

Inhalant Horse Allergens and Allergies: A Review of the Literature

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ABSTRACT A wealth of literature exists regarding common allergies to household pets such as cat or dog. Allergy to horse, however, is infrequently discussed in the medical literature despite significant sensitization rates among urban-dwelling subjects without direct exposure to horses. A literature search was conducted in PubMed and additional references were collected from surveying the references of the pulled articles. This review summarizes aspects of IgE-mediated horse allergy including the prevalence and mechanisms for sensitization, clinical presentation, molecular characterization of the major and minor horse allergens, and the role of allergen immunotherapy. There is currently only one horse immunotherapy study showing significant improvement in clinically sensitive patients. The 1997 World Health Organization Position Paper on Immunotherapy lists horse immunotherapy among the areas needing further clinical research. Inclusion of horse into the standard allergen panel for children and adults has been supported by several authors, although further identification and characterization of horse antigens is needed to provide the most efficacious extract. As clinicians, we need to be aware of the potential cross-reactivity among the common mammalian allergens and consider the possibility of known or occult exposure to horse as a possible source of symptom exacerbation in susceptible individuals.

INTRODUCTION

A wealth of literature exists regarding common allergies to household pets such as cat or dog. However, allergies to other common mammals, such as the horse, are infrequently discussed in the medical literature. Given that horses are no longer relied upon for transportation in the industrialized world, one might infer horse allergy to be insignificant. Except for a few feral populations, horses are now primarily used for recreational riding or showing. The military however continues to utilize horses in several capacities. Horses serve as a source of training for active duty preparing for challenges they may face in foreign territories where horses are used as a mode of transportation. As recently as 2001 horses were considered to be an essential component of a successful special force's mission in Afghanistan against the Taliban following the 9/11 terrorist attacks. Horses are still members of funeral processions honoring fallen heroes, and act as equine ambassadors, linking the civilian public to the military through day camps for children. Interestingly, data collected in Italy and other countries reveal significant sensitization among horse-related occupations as well as higher than expected allergic sensitization rates among urban-dwelling subjects without direct exposure to horses.¹ This review will summarize aspects of IgE-mediated horse allergy including the prevalence and mechanisms for sensitization, clinical presentation, molecular characterization of the major and minor horse allergens, and the role of allergen immunotherapy.

ALLERGEN SENSITIZATION

Individuals can be exposed to horse allergen not only in equestrian occupational environments but also through indirect contact during public transportation, work, or school. Sensitization rates in occupational settings (e.g., stables) varies between 3.6 and 16.5%, whereas individuals with respiratory allergy reported a sensitization rate of 5.38%.¹⁻⁴ Occupational exposure to horse hair is a risk factor for horse sensitization; sensitized individuals can develop asthma or impaired lung function secondary to exposure.² One study showed that 30% of patients referred for indoor pet dander allergy also reported clinical allergic symptoms to horses.⁵ In Spain, horse was positive in 12% of patients who were tested to a battery of aeroallergens. The authors suggested horse sensitization as a "hidden allergy" because of the lack of occupational or recreational exposure to horses.^{6,7} Often, sensitization results from unexpected exposure where horse products are used or incorporated (e.g., antique furniture, brushes, instrument bows). Passive transfer is felt to cause respiratory symptoms in individuals without direct horse exposure.⁸ Stray animal exposure is also identified as a risk factor for horse sensitization during travel or vacationing abroad.⁹

Egmar et al¹⁰ studied whether new mattresses, one-third of which were stuffed with horse hair, had horse allergen; horse allergen was not detected.¹⁰ This finding was contrary to the same investigators identifying horse allergen in a majority of used mattresses, in which horse allergen concentration increased over time despite no horse exposure. The authors concluded that allergens from horse had been deposited from customers and not simply transferred from the interior of the mattresses.¹⁰

Secondary to the concern of horse allergens eliciting asthmatic exacerbations in susceptible individuals, the organization of the Swedish National recommended that all horse stables be located approximately 500 m away from schools

