

Fatalities Following Allergen Immunotherapy

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Abstract

Allergen immunotherapy has been in use for nearly 100 yr and has become an important method of reducing allergic symptoms in select patients with allergic rhinitis, asthma, and insect venom hypersensitivity. Unfortunately, immunotherapy has been associated with anaphylaxis and death. Although the relative risk of severe reactions to immunotherapy is low, the number of such reactions has increased since the introduction of standardized and more potent extracts. There are a number of risk factors associated with such severe anaphylactic reactions. Such risk factors include errors in dosage, failure to reduce the dosage after a longer than scheduled interval, administration of the wrong extract, inadvertent intravenous administration, failure to postpone injection because of infection or asthma exacerbation, failure to observe patients for appropriate length of time, failure to adhere to guidelines for established contraindications, concurrent use of β -adrenergic blocking agents, uses of mixtures of allergens, immunotherapy during the active allergy season, and types of allergens. In this review, we focus on these and other risk factors in attempts to reduce the risk of anaphylaxis following allergen immunotherapy.

Index Entries

Allergen immunotherapy; immunotherapy fatalities; systemic reactions to immunotherapy; anaphylaxis; asthma; rhinitis; insect sting hypersensitivity.

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Introduction

Specific allergen immunotherapy (IT) was first introduced in 1911 and has since been widely used in reducing symptoms and medication requirements in certain patients suffering from allergic rhinitis and asthma. Furthermore, in patients with potentially life-threatening anaphylactic reactions to insect stings, venom IT (VIT) has also been demonstrated to substantially reduce the risk of such reactions to subsequent stings. Unfortunately, IT therapy can cause severe systemic reactions (SRs) and fatalities have been reported. Here we summarize available data on IT-associated fatalities with particular emphasis on risk factors that may predispose a patient to severe and potentially fatal SRs and on international guidelines intended to minimize this risk.

Reported Fatalities

The first known fatalities after injection of foreign proteins, including substances given in the attempt to "desensitize" the patient were summarized by Lamson in 1924 and 1929 (1,2) and described as "sudden death." The majority of IT-associated deaths are attributable to anaphylactic shock, although asthma, airway obstruction, and cardiovascular complications are also frequently listed as causes of death. After the original reports by Lamson, only a handful of IT-associated deaths appeared in the literature until 1980 (summarized in ref. 3). In 1984, questionnaires inquiring about fatalities associated with IT and skin testing were sent to the 3400 members of the American Academy of Allergy and Immunology (AAAI) (4). The results revealed that, between 1945 and 1983, these physicians had witnessed a total of 40 fatalities after IT or skin testing. Only 30 reports, including 24 of fatalities associated with IT, contained enough data for analysis (see Table 1). Follow-up surveys of the members of the AAAI and the American College of Allergy and Immunology (ACAI) uncovered 17 IT-

associated deaths in the United States between 1985 and 1989 and a further 10 in the period 1990–1991 (5,6). Another survey covering the years 1992–1996 added nine fatalities in the United States as well as four international cases—one in Australia, one in Italy, and two in France (7). These data are likely underestimates.

Based on data from the AAAI surveys combined with figures from the National Disease and Therapeutic Index, the risk of death in American patients receiving IT was estimated to have been 1 per 2.8 million injections for 1980–1984 and 1 for every 2 million injections for 1985–1989, which is 0.357 per million for the first period and 0.5 per million for the latter period (5). These numbers are similar to the 0.67 per million injections mentioned in the fact sheet put together in 1997 by the American College of Allergy, Asthma, and Immunology, which was based on 35 deaths following IT and an estimated 52.3 million IT procedures between 1985 and 1993 (8).

Interestingly, the same fact sheet states that data compiled by the Allergen Products Manufacturers Association (APMA) estimated the incidence of fatalities to be approx 1 per 63 million injections, or 0.016 per million injections. No attempt is made to provide an explanation for the striking discrepancy between these figures. It is difficult to understand why the annual injection figure provided by the APMA is approx 20 times higher than indicated by the National Disease and Therapeutic Index data, especially since the trend has been towards a marked decrease in the use of IT at least for asthma patients in the United States (9).

