

16 Occupational Allergens

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INTRODUCTION

Allergen immunotherapy (AIT) is the repeated administration of specific allergens to patients with IgE-mediated diseases, the purpose of which is to provide protection against the allergic symptoms and inflammatory reactions associated with the natural exposure to said allergens (1). This therapy is efficacious to treat patients with allergic rhinitis due to seasonal pollen allergens (2) (e.g., trees, grasses, and weeds) and for perennial allergic rhinitis induced by house-dust mites (3) and cat allergens (4). Similarly, AIT is effective in treating patients with aeroallergen-induced asthma attributable to sensitization with cat and grass pollens (2,5,6).

AIT is seldom considered in the initial management of workers with occupational rhinitis (OR) or occupational asthma (OA). Environmental control measures to reduce exposures to offending workplace aeroallergens are usually prioritized and emphasized and may account for the lack of published clinical studies about efficacy and safety of AIT in patients with occupational respiratory allergic diseases. However, where appropriate, AIT is considered only in workers in whom specific IgE sensitization to natural protein allergens is confirmed by skin testing to commercially available extracts or in vitro specific IgE tests. Although specific IgE is rarely demonstrated to reactive chemicals known to induce OA (7), AIT with chemical antigens (e.g., hapten-conjugated proteins) cannot be safely recommended or considered because of unknown short-term and long-term risks of chemical-induced side effects.

The primary treatment of choice for OA or OR remains the elimination or reduction of occupational exposure to causative aeroallergens. Such interventions consist of reassignment to a different low-exposure job in the same work facility or job transfer to another workplace where exposure is eliminated or reduced sufficiently to control or prevent work-related allergic respiratory symptoms. Failure to reduce exposure to causative agents in patients with uncontrolled OA can result in disability and even fatal asthma (8,9). Therefore, pharmacotherapy and AIT should be used as ancillary treatments in selected patients but not as substitutes for effective environmental interventions.

There are specific situations in which AIT may be appropriate to treat occupational IgE-mediated respiratory disorders. AIT may be considered in symptomatic workers whose exposure to workplace allergens can be reduced but not entirely eliminated. Workers, recognizing the potential impact of a job change on their income and livelihood, may choose to continue work in a job where there is persistent exposure to an occupational allergen. In these cases, the best possible clinical outcomes may result from a combined approach, including institution of personal safety measures (e.g., respirators or masks), pharmacotherapy, and AIT, when appropriate. At the same time, these workers must be medically monitored to assure that persistent exposure does not lead to more severe illnesses or worsening of airway obstruction.

NATURAL RUBBER LATEX

Natural rubber latex (NRL) is derived from the sap of the rubber tree, *Hevea brasiliensis*, a complex mixture of at least 13 allergenic proteins that bind human IgE antibodies (Hev b allergens) (10). NRL gloves are a common source of occupational allergen exposure for health care workers and an important cause of allergic occupational disease. A FDA-approved NRL skin test reagent is not commercially available, although there are FDA-cleared immunoassays to detect NRL-specific IgE in serum (11). The primary intervention for individuals with established NRL allergy is avoidance of NRL-containing products (12).

The first multicenter, double-blind, placebo-controlled trial with NRL was performed in a French cohort for one year in 2000 (13). Seventeen patients had NRL allergy, defined by a clinical history of rhinitis and conjunctivitis, asthma (9 of 17), a positive skin prick test (SPT) with a standardized latex extract (Stallergènes SA, Antony, France), a positive latex conjunctival provocation challenge, and elevated NRL-specific IgE defined as more than or equal to class 2 level (Pharmacia, Uppsala, Sweden).

After six months of NRL subcutaneous immunotherapy (SCIT), there were significant improvements in rhinitis symptom scores ($p < 0.04$) and conjunctivitis symptom scores ($p < 0.02$) compared with placebo associated with NRL exposure. After one year of SCIT, improvement in rhinitis ($p < 0.05$) and conjunctivitis ($p = 0.05$) symptoms was maintained with added improvement in cutaneous signs ($p < 0.03$). No effect on work-associated asthma symptoms was demonstrated after one year. The mean medication scores with treatment also improved by 79%. Conjunctival challenge with aqueous latex extract was performed pre- and post-SCIT; conjunctival reactivity decreased with active versus placebo treatment ($p < 0.02$).

Safety was a concern. There was a higher rate of injection-related reactions in the treatment group as compared to placebo, with almost 50% in the treatment group experiencing immediate large local reactions at injection sites. Almost half of actively treated patients (4 of 9) had at least one anaphylactic reaction to NRL injections, characterized by angioedema, bronchospasm, pharyngeal edema, giant urticaria, and/or hypotension (13).

Another randomized, double-blind, placebo-controlled trial of NRL AIT was reported in 2003 (14). In a six-month trial with an experimental crude NRL extract, 24 patients were randomized to active NRL SCIT treatment ($n = 16$) or placebo ($n = 8$). This Spanish cohort consisted primarily of health care workers with contact urticaria ($n = 24$), rhinitis ($n = 17$), and/or asthma ($n = 15$) related to NRL exposure. Compared to placebo, patients receiving NRL SCIT had a significant decrease in SPT reactivity to NRL ($p < 0.01$), decrease in reactions to a latex rubbing test (NRL glove rubbed on wet skin for 30 seconds) ($p = 0.047$), and in reactions to a glove use test ($p = 0.046$). However, treatment had no effect on NRL-specific IgE levels, symptoms or medication scores, methacholine PC20, or the NRL glove exposure time to elicit a 15% decrease in forced expiratory volume in one second (FEV₁) by specific inhalation challenge. As in the previous study, a high number of systemic reactions were reported. Of 387 injections, there were 31 mild systemic reactions (8% of doses), with a third of these reactions classified as delayed reactions. These systemic reactions occurred in 11 actively treated patients (68.7%). The authors reported no severe systemic reactions.

