

Pet dander and difficult-to-control asthma: Therapeutic options

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ABSTRACT

The prevalence of sensitization to cat and dog allergens is high in the general population and poses a challenge to the physician managing allergic asthma. Adequate allergen avoidance is difficult to achieve because of the physical characteristics of airborne animal allergens and patient noncompliance. Allergen-specific high-dose subcutaneous immunotherapy has shown benefit in cat-allergic patients with asthma and rhinoconjunctivitis, whereas the data for dog-allergic patients are not as convincing. Alternative immunotherapy approaches including the sublingual route or allergen-derived peptide-based immunotherapy remain experimental. Pharmacotherapy of pet-allergic asthmatic patients requires a stepwise approach following established asthma management guidelines. In addition to short-acting beta-agonists and inhaled corticosteroids, prophylactic antihistamines before anticipated pet exposure, the use of intranasal steroids, and the use of leukotriene antagonists may also be considered as adjunctive therapy in pet-allergic patients with asthma and/or allergic rhinitis. Omalizumab appears to have particular efficacy in pet allergen-induced asthma. Novel therapies such as Fcγ1-Fel d 1 chimeric proteins still have to be evaluated in the human setting.

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Allergic sensitization to cat and dog allergens has a high prevalence in the general population (up to 9% for cat) and serves as an important trigger factor in children and adults who suffer with asthma and allergic rhinitis.^{1–5} The major dog allergen, Can f 1, and major cat allergen, Fel d 1, are associated with sensitization at environmental levels as low as 2 µg/g of settled dust and these allergens can provoke asthma symptoms in sensitized individuals at exposure levels as low as 8 µg/g of settled dust.⁶ The management of asthma related to pet allergy poses a significant challenge to the allergist.

CAT AND DOG ALLERGEN DISTRIBUTION

Cat and dog allergens can be found on small particles and exhibit a propensity for prolonged airborne distribution.^{7,8} It has been estimated that 10–20% of Fel d 1 and Can f 1 travel on particles <5 µm in diameter and are thus considered respirable into the small airways. Cat and dog allergens have been associated

with widespread distribution patterns, which may in part explain the prevalence of sensitization to these allergens as well as their reported contributions to ongoing clinical symptoms. One survey found that 37.2% of U.S. households own at least one dog, 32.4% own at least one cat, and 49.1% of households own either a cat or a dog.⁹ Strikingly, in one sample of U.S. homes, Can f 1 and Fel d 1 allergens were detected in 100 and 99.9% of homes, respectively.¹⁰ Mean concentrations of allergen of 4.69 µg/g of settled dust for Can f 1 and 4.73 µg/g of settled dust for Fel d 1 were observed in surveyed homes, levels well above those previously associated with risk of sensitization to these allergens.¹⁰ Another study found that with repeated sampling over 4 weeks, 40 of 40 non-cat-containing homes had detectable airborne levels of Fel d 1.¹¹ Similarly, airborne Can f 1 levels were found in 11 of 36 non-dog-containing homes.⁷ Low airborne levels of cat allergen (<100 ng/m³) may induce upper and lower respiratory symptoms and significant changes in forced expiratory volume in 1 second (FEV₁) in sensitized patients.

Dog and cat allergens easily adhere to vertical surfaces and lodge in carpeting, clothing, and other fomites, making it difficult to eliminate allergen completely.¹² Dog and cat allergens are easily transported on clothing to new locations and can be detected in many areas that are typically free of pets: schools, malls, mass transit vehicles, hospitals, and public