In 1986, the British Committee on Safety of Medicines (CSM) presented data on 26 deaths from anaphylaxis associated with IT since 1957 (10). Expressed per specific desensitising agent, the estimated incidence of fatalities was zero for 9 of 13 products and ranged between 1/8000 courses and 1/321,750 courses for the 4 others.

Of note, 5 of the 26 British deaths occurred in the 18 mo preceding publication of the report.

Table 1
IT-Associated Fatalities^a

<i>n</i> With detailed information/ <i>n</i> total	Period	Country	Female /male	Age	Asthma	Previous adverse reaction	High sensitivity	Injection from a new vial	Injection during seasonal exacerbation	Allergens	Increasing dose; maintenance	Time elapsed till onset of symptoms	Reference
24/40	1945–1984	USA	13/11	33 (7–70)	11/16	4	10/13	4	9/24	Mixed 10 Ragweed 5 Molds 1 Insect allergen 1 NA 7	9; 7 ^b	<30 min 18 >30 min 2 NA 4	(4)
17	1985–1989	USA	11/5 (1 unreported)	36 (10–77)	13/14; 3 of them symptomatic	5/12	13/15	5	5	Pollen 15 HDM 5 1 NA	11; 4	<30 min 1 >30 min 12 NA 4	(5)
10	1990–1991	USA	5/3 (2 unreported)	49 (12–73)	7/7	1/5	6/6 high or moderate	NA	NA	Pollen 6 Mold 3 HDM 3 House dust 4 Cat 2 NA 4 ^c HDM	3; 3	<30 min 5 NA 5	(6)
13	1992–1996	USA 9 Australia 1 Italy 1 France 2	NA	NA	11/13 plus 1 with COPD; 4 of them symptomatic	NA	NA	5	NA	HDM 7 Pollen 2 Mixture of different allergens 17 HDM 18 HDM + house dust 1 Pollen 3 Molds 2 Grass pollen + molds 1 NA 3	3; Cat	NA	(7)
26	1957–1986	Great Britain	13/12 (1 unreported)	31 (11–57)	16/17	6/26	NA	NA	NA	HDM 7 Pollen 2 Mixture of different allergens 17 HDM 18 HDM + house dust 1 Pollen 3 Molds 2 Grass pollen + molds 1 NA 3	16; 4	<0 min 18 >30 min 2 NA 6	(10)
28/40	1977–1994	Germany and Int'l	NA	NA	NA	NA	possibly 1	NA	NA	HDM 7 Pollen 2 Mixture of different allergens 17 HDM 18 HDM + house dust 1 Pollen 3 Molds 2 Grass pollen + molds 1 NA 3	NA	NA	(11)

^a Note that, wherever possible, the number of patients with a certain characteristic was reported in relation to the number of patients for which details on this characteristic are available.

^b NA for 6, 1 decreasing, 1 first dose.

^c Note that the total exceeds the number of fatalities, indicating that some patients received mixtures of two or more unrelated allergens.

A similar clustering of IT-associated fatalities was also noted in a German survey, with 18 of 40 cases reported between 1977 and 1994 occurring in the 5-yr period between 1984 and 1988 (11). The authors emphasized the temporal and possibly causal association between this clustering and the introduction of high potency standardized extracts in the early 1980s.

Data from the United States and other countries may not be directly comparable since there may be marked differences in the types of vaccines used (e.g., aqueous vs adsorbed extracts), the settings in which they are administered, and the guidelines that are followed in doing so (12). There may also be regional differences in the SR patterns possibly due to variations in the length of the pollen season and the allergenicity of the locally prevalent pollens (13).

Risk Factors for Systemic Reactions and Mortality

Even though the risk of fatal reactions to IT is low, any death is unacceptable. Therefore, many investigators have looked for commonalities between fatal cases in an attempt to identify specific risk factors. Since most deaths after IT are attributable to fatal anaphylaxis, the most severe form of a systemic allergic reaction, great efforts have also been made to identify risk factors for SRs in general and severe, but non-fatal, SRs in particular. Unfortunately, widely differing definitions of SR have been used and this is reflected in the great variation in the reported rates of SRs, which range from <1% to 100% of patients, although factors like differences in patient characteristics, types of allergens, and administration protocols are also likely to contribute to the variability of the results.