Sublingual immunotherapy (SLIT) to NRL also reduced skin reactivity to NRL and reactivity on a conjunctival challenge test (14,15). Twenty-four patients with symptoms of urticaria, rhinoconjunctivitis, asthma, and/or anaphylaxis associated with NRL exposure were treated with a commercially available sublingual NRL vaccine in an open uncontrolled study (14,16). After 10 weeks of treatment, a total of 1044 doses were administered. Systemic reactions occurred with 38 doses (3.6%) and in 12 patients (46.2%). One patient developed anaphylaxis. Local oral reactions were reported with 223 doses (21.4%). Compared to baseline, there were decreased symptom scores with the latex glove use test ($p = 0.0004$) and with the latex glove rubbing test (latex glove rubbed on wet skin for 30 seconds) ($p = 0.037$).

Another nonblinded study evaluated the use of NRL SLIT in 24 patients, including 10 health care workers, with symptoms of asthma ($n = 17$), urticaria ($n = 18$), and/or rhinoconjunctivitis ($n = 10$) with NRL exposure (15). All had a positive SPT to a standardized NRL extract. Twelve underwent a four-day rush treatment protocol, and 12 others were untreated and served as controls. Two actively treated patients had local reactions in three months of treatment with NRL SLIT ($n = 12$). No systemic reactions were reported. Significant improvements in symptom scores with NRL challenge were seen in the treatment group before and after treatment with SLIT. The group treated with SLIT also had significant improvements in symptom scores compared with the untreated control group with sublingual NRL challenge ($p < 0.001$), with NRL gloved finger in mouth challenge ($p = 0.0002$), with cutaneous NRL extract challenge ($p < 0.001$), and with conjunctival NRL challenge ($p < 0.01$).

Treatment of NRL allergy with AIT seems to be effective in improving rhinitis symptom scores elicited by NRL exposure. However, proven benefit for asthma or decreased bronchial hyperactivity after NRL-specific inhalational challenge has not been confirmed. The lack of benefit from AIT may be due to inability to achieve optimal maintenance doses, secondary to the unacceptably high risk of systemic reactions associated with the SCIT. Nevertheless, the

Table 1 Summary of Immunotherapy Efficacy Studies for NRL

Allergen (route)	Study design	Number studied	Indication	Results	Level of evidence ^a	Reference
NRL (SCIT)	DBPC	17	Rhinitis, asthma, conjunctivitis	Improvement in rhinitis and conjunctivitis	A	13,41
NRL (SCIT)	DBPC	24	Contact urticaria, rhinitis, asthma	Decrease in SPT reactivity to NRL Decrease in symptoms with glove use	A	14,41
NRL (SLIT)	Unblinded, no placebo	24	Urticaria, rhinitis, asthma, anaphylaxis	Improvement of symptom scores with glove use	C	16
NRL (SLIT)	Unblinded, placebo-controlled	24	Asthma, urticaria, rhinitis, conjunctivitis	Improvement of symptom scores with NRL challenge	B	15

^aLevel of evidence

A: Evidence based on randomized controlled trial

B: Evidence based on controlled trial without randomization or other quasi-experimental study design

C: Evidence based on nonexperimental descriptive studies

Abbreviations: NRL, natural rubber latex; DBPC: double-blind, placebo-controlled; SCIT: subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SPT, skin prick test.

sublingual approach (SLIT) may be helpful if future evidence from placebo-controlled studies supports its safety and efficacy.

On the basis of the evidence, environmental control of the work environment and avoidance of NRL products remains the primary treatment. Since NRL allergy is rapidly declining because of better control of latex allergen exposure in health care facilities, there may be little need for a commercially available AIT product in the future (Table 1).

WHEAT FLOUR

Bakers and pastry makers exposed to wheat flour, containing high molecular weight protein allergens, often develop OR and bakers' asthma. The prevalence of bakers' asthma is estimated to be 9% among bakery employees (17). One double-blind, placebo-controlled study evaluated 139 patients who worked with wheat flour (17). Of the 139 subjects, 35 (25%) had a positive SPT with a crude wheat flour extract or elevated in vitro-specific IgE to wheat flour. Of these, 30 asthmatic patients were selected for the SCIT trial. Eight were treated for 10 months with wheat flour extract, 8 for 20 months with wheat flour extract, and 10 received placebo. Four in the active treatment group stopped therapy because of a change of jobs with resolution of symptoms. AIT-treated patients had a significant decrease in wheat flour extract SPT sensitivity as determined by the wheal area ($p = 0.002$) and a significant decrease in bronchial hyperresponsiveness to methacholine ($p < 0.001$). By 20 months of treatment, there was a significant decrease in wheat flour-specific IgE compared to placebo ($p < 0.005$) and improvement in symptoms associated with exposure to wheat flour compared to placebo ($p < 0.001$). No severe systemic reactions were reported, although one patient developed transient urticaria after an injection. This study indicates that SCIT, with a wheat flour vaccine, may be effective in treating bakers' asthma. However, these positive results will require confirmation in larger controlled clinical trials (Table 2).

Table 2 Summary of Immunotherapy Efficacy Studies for Wheat Flour

Allergen (route)	Study design	Number studied	Indication	Results	Level of evidence ^a	Reference
Wheat flour (SCIT)	DBPC	30	Asthma	-Decrease in SPT reactivity to wheat flour -Decrease in bronchial hyperresponsiveness on methacholine challenge -Decrease in wheat flour-specific IgE -Improvement of symptoms on exposure	A	17

^aLevel of evidence

A: Evidence based on randomized controlled trial

Abbreviations: DBPC, double-blind, placebo-controlled; SCIT, subcutaneous immunotherapy; SPT, skin prick test.

ANIMAL ALLERGY (MAMMALIAN PROTEINS)

Allergic reactions among laboratory animal workers is an important occupational health problem, with an estimated incidence of 1.32 per 100 person years and an estimated prevalence of 22% (18). Of all animal workers, veterinarians are at the greatest risk of developing occupational allergic disorders, such as atopic dermatitis, allergic rhinitis, and asthma. Among veterinarians, 38% report rhinitis or conjunctivitis and 20% asthma symptoms related to their work environment (18). Cats are the most commonly reported (58%) animals causing work-related symptoms.