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buildings.^{13–17} Even complete elimination of cats from a habitat may not completely prevent sensitization. The population of Tristan da Cunha, the most remote inhabited archipelago in the world, eliminated cats from the island in 1974. However, in 1993, a cross-sectional study found that 57 inhabitants (20.1% of the population) were cat sensitized, indicating either persistence of cat allergen or transport of allergen on visitors to the island leading to sensitization.¹⁸ A Swedish group used personal air samplers to compare classrooms occupied by two groups of students. One group was characterized by >25% cat ownership and the other by <10% cat ownership. A fivefold higher level of airborne Fel d 1 was observed in the former classroom compared with the latter.¹⁹ It was additionally shown that allergen was transferred to the students' homes as there was a significantly higher Fel d 1 content in home mattresses of non-cat owners belonging to classrooms with >25% cat ownership than in those of the other group.¹⁹ A subsequent report from the same group documented that children in classrooms with many cat owners had a ninefold increased risk of exacerbated asthma (asthma symptoms, peak expiratory flow [PEF], and the use of asthma medication) after school started compared with children in classes with few cat owners.²⁰

Therefore, even in the absence of pet ownership, cat- and dog-allergic patients may have significant ongoing exposure to cat and dog allergens in multiple environments at levels that cause sensitization or even provoke allergic/asthmatic symptoms. It is important for the health care provider to recognize that such allergens are relevant to disease even in the absence of pet ownership.

ALLERGEN AVOIDANCE

Allergen avoidance is essential in the management of allergic asthma. Potential avoidance strategies in pet allergy might include removal of the pet, restriction of the pet to one part of the home, frequent washing of the pet, removal of soft furnishings, and filtering the air. Much of the published information to date regarding avoidance strategies relates to cat allergen, and there is an assumption that findings related to cat allergen can be extrapolated to other pet allergens.

Complete removal of the pet from the home or moving the pet out of doors is likely the most effective means of decreasing allergen exposure. However, the "stickiness" of these allergens and their small particulate size with facile airborne distribution limit the clinical effectiveness of this process. For example, after cat removal, it may take 20–24 weeks to achieve levels of allergen comparable with levels in homes without cats, despite frequent vacuuming and cleaning.²¹ Many patients will not consider complete removal of the pet

from the home because nearly one-half of pet owners (49.7%) consider their pets to be "family members."⁹ One study found that only 60% of adult patients in an inner city cohort with persistent asthma had ever been evaluated for allergen sensitization; among those who were evaluated, 94.0% were sensitized to at least one antigen: 77.9% to cats and 69.5% to dogs. However, only 35.2% of those who were cat allergic and 34% of those who were dog allergic adhered with recommended avoidance strategies.²²

As a result, less comprehensive strategies such as restriction of pets to certain floors or rooms of their home, or simple exclusion from the bedroom, are used. Unfortunately, limiting pets to certain restricted locations has not been shown to be effective in improving asthma control. This failure to effect improvement likely relates to the previously described physical characteristics of the aeroallergens.^{1,7,8}

Washing of pets has been evaluated as an allergen avoidance strategy and may result in marginal reduction of airborne levels of Fel d 1. Within 30 minutes of entering a small room (30 m³), a cat can increase airborne Fel d 1 by 30–90 ng/m³. After serial weekly washing of the cat this increase was reduced to ≤7 ng/m³, but the effect is transient.

Another study found that brief immersion of cats in water led to a four- to fivefold decrease in airborne Fel d 1 collection at 3 hours, with a return to baseline 1 day afterward.²³ Carpet can accumulate cat allergen at ~100 times the rate of a polished floor, 100 µg/day Fel d 1 compared with 0.5 µg/day Fel d 1, respectively. However, neither pet washing nor room modification reduced Fel d 1 below levels thought to cause sensitization or provoke symptoms.²⁴ Washing with water has been compared with pet shampoo to evaluate respective effectiveness in removing Fel d 1 allergen. Immersion in water once a week for 4 weeks reduced airborne Fel d 1 levels by 79%, whereas nonimmersion shampooing once a week for 5 weeks reduced airborne Fel d 1 by only 44%.²⁵ An alternative grooming strategy that has been evaluated is the use of emollients. One such product, Allerpet (Demite, New York, NY), has been marketed as a way to reduce the amount of allergen on pets as well as moisturize scaly skin when applied weekly. A comparison of cats washed with distilled water, sprayed with Allerpet, or treated with acepromazine (a tranquilizer advocated as efficacious in reducing shedding at subsedating doses) reported that none of these strategies reduced Fel d 1 shedding compared with untreated cats.²⁶ A separate study in dogs found that washing in water would need to be repeated twice weekly to achieve a modest reduction in airborne levels of Can f 1.²⁷

