

Diagnostic testing of dogs for food hypersensitivity

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Summary: Thirteen food-allergic dogs were studied to evaluate the efficacy of feeding a commercially available egg and rice diet, intradermal skin testing, and serologic testing by ELISA for diagnosing and/or characterizing food hypersensitivity. Feeding of a home-cooked whole lamb meat and rice diet for 3 weeks, followed by challenge with each dog's regular diet, served as the standard for diagnosing food hypersensitivity. Each dog underwent provocative testing with 6 individual ingredients to determine as many of its dietary allergens as possible. Prior to skin testing and serologic testing by ELISA, most dogs had been recently exposed to the offending diet and subsequently manifested clinical signs of allergy. All dogs that tolerated the aforementioned commercial diet were exposed to it for at least 7 weeks; 84.6% of food-hypersensitive dogs ate the commercial diet with impunity. Of the 2 reactors to the commercial diet, only 1 became pruritic in response to provocation testing with chicken eggs. Low sensitivity and high specificity were found for skin testing and the ELISA, indicating a lack of true-and false-positive reactions. Neither the positive nor negative predictive values adequately predicted positive and negative reactions, respectively, for either test. On the basis of these results, the commercial diet, skin testing, and anti-IgE ELISA cannot replace an owner prepared food elimination diet for food hypersensitivity testing in dogs.

In dogs, food hypersensitivity (allergy) is typically a nonseasonal, pruritic dermatitis that is occasionally accompanied by signs of gastrointestinal tract dysfunction.^{1,2} Age, breed, gender, or familial predilection has not been reported.^{3,4} Although food allergy is seen in only 1% of cases in general practice, 3 it accounts for 23 to 62% of the

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nonseasonal allergic dermatoses seen by veterinary dermatologists.^{1,5} Pruritus can involve any body part, and seborrhea, otitis, and pyoderma are frequent sequelae.^{1,2} Corticosteroid administration usually is of minimal benefit,⁶ and most dogs have been eating the offending diet for at least 2 years before clinical signs of allergy appear.⁷

An adverse reaction to dietary ingredients is classified into 2 categories: food hypersensitivity and food intolerance. Hypersensitivity is an immunologic reaction to ingested food, whereas intolerance has a nonimmunologic basis.^{5,8,9} In people, hypersensitivity has been further classified into an immediate reaction (typically type I) and a delayed reaction for which the exact immunologic mechanism has not been determined.⁹ Although all 4 types of hypersensitivity are probably represented in human food allergies,¹⁰ only IgE has been proven to be of etiologic relevance.¹¹ In dogs, type-I and type-III hypersensitivity have been proposed,^{7,12,13} but an immunologic mechanism has not been proven.⁵ At best, adverse reactions to food in dogs can be classified into immediate (minutes to hours) or delayed (hours to days) reaction.^{1,2} Despite the inability to prove an immunologic pathogenesis, the term "food hypersensitivity (allergy)" has been traditionally used to describe all adverse reactions to food in dogs, including reactions that may truly be food intolerance.

The standard method of diagnosing food hypersensitivity in dogs involves 3 steps: elimination, challenge, and provocation. An elimination diet typically is fed for at least 3 weeks, during which the dog is exclusively fed a protein and carbohydrate source to which it has never been exposed.^{2,7} The most widely accepted food-elimination diet consists of home-cooked whole lamb meat and long-grain rice; ground lamb meat is potentially mixed or contaminated with ground beef and is not recommended. Secondary seborrhea, otitis and pyoderma should be appropriately treated and resolved by the end of the third week of the diet.² Observation of at least 50% improvement in pruritus is necessary to make a tentative diagnosis of food allergy.⁶ A definitive diagnosis of food hypersensitivity is made