Avoidance of laboratory animals and animal-housing facilities is usually recommended in symptomatic workers. However, because of career and job considerations, it is rarely feasible for affected workers to eliminate all exposure to animals. When complete avoidance is not possible, there have been reported cases when AIT with laboratory animal allergens has been attempted.

Subcutaneous AIT with rodent allergens was used in 11 patients with allergic symptoms upon exposure to laboratory animals and compared with a group of matched untreated control patients in an unblinded manner (19). Laboratory animal allergy was confirmed by intracutaneous skin testing and leukocyte histamine release to animal allergens, such as mouse, rabbit, rat, guinea pig, and hamster. All had rhinoconjunctivitis symptoms upon exposure to at least one of these animals, and most had symptoms on exposure to several different species. Nine of 11 patients reported a decrease in symptoms after SCIT. Active treatment was associated with significantly increased titers of blocking antibody determined by serum inhibition of allergen-induced histamine release with relevant laboratory animal allergens in comparison to untreated controls ($p < 0.0001$). In three of four patients in whom AIT was discontinued, blocking antibodies slowly decreased to pretreatment levels after 16 to 36 months.

Both cat-induced allergic rhinitis and asthma have been effectively treated by use of SCIT (20). In a randomized, double-blind, placebo-controlled trial, 17 patients with asthma associated with cat exposure were followed (5). All patients developed cough, wheeze, or shortness of breath with cat exposure and had a positive SPT and bronchial challenge test result to the major cat allergen, Fel d 1. Compared to placebo ($n = 8$), treatment was associated with a significant increase in PD₂₀ FEV₁ on bronchial provocation with Fel d 1 ($p < 0.05$). A higher concentration of allergen was necessary to induce a 3-mm wheal in the treatment versus placebo group on skin prick titration testing ($p < 0.01$). The treatment group had increased time to ocular ($p < 0.05$) and pulmonary ($p < 0.05$) but not nasal symptoms with cat exposure compared to placebo. Ocular, nasal, and pulmonary symptom scores following cat exposure ($p \leq 0.03$) also improved with treatment. Furthermore, active treatment was associated with increased Fel d 1-specific IgG compared to placebo ($p < 0.001$) (Table 3).

Table 3

Allergen (route)

Rodent (mouse, rabbit, guinea pig, hamster) (SCIT)

Fel d 1 (cat)

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Table 3 Summary of Immunotherapy Efficacy Studies for Animal Allergy (Mammalian Proteins)

Allergen (route)	Study design	Number studied	Indication	Results	Level of evidence ^a	Reference
Rodent (mouse, rabbit, rat, guinea pig, hamster) (SCIT)	Unblinded, matched, untreated controls	11	Rhinitis, conjunctivitis	-Decrease in symptoms on exposure -Increase in titers of blocking antibodies	B	19
Fel d1 (SCIT)	DBPC	17	Asthma	-Increase in PD ₂₀ FEV ₁ with bronchial provocation -Decrease in SPT reactivity -Improvement of ocular, nasal, and pulmonary symptom scores	A	5

^aLevel of evidence

A: Evidence based on randomized controlled trial

B: Evidence based on controlled trial without randomization or other quasi-experimental study design

Abbreviations: DBPC, double-blind, placebo-controlled; SCIT, subcutaneous immunotherapy; SPT: skin prick test.

SEA SQUIRT

Major allergens from the body fluid of the sea squirt, *Styela plicata*, are the acidic glycoproteins, Gi-rep, Ei-M, and DIIIa. Asthma related to exposure to sea squirt allergens primarily occurs among Japanese oyster shucking workers. Oyster shucking workers continuously inhale the sea squirt antigens in the mist of the body fluid of sea squirts. In 1963, the reported prevalence of sea-squirt asthma was 36% (21). With industrial hygiene improvements, the reported prevalence of sea-squirt asthma has decreased to 8%, with an incidence of 10.1% (21).

In an uncontrolled study, 123 asthmatic patients received SCIT with one of three known major sea squirt allergens, Gi-rep ($n = 47$), Ei-M ($n = 62$), or DIIIa ($n = 14$) (22). The maximum dose of each AIT injection was 50 μ g of antigen. After one year of treatment, 72% of those treated with Gi-rep were able to shuck oysters with minimal or no medications. Better results were obtained with Ei-M; 90% of patients reported improved symptoms. DIIIa was the least effective, with only 36% reporting improved symptoms. These results are consistent with a previous study that shows DIIIa is significantly less effective than Gi-rep or Ei-M with AIT (23). Beneficial effects of AIT were maintained over five years of treatment. A significant increase in IgG titer specific for Ei-M occurs within the first year of SCIT and correlates with the therapeutic effect, similar to previous studies (22) (Table 4).

HOUSE-DUST MITE

House-dust mite is the most common indoor allergen (24). Exposure to house-dust mite (DM) allergens occurs in a variety of occupations, including domestic cleaners and janitorial staff personnel. High levels of house-dust mite species allergens, *Dermatophagoides pteronyssinus* (Der p1) and *Dermatophagoides farinae* (Der f1), are present in house dust of rooms with wall-to-wall carpeting.

Several studies evaluated the efficacy of DM AIT, although not specifically in worker cohorts. Twenty-seven patients with a positive SPT to Der p1 and/or Der f1 and perennial

Table 4 Summary of Immunotherapy Efficacy Studies for Sea Squirt

Allergen (route)	Study design	Number studied	Indication	Results	Level of evidence ^a	Reference
Gi-rep, Ei-M, DIIIIa (SCIT)	Unblinded, no placebo	123	Asthma	-Improvement of asthma symptoms -Decrease in medication use with oyster shucking	C	22

^aLevel of Evidence

C: Evidence based on nonexperimental descriptive studies

Abbreviations: SCIT, subcutaneous immunotherapy.

rhinitis and/or mild asthma received SCIT with aluminum hydroxide-adsorbed standardized dust-mite extracts (50% Der p1 and 50% Der f1) and were followed yearly for three years in a double-blind, placebo-controlled trial (25). After three years of AIT, there was a significant decrease in medication scores for asthma ($p < 0.033$) and for rhinitis ($p = 0.0007$). Subjective symptom scores for asthma were significantly improved after one year ($p = 0.016$) and continued through three years of treatment ($p = 0.0008$). Rhinitis symptom scores were significantly improved at both two and three years ($p = 0.0006$). Both SPT reactivity and conjunctival reactivity to Der p1 and/or Der f1 significantly decreased over all three years ($p < 0.0001$). Nonspecific bronchial hyperresponsiveness, as measured by methacholine challenge, also improved after three years of SCIT as compared to placebo ($p < 0.0001$). No significant systemic reactions to injections were reported.