Asthma

Although four to five times more patients with rhinitis than patients with asthma received IT during the period from 1985 to 1989, patients with asthma represented 77% of the fatalities (5) (see Table 1). All other surveys reported similarly high proportions of asthma patients among the deaths associated with IT, particularly patients that received their injection during an exacerbation of their asthma or whose asthma was steroid-dependent and poorly controlled (4–7,10).

Labile or symptomatic asthma is a risk factor not only for fatal SRs, but also for the frequency and severity of SRs overall, as indicated by the finding of a higher risk of SRs during IT in patients with asthma compared to those with rhinitis in several studies with a variety of inhalant allergen vaccines (14–17). This is, however, not an entirely consistent finding (18) and was also not observed in patients undergoing VIT (19).

In patients with asthma, pulmonary function before the initiation of IT following a rush protocol, specifically an FEV1 <80% of the predicted value, was significantly associated with the development of an asthma attack in response to IT injection of *Dermatophagoides pteronyssinus* extract (20). Several guidelines recommend recording peak flow or spirometry readings before and after injections and to abstain from giving the injection if the results are more than 20% below the best recent reading for that patient (21,22). Although they advise special caution in patients with asthma, the American practice parameters do not contain such a specific recommendation (23). Nonetheless, physicians should be aware of this.

Dose-Increase Phase

The limited available data suggest that a majority of the fatal reactions to IT injections occurred during the dose increase rather than the maintenance phase (5,10). An increased frequency of non-fatal SRs during the dose-

increase compared to the maintenance phase has been reported in numerous studies with various inhalant allergen vaccines (15,16) and also with venom allergens (19,24). Others, however, were unable to detect a statistically significant difference in the SR rates observed during the dose-increase and the maintenance phases (25). In a cohort of 1056 children receiving a total of 47,247 injections of house-dust mite (HDM) or one of several pollen vaccines, 90% of the 41 SRs occurred during the maintenance phase (26). It has been suggested that the temporal distribution of SRs depends on the type of allergen, with a majority of SRs to Hymenoptera injections occurring during the initiation phase, but the larger proportion of SRs to mite extract being observed during the maintenance phase (18).

Rapid Dose-Increase Regimens

In the existing surveys of IT-associated fatalities, there is little information on the type of protocol used for the dose-increase phase. With certain types of allergen (e.g., HDM and pollens), cluster and rapid/rush protocols appear to be associated with an increased rate of non-fatal SRs compared to standard protocols (23,27). Some controversy remains over the question of whether rush protocols in VIT entail a heightened risk of SR; however, the safety profile of ultra-rush protocols for VIT is similar to, or even better than, that of more conventional protocols, at least in the case of *Vespula* venom (19,23,28).

High Sensitivity

In a considerable portion of IT-associated fatalities, the subjects were known to be highly sensitized to the injected allergen (see Table 1). A high degree of hypersensitivity either by skin test or by specific IgE measurements is recognized as a risk factor for SRs, including fatal ones (27,29), although a recent prospective study did not find SPT reactivity to be significantly associated with the frequency of SRs (15).

Previous SRs

A number of fatalities after IT administration occurred in patients who had had adverse reactions to previous injections (Table 1). Unfortunately, from the limited information available on most cases, it cannot always be determined whether the dose was adjusted after this occurrence (as is now recommended by European and American guidelines [21,23]). The second AAI survey reported 2 of 17 cases in which the dose was increased, even though the patient had experienced an adverse reaction to the previous injection, and another case in which the dose may not have been reduced sufficiently (5). The German survey indicated that dosage increases despite adverse reactions to the previous dose might have contributed to the fatal outcome in 3 of 28 cases (11).

A recent prospective multicenter study concluded that 40% of the SRs that were observed in 423 patients receiving a total of 17,256 injections could have been avoided if it had been decided before the study to withdraw patients once they had experienced three SRs (17). This study followed the guidelines of the European Academy of Allergology and Clinical Immunology (EAACI), which state that, after SRs (as well as during increased environmental exposure or when changing to a new batch of nonstandardized allergen extract) the dose should be reduced relative to the preceding injection, with the magnitude of the adjustment dependent on the severity of the reaction (28). Current US practice parameters concur, even though there are no evidence-based guidelines concerning the magnitude of the dose reduction (23). The guidelines also recommend re-evaluating the risk-benefit ratio of IT in patients with severe and/or repeated systemic reactions, but do not give a specific number of SRs after which IT should definitely be discontinued.