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only if the dog's former diet is subsequently fed as a challenge, at which time pruritus will return within 4 hours to 7 days.^{2,3} Reinstating the elimination diet for 5 to 7 days resolves the pruritus induced by challenge.¹³ Finally, provocation involves introducing single dietary ingredients 1 week at a time until as many positive reactions as possible can be documented.²

Diagnosing food allergy in dogs by elimination, challenge, and provocation offers the advantage of detecting allergic and intolerant reactions and, for this reason, remains the traditionally used diagnostic test. However, completing the 3-part regimen can be difficult. Home-cooked diets can be expensive and time consuming to formulate. Many dogs will suffer vomiting, diarrhea, or constipation^{4,5} or may dislike the home-cooked diet and obtain food from other sources. Also, owners may dislike the strictness of the diet or be reluctant to pursue challenge and provocation once pruritus is eliminated. In the hopes of minimizing problems associated with home-cooked diets, commercially available lamb and rice canned food and egg and rice kibble have been manufactured for use as elimination diets. In one study,⁴ 54% of food-allergic dogs became pruritic when switched from home-cooked lamb and rice to the canned commercial diet. In view of the reported poor response to the latter, one facet of our study was to evaluate the efficacy of the dry product as a food elimination diet.

Intradermal skin testing and serologic testing are commercially available for the diagnosis and/or characterization of food hypersensitivity in dogs. Skin testing mainly detects IgE bound to mast cells in the skin, whereas a newly available radioallergosorbent test (RAST)^b and assay ELISA^c are designed to detect IgE in serum (type-I hypersensitivity).¹⁴ The obvious advantages of these tests over an elimination diet include faster results, ease of testing, and the ability to determine specific food allergens, thus eliminating the need for provocation. Disadvantages of using skin testing or serologic testing are the expense and lack of proven efficacy for either testing mode. Also, neither test is able to detect food intolerant or type-II, -III, or -IV food hypersensitive dogs. The efficacy of skin testing is unclear, because most of the work was done in the 1930s when positive¹⁵ and negative¹⁶⁻¹⁸ opinions were expressed concerning its diagnostic value. Recent information indicates that skin testing may be of limited value, although specific studies were not cited.² The efficacy of serologic testing for diagnosing food hypersensitivity has also been questioned. One recent study indicated that testing of serum from nonfood-allergic dogs and other animal species yielded many positive reactions, using the RAST.¹⁹ Also, serum obtained from 20 food-allergic dogs for evaluation by use of the RAST had more positive reactions than should have been expected, on the basis of correlation with clinical signs of allergy attributable to

dietary provocation.^d Because of the confusion surrounding the use of skin testing and serologic testing for diagnosing or characterizing food allergy, one of the objectives of the study reported here was to compare results of intradermal skin testing and 1 serologic test (ELISA) with dietary provocation test results from dogs with food hypersensitivity.

Materials and Methods

Dogs—Thirteen dogs of either gender and various ages, breeds, and body weights that had history and clinical signs compatible with food-allergic dermatitis were chosen. Signs of food-allergic dermatitis included all or part of the following: pruritus (typically but not exclusively corticosteroid nonresponsive), erythema, angioedema/urticaria, papular eruptions, otitis externa, seborrhea, recurrent pyoderma, vomiting, or diarrhea. Dogs that manifested food hypersensitivity by recurrent pyoderma or gastrointestinal tract dysfunction alone were excluded from the study.

Experimental protocol—All dogs were fed the elimination diet (consisting of only boiled whole lamb meat and long-grain rice) for 3 weeks, during which at least 50% resolution of pruritus was evident. Pruritus returned within 5 days after challenge by feeding the dog its former diet. Secondary pyoderma, seborrhea, and otitis externa involving infective agents were appropriately treated and resolved before the third week of the elimination diet or were treated beyond elimination and challenge. All dogs with residual pruritus had clinical signs of allergy and intradermal skin testing results consistent with either atopy and/or flea bite allergy. After exacerbation of pruritus attributable to dietary challenge, each dog was again fed cooked lamb and rice until signs related to challenge abated. Each dog was then examined by an investigator, and the owner was questioned to ensure that signs of food-allergic dermatitis had been alleviated. Residual pruritus was eliminated by strict environmental and animal flea control if flea bite allergy concurrently existed, or by oral administration of either antihistamines^e or alternate-day anti-inflammatory doses of corticosteroids^f if atopy was apparent. Prior to consuming the food elimination diet, dogs with concurrent atopy that were successfully maintained on alternate-day oral corticosteroid or antihistamine administration were refractory to similar