In another double-blind, placebo-controlled study, 29 asthmatic patients with SPT positivity to Der p1 were randomized to either SCIT or placebo (26). After three years of SCIT with Der p1, there were no significant differences in the FVC, FEV₁, or FEF₂₅₋₇₅. However, there was a significant decrease in the number of annual asthma exacerbations after one year of treatment ($p < 0.01$). Furthermore, there was a significant increase in the number of medication-free days (e.g., bronchodilators or systemic glucocorticoids) between the treatment and placebo groups ($p < 0.01$). Along with these findings, there was a significant improvement in bronchial hyperresponsiveness to methacholine. As for safety, no major systemic reactions with injections were reported.

A larger randomized, double-blind, placebo-controlled trial included 95 patients with asthma and percutaneous sensitization to Der p1 and/or Der f1 (27). SCIT was administered for three years using extracts containing Der p1 and/or Der f1 allergens; 72 patients completed the study. There was a significant decrease in percutaneous skin sensitivity to Der p1 and/or Der f1 antigens ($p < 0.05$) with AIT. Small, but significant improvements were seen in peak expiratory flow rates in the AIT group (mean increase of 1.6–5.5% of predicted from baseline). Asthma symptom scores did not significantly change, but there was an increase in the proportion of patients not requiring use of bronchodilators in the treatment group ($p < 0.01$). There was no significant change in the FEV₁ or in bronchial hyperresponsiveness to methacholine in the treatment versus the placebo group. Mild bronchospasm after injections was reported on two occasions.

One other study evaluated the effects of rush AIT in 10 Der p1 SPT-positive asthmatic patients to evaluate the underlying immune changes associated with clinical improvement with AIT (28). While treatment was not blinded, the outcomes were compared one to two days prior to the start of rush AIT and one to two days after reaching maintenance in a blinded manner. There was a significant decrease in percutaneous reactivity to Der p1 by endpoint SPT titration with AIT ($p < 0.01$). Decreased nasal reactivity to Der p1, symptom scores, and nasal obstruction was found in the AIT treated versus the placebo group ($p < 0.01$). A significant increase in anti-Der p1 IgG4 was observed in the AIT treated group ($p < 0.01$). There was also a significantly decreased lymphocyte proliferative response to Der p1 after AIT ($p < 0.05$) (Table 5).

Table 5

Allergen (route)

Der p1/D f1 (SCIT)

Der p1 (SCIT)

Der p1/D f1 (SCIT)

Der p1 (Rush SCIT)

^aLevel of Evidence
A: Evidence based on experimental studies
C: Evidence based on nonexperimental descriptive studies
Abbreviations: SCIT, subcutaneous immunotherapy; PEFR, peak expiratory flow rate.
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Table 5 Summary of Immunotherapy Efficacy Studies for House-Dust Mite

Allergen (route)	Study design	Number studied	Indication	Results	Level of evidence ^a	Reference
Der p1/Der f1 (SCIT)	DBPC	27	Rhinitis, asthma	Decrease in medication scores for asthma and rhinitis Improvement of rhinitis and asthma symptom scores Decrease in SPT and conjunctival reactivity Improvement of bronchial hyperresponsiveness by methacholine challenge	A	25
Der p1 (SCIT)	DBPC	29	Asthma	Decrease in number of annual asthma exacerbations Increase in medication-free days Improvement of bronchial hyperresponsiveness by methacholine challenge	A	26
Der p1/Der f1 (SCIT)	DBPC	95	Asthma	Decrease in SPT reactivity Improvement of PEFR Decrease in use of bronchodilators	A	27
Der p1 (Rush SCIT)	Unblinded, no placebo	10	Rhinitis, asthma	Decrease in SPT reactivity Decrease in nasal reactivity and obstruction Decrease in asthma and rhinitis symptom scores	C	28

^aLevel of evidence

A: Evidence based on randomized controlled trial

C: Evidence based on nonexperimental descriptive studies

Abbreviations: DBPC, double-blind, placebo-controlled; SCIT, subcutaneous immunotherapy; SPT, skin prick test; PEFR, peak expiratory flow rate.

HYMENOPTERA VENOM

Stinging insect hypersensitivity is an occupational problem for farm workers, greenhouse workers, forest rangers, biologists, and beekeepers. Hymenoptera insects in the families Apidae (bees) and Vespidae (wasps) are primarily responsible and include the honeybee (*Apis mellifera*), yellow jacket (*Vespula vulgaris*), wasp (*Polistes annularis*), white-faced hornet (*Dolichovespula maculata*), and yellow hornet (*Dolichovespula arenaria*) (29) (see chap. 14).

The prevalence of systemic reactions to Hymenoptera stings ranges from 0.8% to 3.3% in the general population (30,31). Several studies show that the rate of systemic allergic reactions is much higher in beekeepers, between 14% and 35% (32,33). A prospective evaluation of 35 Greek beekeepers was performed to estimate the incidence of sensitization among previously unsensitized workers (30). The workers were evaluated by intradermal skin testing every six months for the five years of the study. During the five-year period, 10 of 35 beekeepers (28.6%) were sensitized to honeybee venom as compared with 3 of 26 controls (8.3%). While none of the sensitized subjects reported a systemic reaction after honeybee stings, 5 of 35 beekeepers (14.3%) experienced large local reactions. Among the beekeepers, the number of stings per year correlated with the probability of sensitization to honeybee venom. In contrast, other studies show that tolerance can be induced by very

frequent stings (34,35). Beekeepers with more than 200 stings per year appear to be protected from systemic sting reactions (no reactions) as compared with beekeepers stung less than 25 times a year (45% with reactions).