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and daycares. Efforts to analyze this recommendation included one group which evaluated the presence of horse allergen in ambient air and settled dust. After obtaining multiple air and dust samples within 500 m of the stable, investigators concluded that significant quantities of horse allergen were limited to the animal location and not spread by environmental factors.¹¹ However, the 500 m mandate did not go away easily. Elfman et al¹² analyzed the dispersion of horse allergen around a stable and included wind speed, wind direction, and vegetation. Air sampling was performed during all seasons at a distance of 50 to 500 m around a stable containing 32 horses. Horse allergen levels were determined with enzyme-linked immunosorbent assay, and employees at nearby offices reported clinical symptoms. Allergen levels were approximately 316 U/m³ near the stable entrance, 40 U/m³ in the horse fields, and 16 U/m³ in the area which horses moved about during the day. At 500 m downwind from the stable, 2 to 4 U/m³ of horse allergen was detected. Interestingly, despite moving the office, employees did not report a change in symptoms. The study also concluded that, much like cat and dog allergens, horse allergen on the clothes of an individual who had direct contact with horses was predominantly responsible for allergens present in non-horse environments.¹² Further research by Emenius et al¹³ concluded that allergens dispersed from horses decline rapidly outdoors and are barely found indoors. Horse allergen levels were high near stables but dispersed poorly through air as evident by low levels found away from the source.¹³ Therefore, exposure to nonindoor pet allergens is not limited to people who have occupational exposure to animals, but is an everyday occurrence secondary to passive transfer from products made from horse hair as well as from horse allergen carried by individuals in direct contact with horses.

Finally, sensitization can vary based on climate, geography, and level of exposure. Surprisingly, individuals riding in the humid coastal region of Sweden had a lower rate of horse sensitization compared to the rate in a much colder city north of the Arctic Circle. This finding is intriguing, suggesting that high allergen exposure can result in tolerance. Also, while girls rode more often than boys, boys had higher rates of sensitization.¹⁴

CLINICAL MANIFESTATIONS

The clinical presentation of horse allergy is variable and can affect both children and adults (Table I). Horse allergy can manifest as allergic rhinitis, conjunctivitis, asthma, anaphylaxis, and food allergy.¹⁵ Roberts and Lack⁷ published a series of case reports suggesting that horse allergy can contribute to persistent asthma. Horse allergy cases also occur in heavily urbanized environments.⁷ Several cases also link respiratory distress and angioedema in children who have positive horse dander allergy skin tests and recall specific horse exposure.

Allergic Rhinitis

A cross-sectional Swedish study identified horse sensitization to be a significant risk factor for rhinitis in 7- to 8-year-old children.¹⁵ Thirty-seven percent of patients presenting with rhinitis were found to be positive to horse on skin prick test (SPT), more common than birch, timothy, mugwort, house dust mite, or mold sensitization.¹⁵ The majority of cases that report horse exposure as a cause of asthma exacerbation also report concurrent rhinitis symptoms.^{7,8}

Asthma

Since Salter's original description of "Animal Emanations" causing asthma in 1860, several reports of horse-induced respiratory symptoms have been described. Huwyler and Wuthrich¹⁶ presented an allergic asthmatic patient with sensitivity to horse who developed an asthma attack upon initial presentation to fallow deer.¹⁶ Suspecting cross-reactivity between horse and fallow deer, researchers performed SPT in 404 atopic patients: 14 were positive to both horse and fallow deer, 24 were positive to horse, but none of the patients reacted to fallow deer only, thus suggesting cross-reactivity to horse IgE.¹⁶ One child experienced late-phase asthma symptoms after only indirect exposure to horse allergen.⁷ In a study in New Zealand, Gallagher et al¹⁷ found evidence that working with horses is a risk factor for organic dust toxic syndrome, farmer's lung, and chronic bronchitis.¹⁷ The study surveyed 383 horse trainers and 249 vegetable farmers. Horse trainers, compared to vegetable growers, were

