, 0.05 cc, 1:100	(because of "nervousness" with preceding reaction)	<3 min	Flushing, athetoid movements Dyspnea	Anaphylactic shock ^a
Waldbott, 1932 (94)	F	40		Ragweed vaccine, 1400 units	Unk	<3 min	Dyspnea	Anaphylactic shock
Vaughn and Black 1939 (83)	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
Vance and Strassman, 1942 (49)	M	35	Asthma	Ragweed vaccine	Unk	1 hr	Unk	Anaphylactic shock ^a
James and Austen, 1964 (50)	M	56		Hay fever desensitization	Unk (11 of 21)	<45 min	Dyspnea	Anaphylactic shock ^a
Rands, 1980 (54)	F	19	Asthma	Pollinex, Migen ^b	Maintenance	3-10 min	Rushing syndrome, tachycardia	Anaphylactic shock ^a
Pollard, 1980 (84)	M	24	Asthma	Bencard Product ^c	Unk (15th injection)	25 min	Unk	Status asthmaticus
CSM Update, 1986 (55)	F, 13 M, 12 Unk, 1	11-57 x, 31	Asthma Hayfever Unk	Varied, mite	Normal course, 16 ^d Maintenance, 4 Unk, 6	<10 min, 14 <30 min, 4 <90 min, 2 Unk, 6	Asthma and anaphylaxis	Asthma and anaphylaxis
Lockey et al., 1987 (85)	F, 13 M, 11	7-70 x, 34	Unk ^e	Varied pollens Molds	Maintenance, 7 Increasing, 9 Decreasing, 1 1st injection, 1 NA, 6	<20 min, 15 20-30 min, 3 >30 min, 2 Unk, 4	Pruritus, 3 A, 0 UAO/LAO and/or asthma, 12 Shock, 4 Coma, 9 Hypotension, 6 Myocardial infarction, 1 NA or unk, 6	UAO/LAO and/or asthma, 13 Cardiovascular, 6 Anaphylactic shock, 13 Others, 4 NA or unk, 3

Reid et al., 1990 (95)	F, 11 M, 5 Unk, 1	10-77 x, 36	Asthma, 13 AR, 7 CV, 3 DM, 1 HtD, 1 Unk, 1	Aqueous, 14 Unk, 2	Maintenance, 3 Increasing, 9 Decreasing, 1 Unk, 3	<20 min, 8 20-30 min, 3 >30 min, 1 ^f Unk, 4	U and A, 1 LAO, 5 UAO and LAO, 4 UAO, 1 Shock, 4 Unk, 5 Unk Shock, 7 Unk, 21	Resp, 8 Shock, 0 Both, 4 Other, 1 Unk, 3 Unk
Reid et al., 1996 (92) Lüderitz-Puchel et al., 1996 (56)	Unk Unk, 40 28 analyzed	12-73 Unk	Asthma, 19 Aqueous, 6 Semidepot, 22	Unk Unk	Unk Unk	Unk Unk	Unk Shock, 7 Unk, 21	Unk
Bernstein et al., 2004 (93)	F, 6 M, 11	5-81 x, 39	Asthma, 15 AR, 2	Mix 14, mite 3	Maintenance 10 Increasing 7	< 30 min, 10 > 30 min, 3 Unk, 4	LAO 8 UAO 2, UAO and LAO 6 Shock 13 Pruritus 3 A 3	Upper airway edema, 5 Asthma, 6 Shock, 6

^aAutopsy confirmed.^bNot in article, listed only as Pollinex, pollen vaccine; Migen, house dust-mite vaccine.^cBencard Allergy Unit, Brentford, Middlesex, United Kingdom.^d? meaning of normal course.^eNot requested.^fNot witnessed.**Abbreviations:** AR, allergic rhinitis; CV, cardiovascular; DM, diabetes mellitus; HtD, heart disease; NA, not available; Unk, unknown. LAO, lower airway obstruction; UAO, upper airway obstruction; U, Urticaria; A, angioedema.*Source:* Adapted from Ref. 85.

events from January 1990 to June 1995 (92). They reported 28 deaths during this time, with an average of five deaths per year with incomplete data for 19 of the 28 reports. One of the 28 deaths was associated with intradermal skin testing and 27 with IT. Four of the IT deaths occurred following home injections or injections given with no physician present, 3 were associated with an incorrect dose, 19 occurred in individuals with atopic asthma, and 5 deaths occurred despite postreaction intervention. The age range at the time of death was 12 to 73 years and there was no gender predilection. Data in this study are similar to previous reports of fatalities.