SCIT with purified Hymenoptera venoms is the treatment of choice to modify future risk of anaphylactic reactions in workers sensitized to insect venoms. Full protection can be achieved in 83% to 95% of patients with a previous history of anaphylactic reactions (33). Four treatment regimens include conventional (weekly intervals for increasing doses as an outpatient), rush (inpatient induction phase over 4–7 days), ultrarush (reaching maintenance dose in 1–2 days), or cluster (a modified rush approach with a cluster of injections given at the first visit and reaching a maintenance dose within 6 weeks).

Studies demonstrate the efficacy and safety of the rush venom protocols. For example, 97 patients received rush AIT to bee venom, *Vespula* venom, or both (32). Severe sting induced allergic reactions were reported in 48 of them. Specific AIT with bee venom alone in 5, *Vespula* venom alone in 73, and with both in 19 was prescribed. The majority of these patients (90) had cutaneous reactions at the injection site. Unusual adverse events included blood pressure elevation in 11 patients, moderate hypotension in 2, and rhinitis in 1. No anaphylaxis was reported, and the protocol was deemed safe by the authors. No evidence of efficacy was presented.

Another study evaluated the safety of rush AIT with Hymenoptera venoms in 101 patients (35). Bee venom was used in 52 and yellow jacket in 49 patients. Maintenance dose was reached in all but one patient. Bee venom injections induced a higher rate of systemic reactions than did yellow jacket. The risk for systemic reactions was 0.79% per injection in the bee venom group as compared with 0.12% with yellow jacket venom. Systemic reactions were reported at all stages of the protocol and were generally mild to moderate, with only two severe reactions reported.

The efficacy and safety of the rush protocol also was evaluated prospectively in 18 patients with a history of allergic reactions to Hymenoptera stings (36). Seven patients were treated with bee venom and seven with yellow jacket venom during a seven-day protocol. After completing one year of AIT, there was a significant increase in specific IgG4 levels compared with baseline levels ($p < 0.05$). There were no changes in specific IgE levels, mean wheal diameter on SPT, or intradermal skin test reactivity after one year of AIT. Four systemic reactions were reported for bee venom (1.7%), while none were reported with yellow jacket venom. During the course of AIT, two patients had field sting events, including a beekeeper who was re-stung several times, without consequence. Another study evaluated 67 patients with confirmed Hymenoptera venom allergy who were treated with an ultrarush protocol (37). Thirty-four were treated with wasp venom, 20 with honeybee venom, and 13 with both wasp and honeybee venoms. The maintenance dose was reached in 97.5% of the ultrarush courses. Side effects showed no dose dependency and were mainly mild, with 14 (17.5%) patients experiencing allergic reactions. Furthermore, there was no significant difference in the number of systemic reactions in those receiving honeybee venom (15.2%) and wasp venom (19.1%).

While bumblebees are generally not very aggressive and allergic reactions rare, the expanding use of domesticated bumblebees for pollination of crops has resulted in an increase number of reports of occupational allergic reactions (38). Patients with allergic reactions to bumblebees are treated with honeybee venom because of the high degree of cross-reactivity with this venom. However, case reports indicate that this may not always be effective (39). Two patients, treated with honeybee venom, were later stung by a bumblebee at work and developed anaphylactic reactions. Repeat AIT was performed using bumblebee venom. An in-hospital bumblebee sting challenge resulted in a local cutaneous reaction but no systemic reaction. Another case series presented seven cases of bumblebee venom allergy among workers on a bumblebee farm, all of whom had anaphylactic reactions to bumblebee stings (40). They were treated with bumblebee venom-specific AIT. During maintenance AIT, at least 36 bumblebee stings were reported, none of which resulted in systemic reactions. Ultrarush AIT with bumblebee venom was evaluated in one case of a biologist with anaphylaxis after bumblebee stings (34). Two months after reaching maintenance, the patient had another sting at the workplace. Despite the re-sting event, the patient experienced no systemic reaction (Table 6).

Table 6

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Table 6 Summary of Immunotherapy Efficacy Studies for Hymenoptera Venom

Allergen (route)	Study design	Number studied	Indication	Results	Level of evidence ^a	Reference
Honeybee, <i>Vespula</i> sp. (Rush SCIT)	Unblinded, no placebo	97	Anaphylaxis	-Protocol appears safe -No episodes of anaphylaxis	C	32
Honeybee, yellow jacket (Rush SCIT)	Unblinded, no placebo	101	Anaphylaxis	-Higher rate of systemic reactions with honeybee venom vs. yellow jacket	C	35
Honeybee, yellow jacket (Rush SCIT)	Unblinded, placebo-controlled	18	Anaphylaxis	-Increase in specific IgG4 -Two field stings without reaction	B	36
Wasp, honeybee (Ultrarush SCIT)	Unblinded, no placebo	67	Anaphylaxis	-Protocol appears safe -17.5% with mild allergic reaction during treatment	B	37
Bumblebee (Rush SCIT)	Case reports	2	Anaphylaxis	-Inhospital sting challenge with local reactions only	D	39
Bumblebee (Rush SCIT)	Case series	7	Anaphylaxis	-36 field stings after AIT without systemic reactions	C	40
Bumblebee (Rush SCIT)	Case report	1	Anaphylaxis	-One field sting after AIT without systemic reaction	D	34
(Ultra-rush SCIT)						

^aLevel of evidence

B: Evidence based on controlled trial without randomization or other quasi-experimental study design

C: Evidence based on nonexperimental descriptive studies

D: Evidence based on expert opinion

Abbreviations: DBPC, double-blind, placebo-controlled; SCIT, subcutaneous immunotherapy; SPT, skin prick test.