Active Allergen Season

Nine of 24 IT-associated fatalities in the first AAAI survey took place during seasonal exacerbation of the patient's disease (4), as did 5 of 17 in the second survey (5).

The EAACI position paper recommends reducing the vaccine dose during periods of increased environmental levels of the relevant allergen (e.g., pollen season) (21) and this is deemed reasonable by the US practice parameters (23). Although some large prospective studies did not detect a significant difference in the rate of SRs between pollinating and non-pollinating seasons even in the absence of seasonal adjustments in the dosage schedule (25,27), it has become common practice to reduce the maintenance dose of seasonal allergens during the pollen season by 40 to 50%. In some recent trials and surveys adopting this strategy, the incidence of SRs was found not to be increased during co-seasonal administration (15,17).

New Vial

As indicated in Table 1, at least 14 of the deaths analyzed in the various surveys of IT-associated fatalities were associated with injections of newly prepared extracts, and the WHO position paper includes changing to a new vial of unstandardized vaccine as one of the risk factors for IT-associated fatalities (29). The EAACI guidelines recommend reducing the first dose from a new vial/treatment set of non-standardized allergen extracts to half of the scheduled dose (21). In at least one study, however this precaution was unable to prevent a reaction; almost a third of all SRs (12 of 35) were associated with the administration of the first dose from a new treatment set (16).

β -Adrenergic-Blocking Agents

Several of the IT-associated fatality surveys include patients treated with a β -blocking agent (4,5). In a prospective study of more than 3000 patients receiving over 56,000 IT injections,

the rate of SRs in the 68 subjects taking β -blockers was actually somewhat lower than expected from the rate observed in the whole cohort (30). Although this suggests that β -blocking drugs do not increase the frequency of SRs, these agents may still increase their severity and may decrease the response to medications used in the treatment of severe SRs, particularly epinephrine. Consequently, treatment with β -blocking agents is considered a relative contraindication, as are other medical conditions that reduce a patient's ability to survive severe SRs, such as severe uncontrolled asthma or significant cardiovascular disease (21,23,31). It may be necessary to make an exception in the case of a patient with life-threatening reactions to Hymenoptera stings who also needs to be treated with β -blockers or has one of the above medical conditions.

Type of Allergen

Unfortunately, information is lacking on the breakdown of annual IT injections by individual allergen types, such as pollens, mites, molds, or Hymenoptera venom. Therefore, the available data do not allow assessment of whether specific types of allergen vaccines are associated with a greater frequency of fatalities than others.

Nonetheless, it is striking how many of the patients in the various American surveys of IT-associated fatalities were treated with some sort of pollen vaccine (Table 1). Note however, that a substantial portion of these patients received injections of mixtures containing not only several different types of pollen but also dust, HDM, molds, and other extracts (4,5). In contrast to the US data, 18 of 20 German and 8 international patients died after an injection of HDM and another fatality was associated with a mixture of HDM and house dust (11). The authors of this survey emphasized that controlled clinical studies had not indicated that HDM extracts were associated with higher reactivity than other allergen vaccines. They

considered multiple sensitization (in three patients), chronic bronchial asthma (4) and extremely high sensibility (1) rather than the allergen type to be the most likely contributors to the lethal outcome in most of these cases. Among 13 fatalities associated with IT in the United States and in several European countries during the years 1992–1996, HDM was apparently implicated in a greater number of cases than any other extract, but information on the exact number of cases is lacking (7). The dose of mite extract may have been excessive in 6 of the 13 fatalities, suggesting that dosage errors rather than the type of allergen played a major role in these fatal reactions.

In several large retrospective and prospective studies, the rate of non-fatal SRs was found to be significantly higher in subjects receiving pollen vaccines than in patients treated with other types of inhalant allergens (18,25,27,32), but opposite results were reported in children (26). In several other studies, the finding of a significantly higher frequency of SRs in patients treated with HDM extract compared to those given pollen vaccines may have been attributable to the high proportion of asthma patients in the group sensitized to *D. pteronyssinus*, i.e., to considerable confounding between asthma status and allergen type (14,16,17).

The type of pollen also seems to influence the risk of SRs (13,14,27,33), although this was not confirmed in another study (15). In addition, differences in the SR rates between extracts of the same allergen from different manufacturers have been reported and are thought to be attributable to variations in potency (18). Furthermore, depot vaccines have repeatedly been found to be better tolerated than aqueous extracts, and their preferential use is recommended by some guidelines (22).