High-efficiency particulate air (HEPA) filters are capable of trapping fine particles (including pet dander and dust-mite feces), which are capable of trig-

gering allergic/asthma symptoms.²⁸ Clinical trials to assess the effectiveness of HEPA filtration in improving clinical outcomes in cat-allergic patients have shown disappointing results. One double-blind placebo-controlled trial evaluated cat-allergic adults with asthma or allergic rhinitis (18–65 years old) who were living with cat(s). Over 3 months, measurements were made of airborne Fel d 1 level rhinitis and asthma symptom scores, PEF rates, specific IgE, and methacholine responsiveness. At the end of the study, although airborne Fel d 1 levels were found to be reduced, settled dust levels were not different, and there were no significant differences in the other more clinical end points.²⁹ Another randomized control crossover trial of 22 asthmatic cat- or dog-allergic children (6–14 years old) also failed to show a significant difference associated with the use of HEPA filters on asthma symptoms or peak flow variation. However, nonspecific airway responsiveness as determined by provocative challenge concentration eliciting a 20% decrease in FEV₁ (PC20) with histamine challenge was significantly reduced.³⁰

The absence of strongly supportive evidence of effectiveness notwithstanding, cat/dog removal from the living environment of a cat-/dog-allergic asthmatic patient, accompanied by extensive environmental control measures such as removal of carpets, upholstered furniture, and other potential allergen reservoirs from the home and purchase of new bedding or impermeable encasements, is strongly recommended.^{21,31}

An option that some families have considered is to keep pets that are reported to shed less allergen and dander (*e.g.*, among cats, Siberian and Russian Blue, Devon and Cornish Rex, and Sphinx; and among dogs, most terriers and poodles, as well as Schnauzer, Portuguese water dog, Chihuahua, Shih Tzu, and Bichon Frise). The clinical effectiveness of this approach is not substantiated in the published medical literature. No canine breed is currently known to be allergen free.³² The major allergens Fel d 1 and Can f 1 are highly conserved throughout their respective species including all domestic breeds. In 2006, a new breed of “allergen-free” cat called Allerca was developed, but no peer-reviewed studies have been performed to confirm the claims of the company.³²

IMMUNOTHERAPY

Subcutaneous immunotherapy (SCIT) involves the gradual administration of increasing doses of allergen in sensitized individuals to attenuate or modulate the allergic immune response to particular allergen(s). The first randomized double-blind placebo-controlled trial using SCIT for cat-induced asthma was reported in 1984. Clinical and *in vitro* responses were compared

between subjects who received SCIT with purified cat pelt allergen ($n = 9$) and those who received placebo ($n = 8$). The treatment group was shown to have delayed onset of ocular and respiratory symptoms with cat exposure, decreased magnitude of skin-prick test reactivity to cats, decreased methacholine responsiveness, and increased serum IgG to cat allergen.³³

A subsequent open placebo-controlled trial compared outcomes in 14 children receiving dog or cat IT to those of 13 children receiving placebo. The treatment groups had decreased bronchial responsiveness and decreased skin-prick test reactivity, but no significant differences in allergen-specific IgE or IgG.³⁴

A 3-year duration open study with 21 patients receiving cat IT and 11 patients receiving dog IT was next reported. Patients underwent annual assessments with bronchial challenges using both allergen and histamine, as well as measurement of serum-specific IgE, IgG, IgG4, and skin-prick tests. It was reported that allergen-induced bronchial reactivity decreased significantly with cats more so than with dogs, and histamine PC20 also decreased significantly with cat but not with dog IT. Skin-prick test reactivity decreased for both groups. Specific IgE increased and then returned to baseline in both groups, and IgG (cats and dogs) and IgG4 (cats only) increased.³⁵