CONCLUSION

AIT is rarely indicated to treat OR or OA. It should be considered only to modify respiratory allergic symptoms associated with workplace exposure to natural allergens and when commercial extracts are available both to confirm sensitivity by skin test and for treatment. AIT should not be considered as an alternative to cessation or modification of exposure to the offending allergens in the work environment. Although there is only modest evidence to

support efficacy and safety in worker populations, it appears reasonable to base treatment decisions on data extrapolated from controlled studies of AIT in nonworker populations.

SALIENT POINTS

- Environmental control measures to reduce workplace exposures is the primary intervention in management of OA and OR and, therefore, AIT to offending aeroallergens is seldom initially considered.
- If appropriate, AIT should be considered in symptomatic workers whose exposure to workplace allergens can be reduced but not entirely eliminated.
- Although AIT may be considered in workers with sensitization to protein allergens encountered in the workplace, it cannot be safely recommended for chemical sensitizers because of potential toxicity.
- Although there is sparse evidence proving efficacy and safety in worker populations, rational treatment decisions for individual workers should be based on controlled clinical trials of AIT obtained in nonoccupational study populations.
- If indicated, AIT should be strongly considered in workers with OA and/or OR caused by workplace allergens for which commercial and preferably standardized allergens are readily available. Examples include house-dust mite in cleaning workers, stinging insect venom in beekeepers, and cat allergen extracts in veterinary workers.

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Figure 3
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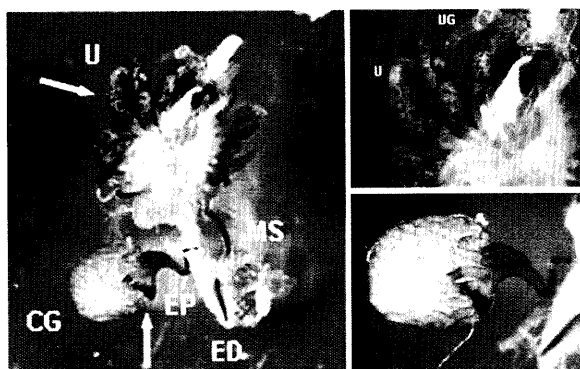


Figure 3.2 Localization of German cockroach allergen Bla g 4 to the male reproductive tissues [conglobate glands (CG) and utricles (U)] by in situ hybridization (left panel). Right panel shows higher magnification. Bla g 4 is only found in male accessory reproductive glands and is transferred to the female during copulation. Source: From Ref. 42 (see page 51).

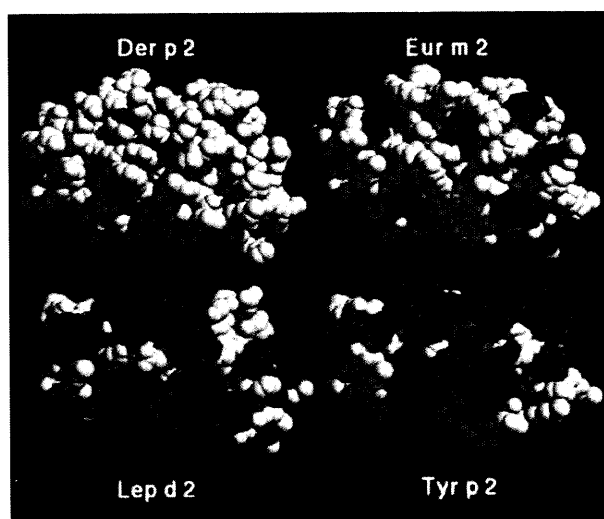


Figure 3.3 Space-filling models of Group 2 allergens from house-dust mite. Amino acid substitutions are shown in gray scale. The space-filling model of Der p 2 (*Dermatophagoides pteronyssinus*) was generated from nuclear magnetic resonance spectroscopy studies and has subsequently been confirmed by X-ray crystallography (22). Eur m 2 (*Euroglyphus maynei*) shows 85% sequence identity with Der p 2 and seven of the substituted amino acids are shown in gray on the surface structure. There is extensive cross-reactivity between Der p 2 and Eur m 2. In contrast, Lep d 2 and Tyr p 2 show only 40% amino acid identity with the other Group 2 allergens. They show many substitutions on the antigenic surface of the molecules and show limited antigenic cross-reactivity for mAb and human IgE. Source: From Refs. 51, 52 (see page 53).

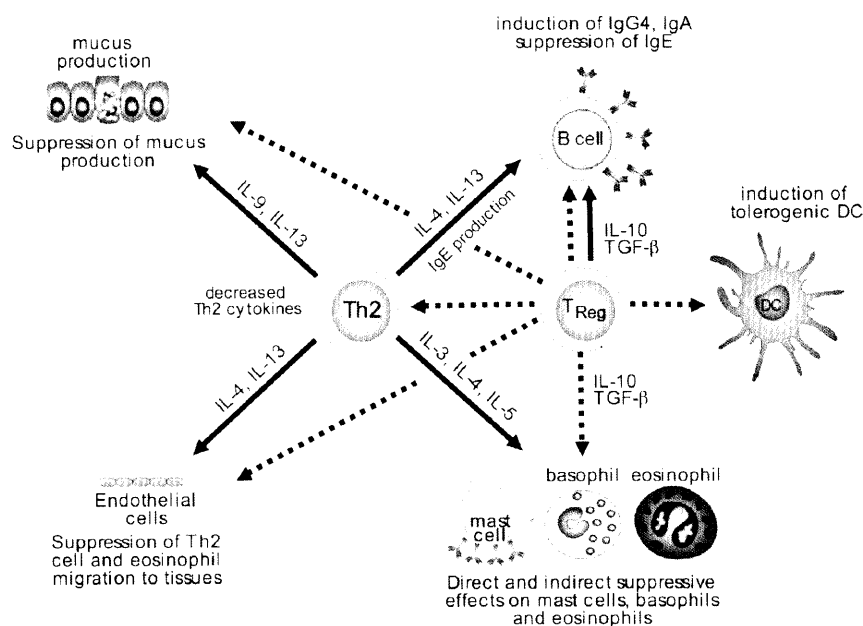


Figure 5.2 Immune deviation toward Treg-cell response is an essential step in SIT and natural allergen exposure of nonallergic individuals. Treg cells utilize multiple suppressor factors, which influence the final outcome of SIT. Treg cells suppress proliferation, tissue infiltration, proinflammatory cytokine production, and injury/apoptosis of epithelial cells by both Th1 and Th2 cells. IL-10 and TGF- β induce IgG4 and IgA, respectively, from B cells as noninflammatory Ig isotypes and suppress IgE production. These two cytokines directly or indirectly suppress effector cells of allergic inflammation such as mast cells, basophils, and eosinophils. In addition, IL-10 induces tolerogenic dendritic cells in experimental models (solid line: activation, dotted line: suppression). Abbreviations: SIT, specific immunotherapy; Treg, T regulatory (see page 75).