Interestingly, even though fatalities from a single insect sting are known to occur, fatal SRs to VIT appear to be very rare. Among the surveys of IT-associated fatalities, there is mention of only 1 case in which a fatal reaction occurred after injection of “stinging insect” (presumably

whole body) extract (4). The administered injection also contained timothy, ragweed, *Alternaria*, and dust making it difficult to determine which of the allergens was responsible for the fatal outcome. Although anaphylaxis and bronchospasms were reported to the CMS or the appropriate pharmaceutical company after injections of wasp and bee venoms, there were no reports of deaths between 1980 and 1986 (10). None of the other surveys contain specific mention of venom as the causative agent involved in fatal reactions to IT (5–7,11). Information on the type of allergen(s) injected is not available for all of the fatal cases reported to date. Nonetheless, the virtual absence of Hymenoptera venom vaccines from the fatal cases in which the allergen extract is known suggests that the fatality rate during VIT is substantially lower than during IT with all other allergen vaccines.

It is tempting to speculate that medical personnel exercise greater caution in administering an allergen known to have caused a severe and potentially fatal reaction in the same subject than they do in the case of inhalant allergens that they may perceive as relatively innocuous. However, greater care in administering VIT injections and monitoring the patient does not appear to be the sole reason that fatalities associated with VIT are essentially unknown. Rather, VIT appears to be associated with fewer and/or less severe SRs than inhalant allergen IT (14,18). The type of venom also plays a major role in determining the frequency of SRs, the rate of SR being significantly higher with bee venom than with wasp and yellow jacket venom for as yet unknown reasons (19,24,34).

Mixtures of Allergens

A considerable number of IT-associated fatalities occurred after the injection of a mixture of a wide variety of unrelated allergens (4,5). Whether this simply reflects the common practice of using multiple vaccines in the IT of

individual patients or constitutes a risk factor for fatalities cannot be determined from the existing data.

Patients with multiple sensitization are less likely to benefit from IT than those in whom one or two dominant allergens cause the majority of the symptoms, and it largely remains to be established whether mixtures of multiple allergens are beneficial for the patient (29,35). Hence, the EAACI and WHO declared it preferable not to use mixtures of unrelated allergens (21,29). These position statements as well as the current US practice parameters emphasize the necessity to guard against excessive dilution of the individual constituents and their accelerated deterioration due to proteolytic activity of some allergens when mixing vaccines (23).

Gender and Age

The second AAAI survey indicated that females were over-represented among the reported fatalities (69%, while only 54% of subjects receiving IT were female) (5), but neither the first AAAI nor the British CSM survey suggested that females were at greater risk of fatal reactions than males (4,10). The findings regarding the role of sex and age in the incidence of non-fatal SRs have also been inconsistent. Some investigators reported no association (15,16,25), whereas others detected an increased risk of SRs for female patients undergoing IT for inhalant allergens or venom hyper-sensitivity (14,19) and in a prospective study involving more than 4800 patients and more than 500,000 injections, both female gender and ages between 16 and 39 yr were significantly associated with the frequency of SRs (27). In a multi-center Spanish study, the percentage of male and female patients experiencing SRs did not differ significantly, but a higher percentage of doses given to male patients was associated with SRs (17). Multivariate logistic regression, however, failed to identify age or sex as significantly associated with SRs with IT.

Treatment Errors and Omissions

In addition to risk factors arising from patient characteristics, lack of appropriate guidelines and/or facilities, nonadherence to existing guidelines and other types of omissions and errors contributed to a significant number of the reported fatalities. For example, a majority of the British fatalities were reportedly attributable to the lack of adequate facilities for cardiorespiratory resuscitation for immediate treatment of patients experiencing anaphylaxis (10). Lack of early treatment with epinephrine was also identified as a risk factor in 3 of 13 fatalities in one of the international surveys (7). In a number of other cases, the appropriate treatment was either never initiated or came too late because patients left the physician's office before the recommended observation period had elapsed (10 cases in refs. 4,5,11) or because the injection was administered at home (4 patients in refs. 4,5,7). These instances reflect failure on the part of the treating physician to fully inform the patient of the risks associated with IT and to ensure patient compliance, particularly with the requirement to remain under observation after the injection.