A subsequent randomized double-blind placebo-controlled trial evaluated 24 asthmatic patients with cat or dog allergy with 15 receiving active therapy and 9 receiving placebo. Bronchial challenge at 5 months indicated a significant decrease in sensitivity to cat IT but no change with dog IT. There was also no change in histamine PC20.³⁶

A landmark study by Alvarez-Cuesta *et al.* investigating “standardized” cat extract IT helped establish the effective dose range for cat IT. Fourteen patients in this double-blind placebo-controlled trial with cat-associated allergic rhinoconjunctivitis and asthma received active treatment and 14 patients received placebo for 1 year. The treatment group received a maintenance dose of 13.2 μ g of Fel d 1 antigen and exhibited improved symptom medication scores, decreased skin-prick test reactivity, increased conjunctival provocation dose requirements, increased allergen bronchial provocation dose requirements, and increased histamine PC20.³⁷

Another randomized double-blind placebo-controlled trial ($n = 28$) indicated that patients with cat-induced allergic rhinoconjunctivitis and asthma receiving IT, compared with placebo, exhibited marked reduction in symptoms during cat exposure, required greater concentrations of extract to elicit a positive conjunctival challenge test, had reduced peak flow response to cat exposure, and had reduced skin sensitivity to cat extract.³⁸

Table 1 Effective doses of cat allergen in placebo controlled studies

Authors	Cat allergens
Alvares-Cuesta ³⁷	11.3 μ g Fel d 1
Hedlin ³⁵	17.3 μ g Fel d 1
Varney ³⁸	15 μ g Fel d 1

Taken together, these studies convincingly suggest that SCIT is an effective treatment for asthma associated with cat allergy, whereas the data for asthma associated with dog allergy are not as robust. One of the difficulties with comparison studies is that dog allergen extracts unlike cat extracts, which are standardized to Fel d 1, are not standardized for specific allergen content (Table 1).

Consensus of opinion is now that 5–20 μ g of the major antigen per maintenance injection is required. Standardized cat extract is available at 10,000 bioequivalent allergy units (BAU)/mL. The 2007 American Academy of Allergy, Asthma, and Immunology Practice Parameters for Immunotherapy suggest that an effective maintenance dose range is 1000–4000 BAU. To provide the lowest effective dose of 1000 BAU, 0.1 mL is required and this would be achieved by placing 2.0 mL in a 10-mL (20-dose) maintenance vial. The highest recommended dose would require 8 mL in a 10-mL vial. Current crude estimates are that acetone precipitated-dog concentrate (1/100) contains approximately 140 μ g/mL of major antigen. To provide 14 μ g at maintenance would require 0.1 mL and this would be achieved by placing 2.0 mL in a 10-mL (20 dose) maintenance vial.

Oral IT and sublingual IT (SLIT) have recently been studied as alternatives to traditional SCIT because of the perceived benefit of convenience and less invasiveness, although questions about cost, safety, and efficacy remain. Data from two studies on the effectiveness of SLIT for pet allergy are somewhat contradictory. An early double-blind placebo-controlled trial compared 20 patients with cat-induced rhinoconjunctivitis on active SLIT for 105 days and 21 patients on placebo SLIT. Effectiveness of treatment was assessed by change in symptoms and nasal blockage index during 90 minutes of exposure in an apartment containing cat dander. Cat-specific IgG and IgE and skin test reactions were also assessed. There was a suggestive trend but no statistically significant difference in terms of decreased symptoms or nasal obstruction index on cat exposure after active therapy (total dose, ~4.5 million allergy units) compared with placebo. Specific IgG and IgE levels and skin-prick test were not different between the groups.³⁹ A later randomized double-blind placebo-controlled trial of cat-allergic patients

with rhinoconjunctivitis with or without asthma compared 25 patients receiving cat SLIT (total accumulated dose of 17 μ g) with 25 patients receiving placebo.⁴⁰ Efficacy was assessed by symptom scores and PEF levels during exposure challenge in a cat room with measured airborne Fel d 1 levels and skin testing. The treatment group showed a marked reduction in symptoms during cat room challenge and an attenuated drop in PEF response. Decreased skin test reactivity to a standardized cat extract was also established.