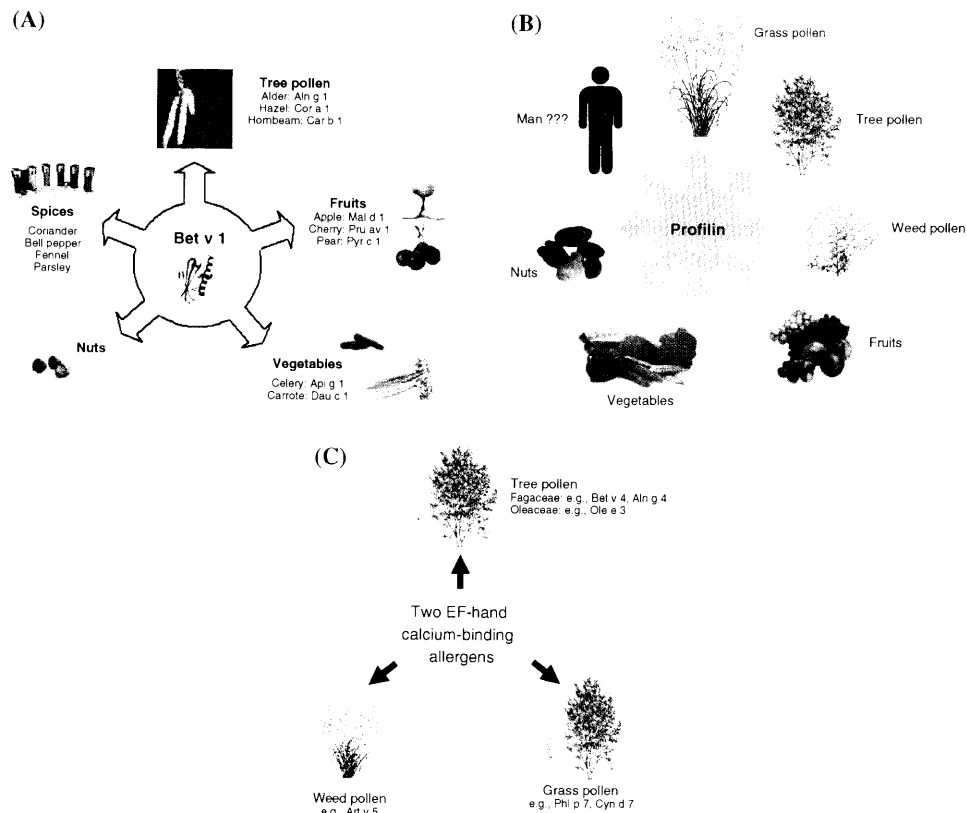


Figure 6.5 (A) Bet v 1 cross-reactive allergens can be found in pollen of trees belonging to the order Fagales as well as in fruits, vegetables, nuts, and spices. (B) Profilins, the most cross-reactive allergens described to date, occur in pollen of botanically unrelated plants (trees, grasses, weeds), in plant-derived food (fruits, vegetables, nuts), and even in man. (C) Two EF-hand calcium-binding allergens can be found in pollen from trees, grasses, and weeds (see page 95).

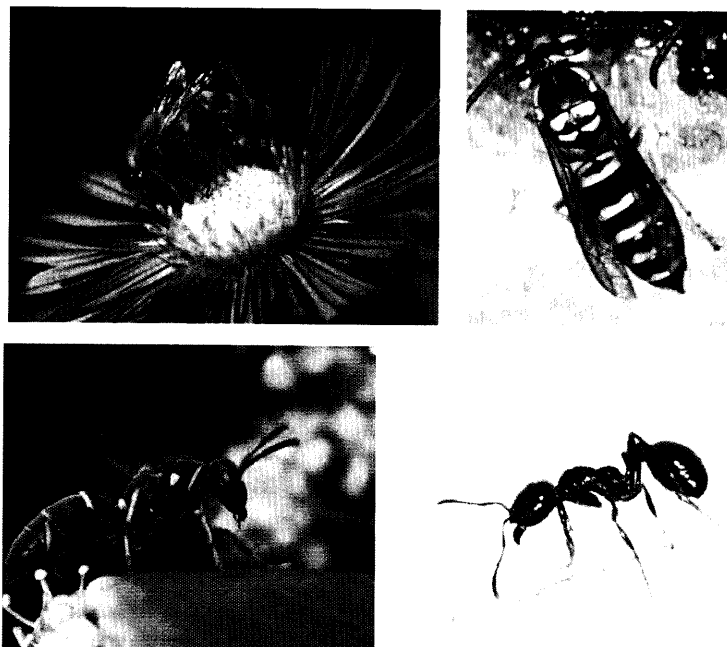


Figure 14.1 Common stinging insects. The photos, starting from top left and going clockwise, show respectively honeybee (*Apis mellifera*), yellow jacket (*Vespula maculifrons*), paper wasp (*Polistes fuscatus*), and fire ant (*Solenopsis invicta*). The approximate lengths of these insects in the order given are 16, 10, 19, and 3 mm, respectively. The photos are of different magnifications (see page 239).



Figure 15.1 Photograph of a blackfly, *Simulium*; note the humped appearance. Source: Courtesy of Jerry F. Butler, University of Florida (see page 252).