The Committee on the Safety of Medicine of the United Kingdom reported in 1986 that 26 deaths from anaphylaxis due to allergen IT had occurred in the United Kingdom since 1957. All died from IT-induced bronchospasm and/or anaphylaxis, 11 of these since 1980 and 5 during the preceding 18 months. In most of the cases, adequate facilities for cardiorespiratory resuscitation were not available. Asthma was the indication for treatment in 16 of the 26, allergic rhinitis in 1, and the indicator was unknown in 9. In two patients, the ultimately fatal systemic reaction allegedly began more than 30 minutes after injection, resulting in a recommendation that patients remain in a medical facility for two hour after their injection (55). Currently, 26 centers throughout the United Kingdom are equipped to perform SCIT in specialist hospital settings. About 500 courses of SCIT are initiated annually, and the minimum waiting period is now 60 minutes (Durham SR, personal communication, 2007; Andersen P, personal communication, 2007).

In Sweden, introduction of potent mite, mold, and animal dander vaccines was accompanied by some anaphylactic deaths that prompted the regulatory agency to restrict the use of these vaccines to physicians and clinics specializing in this issue (97).

The Paul Ehrlich Institute in Germany reported 40 fatalities between 1977 and 1994, with complete data available for 20 reports in Germany and 8 reports elsewhere in Europe. For 23 of the 28 reports analyzed, it was not possible to rule out error on the part of the physician and/or inadequate information given to the patient as factors contributory to the fatal outcomes (56). Three cases with permanent hypoxic brain damage as a result of anaphylactic shock were also reported. Semidepot preparations, which are not used in the United States, were involved in most of the adverse and fatal reactions. Mite allergen vaccines were used in 18 of the cases reported.

There are 41 fatalities identified from SCIT in Bernstein et al. AAAAI physician member survey of fatal reactions and near-fatal reactions (NFRs) from 1990 to 2001 (92). The estimated fatality rate is 1 per 2.5 million injections, (average of 3.4 deaths/yr), similar to the results in the previous AAAAI physician member surveys (85,92,96). One skin test fatality was confirmed in a young woman, with allergic rhinitis, moderate persistent asthma, and food allergy, who had a fatal anaphylactic reaction after application of prick-puncture tests to 90 food antigens (93).

ANAPHYLAXIS ASSOCIATED WITH SKIN TESTING AND SCIT

The study by Van Arsdel and Sherman (1) supports the general safety of IT for the control of IgE-mediated allergic diseases in that over 1 million allergen vaccine injections given to 8700 patients from 1935 to 1955 had been administered without a fatality. Hepner et al. prospective study on IT, reported in 1987, that 25 out of 2989 patients, over a seven-month period, experienced systemic reactions and there were no fatalities (6). On the basis of annual studies from a panel of 2000 physicians in the United States, the National Disease and Therapeutic Index indicated that in each of the five previous years, 7 to 10 million allergen injections had been given (98). Since so many injections are administered yearly, the risk of a fatal reaction is low. Lockey et al. reported that 45 (1.4%) of 3236 patients who had a clinical history of Hymenoptera hypersensitivity and were skin tested had systemic hypersensitivity reactions during skin testing, and eight of these (0.25% of the subjects tested) were severe (99). Of 1410 patients placed on IT, 171 experienced 327 systemic reactions, of which 28 reactions (9%) were severe but not fatal (100). These studies illustrate that IT with a standardized vaccine, used as indicated, in individuals with an allergic disease that may be life threatening, induces a low incidence of adverse reactions, most of which are mild to moderate.

The systemic reaction rate to skin testing is significantly lower than the rate of reactions to SCIT, but it is not negligible. Lin et al. reported only two patients with systemic allergic

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reactions to skin testing in 10,400 patients tested (101). The overall risk of inducing anaphylaxis by skin testing was 0.02%; other studies have produced similar results (101–103). The rate of systemic reactions to skin testing is likely under reported. Thompson et al. reported a systemic reaction rate of 6% of patients receiving skin testing (104). At the 2007 World Allergy Congress meeting, Bagg et al. reported a 3.5% systemic reaction rate of 1456 patients receiving skin testing in a retrospective review over one year (105). All patients were given epinephrine for any systemic symptoms that occurred during skin testing. All patients readily responded to early intervention with epinephrine (105). It is important to recognize the risk of systemic reactions from skin testing as well as the treatment for these reactions to prevent progression. The early administration of epinephrine appears to prevent more serious and late-phase reactions.

The incidence of unconfirmed NFRs from 1990 to 2001 was 23 per year (5.4 events per million injections) in the latest mentioned AAAAI survey of fatal and NFRs from SCIT (106). There were 115 systemic reactions (5.2% of patients and 0.06% of injections) from 1981 to 1990 (107) and 26 systemic reactions (1.08% of patients and 0.01% of injections) from 1991 to 2000 (108) in another retrospective analysis of nonfatal systemic reactions to SCIT.

A review by Stewart and Lockey (109) in 1992, which examined the incidence of systemic reactions to IT, concluded that the percentage of subjects experiencing a systemic reaction from IT is small but will probably increase as the IT schedule is accelerated and when or if high-dose regimens are required in highly sensitive subjects. In addition, maintenance IT is associated with fewer systemic reactions than the buildup period of rush and accelerated schedules of IT.