The optimal dosing regimens and duration of treatment have not been established for SLIT, relegating it to the category of experimental at this time. Issues regarding cost-effectiveness and practicality of SLIT need also to be further evaluated. The Nelson study used the Food and Drug Administration–approved allergen extracts for high-dose SLIT applying a total dose of 45,000 BAU (containing 3240 μ g of Fel d 1) over 105 days, which would cost nearly \$500/patient for 105 days of treatment.^{39,41}

Peptide-based IT in cat-allergic asthma has been studied as an approach for targeting allergen-specific CD4⁺ T cells using allergen-derived peptides that contain short linear, non-IgE-binding, T-cell epitopes. This approach would potentially afford the benefit of enhanced induction of tolerance without the risk of anaphylaxis from IgE cross-linking. Theoretically, this approach should confer the ability to tolerate IT with fewer side effects. In the first such study, T-cell lines derived from cat-allergic humans were used to map T-cell epitopes for Fel d 1. Two peptides of 27 amino acids were synthesized to contain the dominant Fel d 1 epitopes (*i.e.*, the epitopes that most frequently induced T-cell proliferative responses). Ninety-six cat-allergic patients were then randomized to subcutaneous treatment with placebo, 7.5, 75, or 750 μ g peptide IT for 4 weeks. Patient responses were elicited after placement in a cat exposure room. Nasal and lung symptom scores together with “survival time” and spirometry were recorded. Clinical efficacy was observed for the highest treatment group at 6 weeks.⁴² Unexpectedly, despite negative allergy skin-prick tests to the peptides, early and late adverse events of an allergic nature were observed in a subset of patients and included chest tightness, nasal congestion, and flushing. In the highest dose group, the severity of symptoms diminished with subsequent injections. Three subsequent related studies showed small clinical benefit but confirmed the elicitation in some patients of allergic side effects, including late asthmatic reactions.^{43–45} However, despite the aforementioned short-term risks, intradermal challenge of allergen-derived T-cell peptide epitopes may eventually lead to long-term development of bronchial hyporesponsiveness^{46–49}; decreased production of IL-4,^{46,47} IL-13,^{46,47,50} and/or interferon γ ^{46,47}; and increased production of IL-10.⁴⁹

PHARMACOTHERAPY

The key recommendation in the management of pet allergen-exacerbated asthma is allergen avoidance. In those individuals who are either unable to institute effective allergen avoidance or who remain symptomatic despite environmental modifications, asthma pharmacotherapy is necessary. Treatment should be prescribed in a stepwise fashion as recommended by the National Institutes of Health Expert Panel Report 3.⁵¹ Appropriate therapy should be recommended based on a pretreatment assessment of impairment and risk. Comorbidities such as chronic rhinosinusitis, gastroesophageal reflux, obesity, obstructive sleep apnea, and aspirin-exacerbated respiratory disease need to be addressed concurrently. Posttreatment assessment of impairment and risk should guide step-up or step-down of therapy as appropriate, particularly in light of the new safe use requirements released by the Food and Drug Administration regarding long-acting β -agonists in February 2010. As with all asthmatic patients, there should be an emphasis on adherence and regular monitoring to ensure that patients are responding well to therapy. For those who anticipate entering an environment where they may be exposed to pets, prophylaxis with fexofenadine or another non-sedating antihistamine may mitigate the worsening of allergic rhinitis symptoms induced by exposure to cat allergen.⁵² For long-term management of pet allergen-exacerbated asthma, the benefits of short-acting β -agonists and inhaled corticosteroids are already well established.