TABLE I. Clinical Manifestations of Horse Allergy

Reference Number	Age/Sex	Symptoms	Suspected Allergen
7	8/M	Angioedema, Respiratory Distress	HD
7	9/M	Uncontrolled Asthma	HD
7	5/M	Wheeze, Sneeze	HD
8	17/F	Rhinoconjunctivitis, Bronchial Asthma	HD
8	33/M	Rhinitis, Bronchial Asthma	HD
18	6/F	Anaphylaxis	HE
19	42/F	Anaphylaxis	HD
20	35/F	Urticaria	HS
26	53/F	Conjunctivitis, Dyspnea, Generalized Erythema, Pruritis	HE, MM
27	30/F	Urticaria, Angioedema, Asthma	MM
42	27/F	Rhinitis, Cough, Wheeze, Dyspnea	HE, HSA

HE, horse epithelium; HS, horse saliva; MM, mare's milk; HD, horse dander; HSA, horse serum albumin.

found to have a higher rate of chronic bronchitis (odds ratio = 6.8, 95% confidence interval 2.2–21.4) and organic dust toxic syndrome/farmer's lung (odds ratio = 3.5, 95% confidence interval 1.8–6.8).¹⁷

Contact Urticaria and Anaphylaxis

Gawlik and Pitsch¹⁸ reported an atopic girl who experienced sneezing, angioedema, dyspnea, wheezing, and hypotension while sleigh riding. SPT was positive to horse epithelium, and in vivo testing demonstrated horse dander IgE greater than 100 kU/L. Repeat exposure to horse allergen resulted in a drop in forced expiratory volume of 25%.¹⁸ Guida et al¹⁹ reported a case of anaphylaxis in a 42-year-old woman who, after being bit, developed large local erythema and edema followed by generalized urticaria, rhinitis, and wheezing.

A 35-year-old veterinary employee experienced an episode of sneezing, rhinitis, and urticaria following a period of postoperative care for a horse, which included intense contact with horse saliva.²⁰ SPT and specific serum antibodies against horse saliva were positive; however, these tests were negative in control subjects, implying a type I IgE-mediated hypersensitivity reaction in the employee.

Food Allergy

Although allergic reactions to mare's milk have been described, the incidence of cow's milk allergy has prompted the search for alternative milk sources. Research by Godovac-Zimmerman et al²¹ revealed different amino acid sequences of mare's milk proteins compared to cow's milk, implying distinct IgE binding. Furthermore, the composition of mare's milk is felt to be closer to human milk than cow's milk.^{21,22} Businco et al²³ evaluated alternatives for children with severe IgE-mediated cow's milk allergy. Double-blind-placebo-controlled food challenges (DBPCFC) showed that mare's milk could safely be substituted for cow's milk in 96% of children. Fifty percent who failed the DBPCFC had positive SPT to mare's milk.²³ Restani et al²⁴ found weak cross-reactivity between equine and cow milk. Foekel et al²⁵ performed a DBPCFC in 23 patients with atopic dermatitis.²⁵ A subset of patients avoiding mare's milk reported reduction of pruritis during the 16-week trial. A 53-year-old female with asthma and rhinitis to horse epithelium developed pruritis, generalized erythema, conjunctivitis, and dyspnea within 1 hour after drinking mare's milk.²⁶ The patient demonstrated positive in vitro and in vivo testing for horse-specific IgE as well as basophil activation to both mare's milk and horse epithelium.²⁶ A similar case of mare's milk allergy was described in an atopic 35-year-old female who initiated horse riding therapy to restore equilibrium after cranial trauma.²⁷ During horse riding therapy, her asthma clinically deteriorated and she consumed mare's milk assuming it would strengthen her. Minutes after ingestion, she developed oral pruritis, followed by generalized urticaria, angioedema, and an asthma exacerbation. SPT and radioallergosorbent

tests (RAST) were both positive to mare's milk and horse dander. Immunoblot testing showed IgE binding to two horse proteins—30 and 69 kDa. Fanta and Ebner²⁷ concluded that cross-reacting epitopes in mare's milk and horse dander resulted in positive inhibition studies, and thus sensitization to horse dander can lead to mare's milk allergy.