Premedication with a combination of methylprednisolone, ketotifen (a mast-cell stabilizer not available in the United States), and long-acting theophylline may decrease the incidence of systemic reactions associated with rush protocols. Concern was voiced over masking a mild reaction by using premedication, which might therefore be followed by a later, more serious, reaction or delay the onset of a reaction beyond the waiting period. However, premedication with antihistamine reduced the frequency of severe systemic reactions caused by conventional IT and increased the proportion of patients who achieved the target maintenance dose in one randomized controlled study (110). In other studies premedication with antihistamines significantly reduced the incidence of systemic reactions during rush IT or specific cluster IT (111–113). There was no evidence that antihistamines masked the early warning signs or delayed the onset of systemic reactions. In the Casale et al. study, pretreatment with omalizumab resulted in a fivefold decrease in risk of anaphylaxis caused by a ragweed rush protocol (114). Further studies involving larger groups of patients and different dosage regimens are necessary to define the future role of antihistamines and other pharmacological pretreatment in IT. Finally, a minimum 30-minute waiting period, as recommended by the AAAAI and the ACAAI *Allergen Immunotherapy: A Practice Parameter Second Update*, was deemed appropriate with a longer waiting period for high-risk patients (115).

RISK FACTORS FOR SKIN TESTING AND IMMUNOTHERAPY

It is essential that strict attention be paid to risk factors for systemic reactions and that techniques of management are initiated both before and after skin testing or IT to minimize these risks. Several guidelines have been suggested which emphasize thorough training of all personnel involved in these procedures as well as the prompt treatment of systemic reactions (85,97). These have encouraged the development and use of standardized vaccines and emphasize certain risk factors, including the following:

1. Patients, particularly asthmatics, suffering a seasonal exacerbation of their symptoms
2. Patients who demonstrate exquisite sensitivity to particular allergen(s) (116).
3. Patients on β -blockers (116,117)
4. Patients with asthma, especially when their asthma is unstable (118)
5. Patients in whom rush IT is used (both venoms and inhalant allergens) (109,111,113,116)
6. Patients in whom high doses of potent standardized allergen vaccines are used
7. Injections from new vials (116)
8. Dosing errors (116)

PRECAUTIONS FOR SKIN TESTING AND IMMUNOTHERAPY

The following guidelines are suggested:

1. Always begin with a percutaneous procedure for skin testing (i.e., prick-puncture).
2. When possible, do not use β -adrenergic blocking agents concomitantly during skin testing or IT.
3. Keep patients under observation for at least 30 minutes or even longer for those at greatest risk since most fatal systemic reactions begin within that time (115).
4. When SCIT is prescribed, give the patient written and/or verbal guidelines outlining methods of IT and the importance of adherence to these guidelines to prevent an adverse reaction (see chap. 32).
5. Inform patients receiving IT of its potential risk and obtain informed consent.
6. Administer IT in an office or clinical setting with a physician present and with optimal care available for the treatment of a systemic reaction.
7. Monitor patients to assure they are waiting a proper time in the facility where they receive their IT.
8. Provide adequate instructions to another physician who may give the injections elsewhere from vials of vaccine taken from the prescribing physician's office or clinic (see chap. 32).

The safety of allergen IT has been reviewed in detail by Norman and Van Metre (119).

EQUIPMENT RECOMMENDED FOR SETTINGS WHERE ALLERGEN IMMUNOTHERAPY IS ADMINISTERED

The following equipment are recommended by the Joint Task Force on Practice Parameters (115):

1. Stethoscope and sphygmomanometer.
2. Tourniquets, syringes, hypodermic needles, large-bore needles (14 gauge).
3. Aqueous epinephrine HCL 1:1000 w/v.
4. Equipment to administer oxygen by mask.
5. Equipment to administer intravenous fluids.
6. Antihistamines for injection (second-line agents for anaphylaxis, but H1 and H2 antihistamines work better together than either one alone).
7. Corticosteroids for intravenous injection.
8. Vasopressors.
9. Equipment to maintain an airway appropriate for the supervising physician's expertise and skill.

The prompt recognition of systemic reactions and the immediate use of epinephrine are the mainstays of therapy (120-122).

SALIENT POINTS

- Physicians who administer allergen IT should have the appropriate equipment and personnel to treat a systemic reaction.
- No allergen vaccine can be considered completely safe for a given patient allergic to that vaccine.
- The risk of a fatal reaction can be reduced and even eliminated by the careful selection and monitoring of allergic patients on IT, by using improved biologically standardized vaccines and by skilled and timely treatment of systemic reactions.
- The wait period of 30 minutes is adequate for most patients, but should be extended for high-risk patients.
- Patients at highest risk for allergen IT are patients with asthma, especially unstable asthma.

- Other high-risk patients include those with a seasonal exacerbation and exquisite sensitivity, those regularly treated with β -blockers, and those receiving rush or accelerated schedule immunotherapy.

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