^dMcDougal BJ. Correlation of results of the radioallergosorbent test and provocative testing in 20 dogs with food allergy, in *Proceedings* (abstr). 3rd Annu Meet Am Acad Vet Dermatol Am Coll Vet Dermatol 1987; 42.

^eHydroxyzine HCl, Pharmafair Inc. Hauppauge, NY.

^fPrednisolone, Roxane Laboratories Inc, Columbus, Ohio.

^dMcDougal BJ. Correlation of results of the radioallergosorbent test and provocative testing in 20 dogs with food allergy, in *Proceedings* (abstr). 3rd Annu Meet Am Acad Vet Dermatol Am Coll Vet Dermatol 1987; 42.

^eHydroxyzine HCl, Pharmafair Inc. Hauppauge, NY.

^fPrednisolone, Roxane Laboratories Inc, Columbus, Ohio.

or higher orally administered doses of corticosteroids or antihistamines.

If all criteria were satisfied, each dog was fed the commercial dry diet, as directed by the manufacturer, for 7 days. A daily log was kept by the owner to assess and grade clinical signs of food-allergic dermatitis over the 7-day period. After 7 days, each dog was reevaluated by an investigator, and the efficacy of the dry product as an elimination diet was calculated. Each dog was then individually fed the following provocation test ingredients 1 week at a time: beef, cows milk, chicken, chicken eggs, wheat, and soybean. Beef and cow's milk were chosen for provocation testing because of their frequent mention in the literature as food allergens^{2,3,5,13} and presence in many commercial dog foods. Next to beef, chicken is the most commonly used meat protein source in commercial dog foods. Because chicken eggs are the protein source in the dry commercial diet, it was necessary to provocation test all dogs by feeding them hardboiled eggs. Finally, wheat and soy were arbitrarily chosen to represent other ingredients commonly found in commercial dog foods. Many other potential allergens were not tested owing to impracticality when using client-owned dogs in a study.

To ensure adequate exposure to the commercial dry diet, all provocation test ingredients were added to the dry diet for dogs that failed to manifest pruritus when eating the dry diet alone. For those that became pruritic after eating the dry diet alone, provocation test ingredients were added to the home-cooked lamb and rice. For every dog that had pruritic skin signs in response to a provocation test ingredient, the owner was required to stop, the ingredient and allow the pruritus to abate before continuing the provocation test.

Evaluation of testing methods—To evaluate the intradermal skin testing and ELISA portions of this study, as many dogs as possible that were diagnosed as food hypersensitive and being fed cooked lamb and rice were challenged with their former allergy-inducing diet (10 of 13; 77%). If adverse food reactions in dogs involve reaginic antibodies, recent challenge would presumably increase serum or mast cell-bound IgE. Prior to testing, all dogs were withdrawn from parenterally administered corticosteroids for at least 6 months and from orally administered corticosteroids for at least 4 weeks. Within 1 week from the time when signs of allergic dermatitis returned, each participant underwent standard intradermal skin testing^{2,14} for 25 inhalant allergens, 2 dilutions of flea antigen, and 17 foods⁵ (beef, lamb, pork, chicken, turkey, fish, whole chicken egg, cow's milk, barley, carrot, corn, pea, potato, rice, soybean, wheat, and yeast). Most of the food allergens available from the manufacturer were included in the 17 allergens chosen.