Most severe SRs associated with IT have been found to occur within 30 min of the injection, as did a majority of the fatal reactions (Table 1). The AAAI originally recommended a waiting period of 20 min (12), while current US recommendations are for patients to remain in the physician's office at least 20–30 min (23). Most European countries follow the EAACI guidelines of observing patients for 30 min (21), and in Australia and New Zealand, a 45-min observation period is recommended (22). Longer waiting periods are advised for high-risk patients, a group that includes patients: 1) receiving rush IT (because SRs can occur for ≥ 2 h after the final injection); 2) with a high degree of sensitivity; 3) with unstable asthma (although control of asthma with drugs is required before any injection); and 4) receiving β -blockers.

Table 2
Possible Treatment Errors in Immunotherapy

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- Errors in dosage, including failure to reduce the dosage after a longer than scheduled interval between injections or after an adverse reaction to a previous injection or when injecting extract from a new vial, particularly one from a different manufacturer.
 - Administration of the wrong extract.
 - Inadvertent intravenous administration.
 - Failure to postpone the injection because of an existing infection or asthma exacerbation.
 - Failure to adhere to guidelines for established contraindications of IT.
 - Mixture of seasonal and perennial allergens.
 - Failure to observe the patient for the appropriate length of time after the injection.
 - Failure to provide the patients with all the appropriate information.
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In some large prospective studies, a substantial portion of non-fatal SRs was observed to occur up to 6 h after the injection, including some that involved the upper and lower airways and required treatment with epinephrine (25,27). Two of the 26 British fatalities also took place more than 30 min after the injection, which prompted the British CSM to recommend keeping patients under medical observation for a period of 2 h (10), but this has since been reduced to 1 h.

Possible treatment errors are summarized in the German fatality survey (11) and noted in Table 2. One or more of these errors were noted in 23 of the 28 cases reported in this survey, leading the authors to conclude that it could not be ruled out that errors and negligence by the treating physician were at least partly responsible for the lethal outcome (11). Similarly, failure to adhere to recommended procedure was implicated in all five deaths reported in Australia between 1972 and 1993 (22). Definite errors of administration (incorrect dose, wrong extract) were deemed responsible in 3 of 24 (4), 5 of 17 (5) and 2 of 10 fatalities (6) in the AAAI surveys; however, a careful examination of the available data suggests that other errors not unlike the ones listed in the German study may have contributed to fatal outcomes with a frequency similar to that observed in the German and the Australian cases. From these findings, it appears that human error constitutes one of

the most important risk factors for fatal reactions to IT and that many of the IT-associated deaths reported to date could have been prevented if proper procedure had been followed and more stringent measures had been taken to insure avoidance of errors of administration, availability of the appropriate equipment, and patient compliance.

That IT can be quite safe when administered by well-trained physicians who strictly adhere to existing guidelines, particularly the somewhat more stringent European and Australian ones, has been documented by the relatively low frequency of SRs and the complete absence of fatalities in recent large clinical trials and surveys (15,17,18,26).

Discussion

The only absolute indication for IT is a history of severe SR to Hymenoptera venom combined with evidence of clinically relevant specific IgE antibodies. The indication of IT in patients with asthma and allergic rhinitis is relative. This distinction is mirrored in the major goals of IT in these patient groups, which are to reduce the incidence of life-threatening anaphylaxis in the case of VIT and to reduce symptoms and medication requirements in the case of IT for asthma and allergic rhinitis.

Whether VIT is indeed life saving can only be assessed against the background of the epi-

demology and natural history of insect sting allergies. Estimates of the rate of sensitization to bee and vespid venom range between 9% and 29% in adults, with the variability largely due to differences in the exposure level (36). The prevalence of SRs to stings by these Hymenoptera species is considerably lower, ranging between 0.15% and 3.3% in the general population of a variety of European countries and in the United States and between 0.4% and 0.8% in children.