The benefits of leukotriene antagonists, intranasal steroids, and omalizumab in the treatment of cat allergy have been specifically evaluated. An early randomized double-blind, placebo-controlled, crossover study compared cat-allergic male patients treated with placebo or 40 mg of ICI 204,219 (zafirlukast). Each subject underwent provocation testing with cat allergen, with the treatment group showing a 10-fold increase in provocative dose concentration eliciting a 20% decrease in FEV₁ (PD₂₀) of allergen compared with the placebo group, indicating that zafirlukast can attenuate allergen-associated bronchoconstriction.⁵³ A double-blind placebo-controlled crossover study investigated the effectiveness of intranasal steroids in the treatment of cat allergy-associated upper and lower airway symptoms. Twelve cat-allergic subjects underwent 1 hour of cat exposure at baseline followed by 1 week of treatment with either intranasal triamcinolone acetonide or placebo. Nasal symptoms and lower respiratory symptoms were significantly decreased in the treatment group, but the study was not powered to determine effectiveness in reducing airway reactivity as assessed by change in FEV₁. There were no significant differences in nasal histamine or *N*- α -Tosyl L-arginine methyl ester (TAME) esterase levels, markers of nasal inflammation.⁵⁴

There are a small number of studies investigating the effectiveness of omalizumab in the treatment of cat allergen-exacerbated asthma. A *post hoc* pooled analysis of the original trials that supported approval of omalizumab in the United States revealed that compared with placebo, omalizumab treatment led to significantly lower asthma symptom scores, less rescue medication use, and improvement in FEV₁.⁵⁵ A randomized, double-blind, placebo-controlled study investigated individuals with moderate asthma who had suffered cat dander-induced asthma exacerbations; one group was assigned to omalizumab and the other to placebo. Challenge was performed with exposure to cat dander for up to an hour in an environmental chamber with spirometry and symptoms recorded. Omalizumab attenuated bronchoconstriction and led to improved respiratory and nasal-ocular symptoms.⁵⁶

Novel therapeutics for cat allergy may be on the horizon and have been looked at in animal studies; however, their safety and efficacy remain to be determined in human studies. One novel strategy used a chimeric human-cat fusion protein (Fc γ -Fel d 1 incorporating truncated human IgG Fc γ 1 and Fel d 1 as a new approach for possible allergen IT.⁵⁷ The Fc γ -Fel d 1 protein induced dose-dependent inhibition of Fel d 1-driven IgE-mediated histamine release from both cat-allergic donor basophils and sensitized human cord blood-derived mast cells. This inhibition was shown to be Syk- and ERK-mediated. Also, in Fc ϵ RI α -transgenic mice passively sensitized with human anti-cat IgE antibody and in Fel d 1-sensitized Balb/c mice, the chimeric protein also blocked *in vivo* allergen-specific immune responses. Another study found that injection of this chimeric protein in sensitized mice 6 hours before Fel d 1 challenge blocked both systemic events and skin reactivity to Fel d 1 challenge. In addition, mice given SCIT with this chimeric protein on 3 consecutive days showed inhibition of systemic, lung, and cutaneous reactivity to Fel d 1 two weeks later.⁵⁸

CONCLUSION

The prevalence of sensitization to cat and dog allergens and their role in exacerbation of asthma and allergic rhinitis in adults and children continue to pose a challenge to the allergist. Because of the ubiquity and "stickiness" of cat and dog allergen, allergen avoidance is difficult. Avoidance remains an important recommendation for reducing allergen burden and allergen-associated symptoms. SCIT has shown real benefit in cat-allergic patients with allergic asthma and allergic rhinoconjunctivitis. The data for dog are less robust. Sublingual and peptide IT remain experimental and there are lingering questions about cost, safety, and efficacy. With regard to pharmacotherapy in pet-allergic patients, a stepwise approach to asthma therapy

should follow established asthma management guidelines. In addition to short-acting β -agonists and inhaled corticosteroids, prophylactic antihistamines before anticipated pet exposure, the use of intranasal steroids, and the use of leukotriene antagonists may also be considered as adjunctive therapy in pet-allergic patients with asthma and/or allergic rhinitis. Omalizumab appears to have particular efficacy in pet allergen-induced asthma. Novel therapies such as Fc γ -Fel d 1 chimeric proteins still have to be evaluated in the human setting. With continuing implementation of current management strategies, careful monitoring of patient adherence and response to therapy, and ongoing research into novel therapies, allergists may be able to more effectively manage the pet-allergic patient.

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