Table 1—Offending allergens from dietary provocation and of skin testing and ELISA in food-allergic dogs. **Previously challenged. Did not undergo provocation testing with milk, wheat, soybean. Did not undergo provocation testing with milk.**

The standard 1,000 protein nitrogen units/ml dilution² was used for food and most inhalant allergens, whereas the flea antigen was tested at 1:1,000 and 1:10,000 dilutions. All dogs, regardless of temperament, were sedated (0.25 mg of xylazine/kg of body weight and 0.01 mg of atropine sulfate/kg,) to minimize the detrimental

Dog No.	Offending food allergens	Positive skin test results	Positive ELISA results
1	Beef	None	None
2	Milk, wheat	None	Wheat, corn, soybean
3	Beef, wheat	Wheat	Milk, yeast
4	Beef, milk, soybean, thickener, whole egg	Pork, soybean, wheat	None
5	Beef, soybean	Soybean	None
6*	Beef, milk, Beef	None, Barley, carrot, corn, potato, wheat	Milk, Corn, soybean
3 r	Beef, chicken, commercial dry diet	Corn	Beef, fish, whole egg, milk, yeast, wheat, corn, soybean, American cheese
9	Beef, milk, wheat	None	Milk, corn, soybean
10	Beef	None	None
11*	Beef, chicken	None	Milk, yeast
12	Beef, milk, wheat, soybean, whole egg, commercial dry diet	None	None
13	Beef	None	Soybean

*Previously challenged. †Did not undergo provocation testing effects of stress on skin test reactions without sedation decreasing wheal size^{h,i}. At 10 and 20 minutes after the last injection, all skin tests were read by 2 of the authors (JGJ and KJS). None of the intradermal skin test results were read at 24 to 36 hours. Results for each allergen had to be read as positive by both authors to be considered a relevant reaction (Table 1). A positive skin test result was defined as both of the following: palpably firm, erythematous wheal that felt at least as large as the average diameter of wheals for control solutions— 0.9% saline solution and 1:100,000 histamine phosphate (subjective evaluation); and millimeter diameter of the wheal measures at least as large as

^hMoriello KA, Eicker SW. The influence of sedatives and anesthetics on intradermal skin test reactions in dogs, is *Proceedings* (abstr). 5th Annu Meet Am Acad Vet Dermatol Am Coll Vet Dermatol 1989:33.

Beale KM, Kunkle GA. The effects of xylazine, ketamine, valium, acepromazine and oxymorphone sedation on the intradermal skin test in *Proceedings* (abstr). 5th Annu Meet Am Acad Vet Dermatol Am Coll Vet Dermatol 1989; 34-35.

⁴McDougal BJ. Correlation of results of the radioallergosorbent test and provocative testing in 20 dogs with food allergy, in *Proceedings* (abstr). 3rd Annu Meet Am Acad Vet Dermatol Am Coll Vet Dermatol 1987; 42.

⁵Hydroxyzine HCl, Pharmafair Inc. Hauppauge, NY.

¹Prednisolone, Roxane Laboratories Inc, Columbus, Ohio.

Table 2—Food hypersensitivity intradermal skin testing results Table 3—Food hypersensitivity ELISA

Value	Recently challenged (within 1 week)	Previously challenged (2 months to 2 years)	Total
Sensitivity	3/24(12.5)	0/5(0.0)	3/29(10.3)
Specificity	34/35(97.1)	9/10(90)	43/45(95.6)
Positive predictive value	3/4(75.0)	0/1(0.0)	3/5(60.0)
Negative predictive value	34/55(61.8)	9/14(64.3)	43/69(62.31)
Data are expressed as No. positive/No. tested, with percentage in parentheses.			