Worldwide, the venom of eight genera of ants is known to cause allergic reactions, but most of the existing literature has focused on the imported fire ant (*Solenopsis spp.*) in North America and the jack jumper ant (*Myrmecia pilosula*) in Australia (37). The prevalence of hypersensitization to these ant species is estimated to be at least as high as that of bee and wasp venom allergies and appears to considerably exceed it in endemic areas. In addition, whereas re-sting reaction rates in subjects allergic to wasps and bees range between 30% and 60%, the corresponding rate for jack jumper stings was found to be 70% (37). Overall, in somewhat more than 15% of patients discharged from emergency departments after anaphylaxis, insect stings are identified as the cause of the anaphylactic reaction (36) and *M. pilosula* stings caused almost twice as many emergency department visits owing to insect sting anaphylaxis as did honeybee stings (38).

Fatalities from Hymenoptera stings are rare, ranging between 0.03 and 0.48 per 1 million inhabitants per year in Europe and the US (36), or approx 30 to 50 fatalities from Hymenoptera stings per year in the US. Deaths from fire ant and jack jumper ant stings have also been reported. A substantial number of deaths from insect stings are likely to go unrecognized and unreported, meaning that these figures underestimate the true incidence of insect sting fatalities.

VIT is highly effective in patients with severe allergic reactions to bee and wasp

stings, with protection provided to at least 75% of patients in earlier studies and more than 95% in more recent ones (28). A recent randomized controlled trial showed IT with *M. pilosula* venom to be highly effective in the prevention of sting anaphylaxis (39). It is to be feared, however, that jack jumper ant venom may never become widely available (37). Whole body extracts of bees, wasps, and jack jumper ants are ineffective. For the treatment of patients with severe allergies to imported fire ant stings, only whole body extracts are available. Although there is as yet no conclusive evidence attesting to their efficacy, they appear to provide protection from severe SRs in a majority of subjects (37).

The vast majority of fatal reactions to Hymenoptera stings occur in subjects aged over 30 yr, a majority of them male. Therefore, as a means of reducing insect sting mortality VIT is likely to be most effective in this age group. Yet anaphylactic reactions to bee and wasp stings appear to be more common in younger subjects, an observation prompting some authors to question whether prevention of fatalities provides a strong rationale for using VIT in children and young adults (40). Others pointed out that the improvement in quality of life provided by VIT is enough to warrant its use in younger people (37).

The impact of VIT on fatality rates from Hymenoptera stings is virtually impossible to assess, especially because 1) the re-sting reaction rates in subjects with strong allergic reactions to a previous sting can be as low as 35% after yellow jacket stings and as high as 70% after jack jumper ant stings; and 2) an estimated 40% of insect sting-related deaths occur in people who are unaware of their sensitization to Hymenoptera venom. Even though a large proportion of fatal anaphylactic insect sting reactions can, therefore, not be prevented, there are indications that VIT could have a considerably greater effect on mortality reduction if awareness of the availability and enormous

effectiveness of VIT were promoted among physicians and patients (36). Given the great effectiveness and the comparative safety of VIT, particularly the virtual absence of VIT-associated fatalities, it would seem that the benefits of preventing severe and fatal anaphylactic sting reactions far outweigh the risks associated with this form of therapy.

It should not be overlooked that asthma exacerbations can also be not only disabling but even life threatening and the mortality in asthma has increased in recent years. Hence, it is felt that every approach that can contribute to the control of asthma should be explored (21,23). Inclusion of IT among these approaches is fully justified since, in properly selected patients, it has been shown to be effective in reducing not only symptoms and medication requirement but also allergen-specific bronchial hyperreactivity (29,41). In addition, preliminary data suggest that IT may prevent the development of asthma in children with allergic rhinitis, may decrease the risk of new sensitization and may inhibit the development of irreversible changes in lung structure and function often seen in patients with asthma (23). Nonetheless, the risks and benefits have to be carefully weighed in patients with asthma as well as those with allergic rhinitis.

Administration of IT by routes other than subcutaneous injection are increasingly being tested in randomized controlled clinical trials and particularly sublingual (sublingual-swallow and possibly sublingual-spit) routes of administration have shown effectiveness in allergic rhinitis (42). The few studies available to date on direct comparisons between sublingual and subcutaneous IT suggest that SLIT may be of somewhat lower efficacy, but may be preferable because of its substantially better safety profile. To date, almost all SRs associated with SLIT have been mild or moderate and there have been no reports of life-threatening events in several post-marketing surveillance studies. Although some organizations recommend considering these alternative routes

of IT administration in certain patients, this is not (yet) relevant in the United States owing to the unavailability of the appropriate vaccines (23).

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