Figure 15.2 A deerfly, *Chrysops*, in biting position. The insect is usually yellow or green, and the bite is painful. Source: Courtesy of Jerry F. Butler, University of Florida (see page 252).

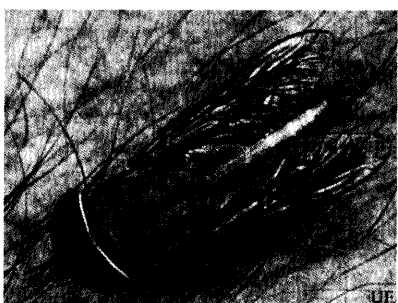


Figure 15.3 A horsefly, *Tabanus*, biting. Horseflies are typically larger than deerflies, have very noisy flight, and the bites are quite painful. Source: Courtesy of Jerry F. Butler, University of Florida (see page 252).

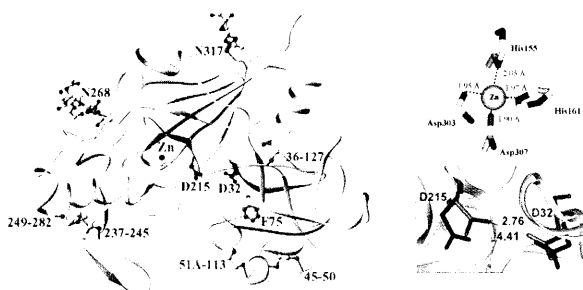


Figure 11.1 Crystal structure of the cockroach allergen Bla g 2. (Left) Bilobal structure of Bla g 2 showing residues at the region of the catalytic site (D215, D32) and F75 (previous to insertion F75a), carbohydrates and the five disulfide bonds (1yg9.pdb). (Right) The zinc ion (yellow sphere) with coordinating residues and interatomic distances (top); and aspartate positions in Bla g 2 (red aspartates on blue ribbon) and in pepsin (orange aspartates on yellow ribbon) (bottom). Source: Reprinted with permission from Ref. 39 (see page 188).



Figure 32.1B Reporting allergy skin test results as a measurement in millimeters of longest diameter of the wheal and flare/erythema. Source: From Ref. 12. (see page 501).

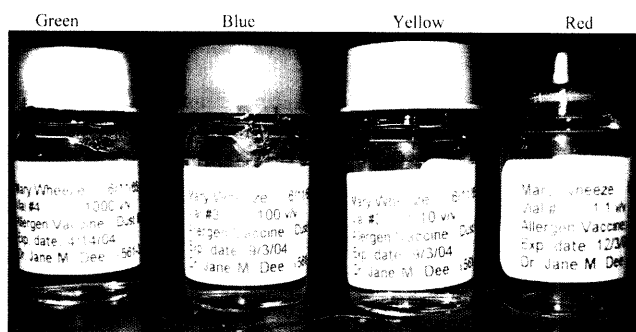


Figure 32.4 Picture of color-coded labeled allergen immunotherapy extracts with dilutions from maintenance concentrate (see page 505).

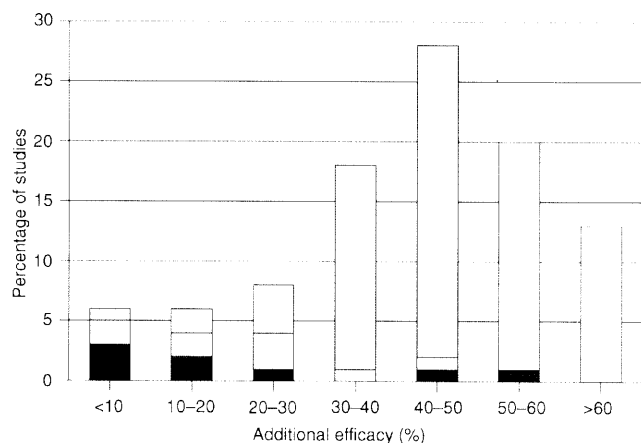


Figure 22.2 Graded magnitude of clinical efficacy of placebo-controlled, double-blind rhinitis immunotherapy studies published in 1980–2007, including 2253 actively treated patients (1776 rhinitis patients and 477 asthma patients). The additional efficacy compared to placebo is given in intervals of 10%. The 80 clinical studies result in 90 groups comparable with placebo as some studies include two actively treated groups. Furthermore, the statistical significance is related to the magnitude of efficacy: green indicates significant difference from placebo for both symptom scores and drug scores (clear cut clinical efficacy), yellow indicates significance for either symptom scores or drug scores (possible clinical efficacy), and red indicates no significant difference for either symptom scores or drug scores (no efficacy) (see page 347).

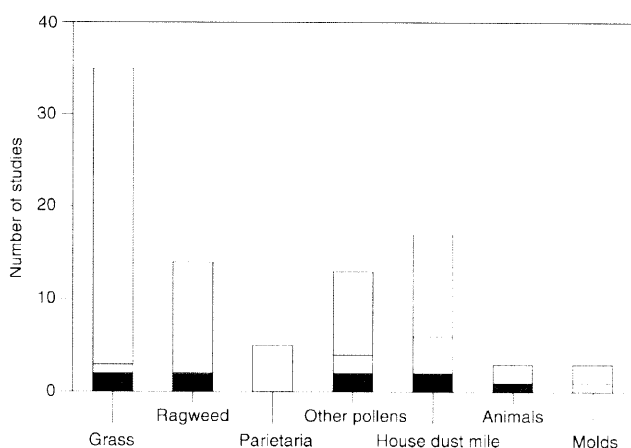


Figure 22.3 Allergen vaccines used in placebo-controlled, double-blind rhinitis immunotherapy studies published in 1980–2007. Clinical efficacy is graded based on statistical significance (green indicated significance for both symptoms scores and drug scores (clear cut clinical efficacy), yellow indicates significance for either symptom scores or drug scores (possible clinical efficacy); and red indicates no significant difference for either symptom scores or drug scores (no efficacy) (see page 348).

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