HORSE ALLERGEN

Since studies in the early 1900s revealed mixed clinical reactions to horse hair, albumin, dandruff, and horse serum, horse allergens are now classified as either major or minor allergens. A major allergenic protein is defined as a protein recognized by more than 50% of allergic individuals while minor allergens are recognized in less than 50% of individuals. Dandeu et al²⁸ used a salting process combined with chromatography to identify a 20 kDa protein, which was designated *Equus caballus* allergen 1 (*Equ c 1*).²⁸ This finding was commensurate with the previous investigators demonstrating IgE against *Equ c 1* in 76% of horse allergic subject's sera.^{28–31} Using cDNA sequencing, Gregoire et al³² described *Equ c 1* to be a glycoprotein of the lipocalin superfamily. The lipocalin superfamily contains several allergens such as the major mouse urinary protein (*Mus m 1*), rat alpha-2microglobulin (*Rat n 1*), dog (*Can f 1*, *Can f 2*), rabbit (*Ory c 1*), and the bovine dander allergen (*Bos d 2*) among others. *Equ c 1* concentration was greatest in horse saliva but was also found in dander and urine.³² Thirty-four antigenic determinants have been identified through crystallographic and immunochemical studies of recombinant *Equ c 1*, delineating regions of the protein surface responsible for IgE binding in allergic patients.³³

Three other proteins, *Equ c 2*, *Equ c 3*, *Equ c 4*, were also isolated and classified as minor antigens. Bulone et al³⁴ identified and characterized two distinct nonglycosylated lipocalins within horse dander and named these proteins *Equ c 2.0101* and *Equ c 2.0102*. Further research by Bulone et al³⁵ concluded that both the glycan and protein moieties, rather than the glycan moiety alone, are responsible for eliciting allergic responses. Goubran Botros et al³⁶ characterized two antigens that were subsequently identified as the minor allergens, *Equ c 2* and *Equ c 3*, with 33% and 23% binding respectively.³⁶ As opposed to horse dander and saliva, which were used as a source to purify *Equ c 1*, horse sweat contains high concentrations of *Equ c 2* and *Equ c 3*. Goubran Botros et al³⁷ also reclassified *Equ c 2.0101* and *Equ c 2.0102* as *Equ c 2* and *Equ c 4*, respectively. *Equ c 3* was identified as horse albumin and has an IgE reactivity near 20%.³⁸ *Equ c 5* was also identified but has unknown clinical significance.^{36,37}

Given popular belief regarding "nonallergenic breeds," Felix et al³⁹ compared different breeds for their relative presence of horse allergens through the use of immunoblotting. The study revealed qualitative and quantitative interbreed and within-breed variation, but no breed-specific allergens were identified. Dander from all breeds investigated contained major and minor allergens.³⁹

Using rabbit antiserum and rocket immunoelectrophoresis, Guinnepain et al⁴⁰ assessed the presence of *Equ c 1* in samples of dust from an equestrian's clothing, vehicle, sofa, and living room floor. Samples contained 200, 800, and 400 µg *Equ c 1* per gram of dust in clothing, car, and sofa dust, respectively. Guinnepain et al⁴⁰ concluded that occult exposure to sensitizing quantities of horse allergen can occur and potentially induce symptoms in genetically susceptible individuals.