Value	Recently challenged (within 1 week)	Previously challenged 12 months to 2 years)	Total
Sensitivity	2/24(8.3)	2/5(40.0)	4/29(13.8)
Specificity	31/35(88.6)	8/10(80.0)	39/45(86.6)
Positive predictive value	2/6(33.3)	2/4(50.0)	4/10(40.0)
Negative predictive value	31/53(58.5)	8/11(72.7)	39/64(60.9)
Data are expressed as No. positive/No. tested, with percentage in parentheses.			

the average diameter of wheals for the control solutions (objective evaluation). Acting as controls, B clinically normal or flea-bite allergic and/or inhalant-allergic dogs in which pruritus failed to decrease while consuming home-cooked lamb and rice food elimination diets underwent similar intradermal skin testing as did the food-allergic patients.

At the time of intradermal skin testing, serum obtained from food-hypersensitive and control dogs was immediately frozen at -70 C and analyzed for IgE against 11 foods (beef, chicken, pork, fish, whole chicken egg, cow's milk, yeast, wheat, corn, soybean, and American cheese), using an ELISA (Table 1). All 11 foods were those included in the manufacturer's standard food panel. All ingredients chosen for provocation diet testing were components of the intradermal skin test and ELISA. Lamb and rice were only included in the intradermal skin test because the standard ELISA profile does not contain lamb or rice.

Intradermal skin testing and the ELISA were performed in similar manner on dogs that the owners refused to challenge by feeding the offending diet (3 of 13;23%). For these 3 dogs, time from exposure to their allergic diets ranged from 2 months to 2 years.

Analysis of data—Specificity, sensitivity, and positive and negative predictive values of skin testing and the ELISA were calculated, using the provocation diet test results from both populations of food allergic dogs as the standards. Reactions of skin testing and the ELISA to foods not used in dietary provocation were not included in the calculations. Repeatability of the ELISA was determined by randomly splitting 8 serum samples from the population of food-allergic dogs and submitting the split samples under other names.

Results

Of 13 dogs diagnosed as food allergic when fed a home-cooked lamb and rice diet, 11 (34.6%) tolerated the commercial rice diet without manifesting clinical signs of food allergy (Table I). All 11 dogs ate the diet for a minimum of 7 weeks. None of the dogs had gastrointestinal tract dysfunctions. Although all dogs ate the dry diet, 5 of 13 owners reported palatability problems.

Sensitivity, specificity, and positive and negative predictive values were determined for intradermal skin testing and the ELISA (Tables 2 and 3). Sensitivity indicates the ability of a test to detect all food-allergic animals (or to exclude false-negative reactions) and specificity indicates the ability to identify only diseased animals (or to exclude false-positive reactions). The positive predictive value is the probability that a positive test result will detect a diseased animal, whereas the negative predictive value determines the chance that a negative test result will appear in a healthy animal.

The 8 split serum samples were used to calculate repeatability of the ELISA. Because 11 foods were used in each assay, a total of 88 test pairs was generated. Discordance and concordance were based strictly on whether the reaction was positive or negative, not on absolute numbers. A value greater than or equal to 100 ELISA (EA) units is considered a positive reaction by the manufacturer of the ELISA^C, whereas a value <100 EA units is interpreted as a negative reaction. The repeatability (concordance) of the ELISA was determined to be 93.2% (82 of 88).

Discussion

Even though it will not diagnose all cases of food hypersensitivity in dogs, use of the commercial dry diet as a food elimination diet adds flexibility to the diagnostic armamentarium for food hypersensitivity owing to its 84.6% efficacy. Only 1 of the 2 reactors to the dry diet had pruritus when provocation tested by feeding chicken eggs. Interestingly, 1 dog with reaction to eggs in response to provocation ate the dry diet with impunity, whereas another dog with severe pruritus while consuming the dry diet was not allergic to rice or hard-boiled eggs in response to dietary provocation. This collectively indicates that the processing of food may either partially or totally alter antigenicity, at least of eggs.^{2,8,20} or that the concentration of antigen may have an important role. Despite good results, the commercial dry diet should not replace home-cooked diets as a food elimination diet. The determined 84.6% efficacy is not sufficient when using an elimination diet as the single diagnostic criterion. Only diets nearly 100% effective can be trusted when diagnosing food allergy. Also, poor palatability was a complaint by 5 of the 13 owners. Despite these drawbacks, the dry diet has a place