CROSS-REACTIVITY BETWEEN HORSE AND OTHER MAMMALS

Initial allergic sensitization to horse has not only occurred through passive transfer (e.g., from clothing) but can occur via cross-reactivity through lipocalins and serum albumin. Spitzauer et al⁴¹ sought to identify the significance and degree of IgE cross-reactivity amongst various albumins in animal-allergic patients. Two-hundred patients were evaluated with 60 (30%) displaying IgE reactivity to various albumins. All patients with positive SPT to horse serum albumin also demonstrated positive reactions to at least one other animal albumin (e.g., dog, cat, pig, cattle, guinea pig, or rabbit), demonstrating that most patients with animal allergy have cross-reactivity.⁴¹ Cabanas et al³⁸ observed that cross-reactivity among patients sensitized to cats, dogs, and horses was secondary to related albumin epitopes in one-third of patients. They also noted that 50% of specific IgE that cross-reacted with cat, dog, and horse was directed against allergens other than albumin.³⁸

Other investigators also concluded that cross-reactivity between animals occurred via serum albumin. A case report in 2010 described respiratory allergy induced by serum albumin to several furry animals, emphasizing the cross-reacting ability of albumin.⁴² Vicente-Serrano et al⁴³ proposed that first contact with serum albumin may even occur through cow's milk consumption, accounting for sensitization in individuals who have not had direct contact with animals.

Regarding the major horse allergen, *Equ c 1*, Saarelainen et al⁴⁴ identified IgE cross-reactivity between *Equ c 1* and the major mouse allergen *Mus m 1*. It has also been inferred that other animal lipocalins found in cow, dog, guinea pig, rabbit, rodent, and cat allergen may also exhibit cross-reactivity to horse.⁴

DIAGNOSTIC TESTING

In 1977, Leegaard and Roth⁴⁵ evaluated the reliability of SPT and RAST in the diagnosis of horse allergy using horse epithelium. Forty patients with a strong history of horse allergy and 43 patients without a history of horse sensitivity were tested. The results demonstrated a 91% agreement between the history and SPT, 89% for the history and RAST, and 90% for RAST and SPT.⁴⁵ However, Berrens and Koers⁴⁶ observed that a positive SPT to horse dander extract did not correlate with clinical history. Therefore, caution should be exercised when interpreting a positive SPT. One hypothesis for the pos-

itive horse SPT with a negative clinical history was the potential poor quality of the allergen extract.⁴⁶

Liccardi et al¹ found no difference between SPT and serum horse dander IgE for patients with either direct contact with horses, indirect exposure, or no apparent contact with horses. On the other hand, specific IgE antibodies against Re 205, a horse serum protein, were significantly higher in patients with direct contact vs. those with either indirect exposure or no apparent contact.¹

Frequent horse exposure is a risk factor for developing a positive SPT. Tutluoglu et al² performed a cross-sectional study evaluating 125 atopic grooms compared with 92 control subjects. SPT revealed significantly more sensitization in grooms (12.8% vs. 4.3%, $p = 0.0035$) as well as asthma, allergic rhinitis, conjunctivitis, and skin disease (14.4% vs. 5.4%, $p = 0.043$; 42.4% vs. 18.4%, $p = 0.0002$; 35.2% vs. 15.2%, $p = 0.001$; and 32.8% vs. 13%, $p = 0.003$, respectively). Multivariate analysis also indicated that occupational exposure to horse was associated with lung impairment ($p < 0.001$).²

When a sample of mixed allergic and nonallergic asthmatics was skin tested to variety of animals and compared to healthy volunteers, 22% were found to have positive intradermal skin tests as opposed to only 10% of healthy volunteers. In this study, horse was found to represent the highest percentage of positive skin tests among animals.⁹

Because of the potential for minor allergens such as albumin to elicit false-positive skin tests, Franke et al⁴⁷ recommended using either horse dander, horse hair skin scrapings, or horse hair as raw materials for skin-test extract production. Fjeldsgaard and Paulsen⁴⁸ compared the IgE-binding antigens in horse dander and a mixture of horse hair and skin scrapings. Although both extracts contained the major allergens, each also contained unique minor allergen. Therefore, multiple skin testing extracts from various sources may be required in patients with a high clinical suspicion for horse allergy.⁴⁸

EFFICACY OF HORSE IMMUNOTHERAPY

In 2002, Fernandez-Tavora et al⁶ published the only clinical study regarding horse dander immunotherapy safety and efficacy.⁶ Twenty-four horse-allergic patients, 16 of whom had asthma, underwent immunotherapy with extracts containing *Equ c 1*, *Equ c 2*, and *Equ c 3*. Cluster immunotherapy was performed in 21 patients, whereas 3 underwent conventional immunotherapy. Two (0.33%) systemic reactions and 3 (0.5%) large local reactions occurred in 4 subjects during the induction phase. Sensitivity to horse dander as assessed by deliberate exposure with horse riding decreased significantly on maintenance dosing (0.8 mL of 80,000 Alutard SQ-units). Conjunctivitis was reduced in all patients, rhinitis in 93%, cutaneous symptoms in 87%, and asthma symptoms in 90% of those studied. Ninety-five percent of patients were highly satisfied with the therapy. Long-term follow-up found immunologic cure in 29% of participants after 2 to 5 years of treatment.⁶

Although this study demonstrated effectiveness, characteristics of patients and the composition of the extracts vary.

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For instance, the protein content in horse dander can be two to ten times that of horse hair and skin scrapings.^{47,48} On the other hand, albumin is found in large amounts in epithelial extracts but is barely detectable in the horse dander extract.⁴⁷ Current horse extract may contain varying amounts of immunologic allergens and is not standardized. Based on these differences, Fjeldsgaard and Paulsen⁴⁸ concluded that allergen extracts used for diagnosis and immunotherapy should be prepared from both horse dander and hair and skin scrapings. Franke et al⁴⁷ investigated five horse epithelial allergen extracts from various qualities of raw material by several immunochemical and biochemical methods. The allergen present in each commercially available extract was variable and depended on the origin of the raw material.⁴⁷

With the interest in peptide-based immunotherapy, Immonen et al⁴⁹ mapped the T-cell determinants of *Equ c 1* to identify peptides that may be useful in allergen specific immunotherapy. They concluded that the 18-mer peptide p 143-160 from the immunodominant region of *Equ c 1* is a potential candidate for the peptide-based immunotherapy of horse-sensitized subjects with enzyme-linked immunosorbent assay.⁴⁹

CONCLUSIONS

A variety of expected and unexpected clinical reactions has been reported after exposure to horse allergen. The interesting aspect of horse allergy is that IgE sensitization occurs despite the absence of reported horse exposure. This may be occurring as a result of passive transfer, false-positive skin testing, or cross-reactivity. Although there is a definite risk for individuals who directly interact with horses for recreation, professional, and military purposes, the degree of prevalence in individuals not directly exposed to horses is surprising. Some researches observe that horse allergen is as tenacious and problematic as cat allergen, given its potential for passive transfer.^{6,7} Fortunately, despite the frequency of sensitization, reported cases that result in angioedema or anaphylaxis is limited.

Numerous allergens have been characterized, with at least 16 allergens isolated to date. The major horse allergen *Equ c 1* as well as *Equ c 2* are lipocalins, whereas *Equ c 3* is horse albumin. *Equ c 4* and *Equ c 5* have yet to be fully characterized but are likely minor allergens. Despite one horse immunotherapy study showing significant improvement in clinically sensitive patients, the 1997 World Health Organization Position Paper on Immunotherapy lists horse immunotherapy among the areas needing further clinical research. Inclusion of horse into the standard allergen panel for children and adults has been supported by several authors.^{50,51}

Additional knowledge gaps include further identification and characterization of all the horse antigens to provide the most efficacious extract. As clinicians, we need to be aware of the potential cross-reactivity among the common mammalian allergens and consider the possibility of known or occult exposure to horse as a possible source of symptom exacerbation in susceptible individuals.

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