in the following situations: when home-cooked diets are cost prohibitive in large- or giant-breed dogs; when client compliance with home-cooked diets is poor; in dogs that cannot tolerate home-cooked diets (gastrointestinal tract dysfunction or refusal to eat); and as a potential maintenance diet if the client refuses to challenge the dog or if the dog has multiple allergies.

Results of this study also document the failure of intradermal skin testing and the ELISA to accurately predict and/or characterize food hypersensitivity in dogs. The 10.3% sensitivity value for skin testing indicates its poor ability to detect true-positive reactions based on dietary provocation, whereas the 95.6% specificity value reflects a small number of false-positives reactions. Similar percentages were seen for the ELISA (sensitivity, 13.8%; specificity, 86.6%). On the basis of the positive predictive value, if a positive reaction is detected by skin testing, only a 60% chance exists that the dog is truly allergic to that ingredient. On the other hand, a negative skin testing result indicates a 62.3% chance that the dog is not allergic to that ingredient. Values for the ELISA were similar, having even smaller positive (40.0%) and negative (60.9%) predictive values. Although they were a poor predictor of food hypersensitivity, the ELISA results were highly repeatable.

Skin testing and anti-IgE serologic testing are used in human medicine to aid in diagnosing adverse reactions to food. The ability of intradermal skin testing and use of the RAST to accurately detect all food allergens responsible for causing adverse reactions is directly proportional to the number of clinical cases in the study that had an immediate reaction to the ingested food allergen. The diagnostic ability of both tests decreased appreciably as people with delayed reaction to ingested food allergens were included in the study.²¹⁻²⁷ When comparing skin testing and the RAST both were found to be equal in diagnosing food allergy,²¹ or skin testing was judged to be superior to the RAST. Concordance between skin testing and the RAST^{23,25} was 73%.²¹ To the authors knowledge, information has not been published on use of the ELISA for diagnosing food hypersensitivity in people. Most authors agree that in people, the most convincing way to diagnose adverse food reactions is history plus a provocation trial,²⁸ and that no test for food hypersensitivity makes the diagnosis.²⁹

In this study, the failure of skin testing and the ELISA as diagnostic tools was disappointing. Several explanations for failure exist. Technical errors in skin testing^{30,31} or technical inaccuracies in the ELISA¹⁹ are possible. Unsatisfactory antigens maybe represented in skin testing antigens or the ELISA pollens may cross-react with food antigens,²⁴ and allergen-specific non-IgE antibodies (ie, IgG₄) may alter reaction to the food antigen.³² Because skin testing and the anti-IgE ELISA only detect reaginic (type I) hypersensitivity, nonallergic reactions (intolerance) would not be detected by use of

either test² nor would reactions attributable to nonreaginic immune mechanisms (types II-IV) or nonimmunoglobulin immunologic mediators.²³⁻²⁵ Even if the mechanism is reaginic, IgE concentration may be too low to be detected.²⁵ In a study involving children with immediate-type clinical food allergy, serum IgE concentration, although often high, was found to be low or normal in many.³ Also, sensitization is not always followed by clinical signs of allergy and could contribute to false-positive reactions.²³⁻³¹ The reliability of both tests for diagnosing food hypersensitivity may not be improved until the mechanism of action, whether immunologic or not, can be further defined in dogs. In conclusion, none of 3 diagnostic tests (feeding the commercial dry diet, intradermal skin testing, and ELLA) worked well enough to replace a home-cooked diet as the recommended diagnostic test for food allergy in dogs. Of the 3, the commercial dry diet offers the most benefit by adding flexibility to the food elimination diet.

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