INTRODUCTION

Food allergy (food hypersensitivity) is the term used to describe the clinical disease induced by food ingestion in which there is an immunological reaction. The immunological reaction is usually associated with dietary water-soluble glycoproteins that have molecular weights ranging from 10,000 to 70,000 kD. Food intolerance is the term used for a non-immunological abnormal physiological response including metabolic, toxic, idiosyncratic or pharmacological effects of foods or food additives. Food intolerance may be caused by digestive enzyme deficiencies, proteins, toxins, food additives, vasoactive amines and contaminants such as bacteria. In a clinical setting, food allergy and food intolerance are rarely differentiated. Thus, the phrase cutaneous adverse reactions to foods (CARF) is used to reference both conditions. One should note that this differentiation of hypersensitivity versus intolerance has been discussed for many years but, in reality, there are virtually no well-documented cases of skin-related food intolerance reported in the dog or cat. Cutaneous disease appears to be seen only in truly food allergic patients.

PATHOGENESIS

The true pathogenesis of food allergy in dogs has not been fully defined. Types I, III and IV reactions have been reported. Oral allergy syndrome, a localized IgE-mediated reaction, has also been reported in dogs (Fujimura et al., 2002). Mixed IgE-mediated, non-IgE-mediated and late-phase IgE reactions are also implicated. Results of several studies suggest that IgE-mediated adverse food reactions are dependent on genetic predisposition and an abnormality in gastrointestinal function.

A prospective study was conducted in 25 dogs to characterize specific food ingredients causing adverse reactions (Jeffers et al., 1996). Single-ingredient provocation trials were conducted with beef, chicken, chicken eggs, cows’ milk, wheat, soy and corn. Beef and soy most often caused cutaneous adverse reactions, although all ingredients induced clinical signs in at least one dog. Thirty-six percent of dogs reacted to one protein and the mean number of suspected allergens per dog was 2.4.

More recently, 15 different studies, representing 278 dogs from several continents were reviewed to determine ingredients commonly associated with adverse food reactions (Roudebush et al., 2010). Beef, dairy products and wheat accounted for 69% of reported cases while lamb, chicken
egg, chicken and soy accounted for 25% of the dogs. In 10 studies representing 56 cats, beef, dairy products and fish were associated with reactions in 80% of the patients.

In one beef allergic dog, bovine serum albumin was the target of anti-beef IgE (Ohmori et al., 2007). Commercial vaccines often contain bovine serum albumin. Whether vaccinating a dog with this molecule can sensitize a patient to this bovine allergen or cause flares in an existing hypersensitivity disorder requires further study. Other factors which may affect allergenicity of a diet include number, quantity, digestibility, allergenicity, and molecular weight of proteins, manufacturing techniques, and number and types of additives.

**CLINICAL DISEASE**

**Dogs**

The prevalence of CARF in dogs is unknown with a wide variation of opinion among general practitioners and among veterinary dermatologists. Several reports (as reviewed by Roudebush et al., 2010) suggest that CARF represents from 1 to 6% of all dermatoses in general practice and 10 to 49% of responses in allergic dogs and cats. Other reports suggest that of dogs presented to dermatology practices with cutaneous signs, the prevalence is 7.6% to 12% (Chesney, 2002; Proverbio et al., 2010). Among dogs with allergic skin disease, the prevalence is higher at 9% to 36% (Chesney, 2002; Proverbio et al., 2010; Wilhelm et al., 2005; Picco et al., 2008). The wide variations are likely explained by coexistence with other allergic conditions, similarity of clinical signs among different types of allergies, variability among diets used in elimination trials and poor owner compliance in completion of trials.

Age of onset of CARF is highly variable. In a study by Rosser (1993-A), 51% of the dogs developed clinical signs between 1 and 3 years of age, 33% at less than 1 year of age and 16% at over 4 years to as old as 11 years of age. Harvey (1993) found that 52% of dogs developed clinical signs at less than 1 year of age and Leistra et al. (2001) found this in 53% of cases. Chesney (2002) reported 8 of 9 dogs that developed their pruritus from 6 to 30 months of age with a mean of 16 months. **CARF should be considered a differential for pruritus in any age of dog.**

There is no reported sex predilection. Several studies (White, 1986; Harvey, 1993; Carlotti et al., 1990; Leistra et al., 2001) report no breed predilection. Labrador retrievers, cocker spaniels, golden retrievers, soft-coated wheaten terriers, Dalmatians, West Highland white terriers, collies, Chinese shar-pees, Lhasa apsos, springer spaniels, and miniature schnauzers are breeds that were found to be at increased risk for CARF in one study (Rosser, 1993-A) that was conducted in the United States. In more recent studies in Europe (Chesney, 2002; Loeffler et al., 2004; Loeffler et al., 2006) Labrador retrievers, German shepherd dogs, West Highland white terriers and spaniels were overrepresented.

In Rosser (1993-A), sixty-eight percent of dogs had been fed the offending diet for at least 2 years before onset of clinical signs. **Thus, the onset of CARF is not usually associated with a recent change in diet.** Theoretically, it would seem that food intolerance would more likely occur after a recent dietary change but this has not substantiated.
Non-seasonal pruritus is the most common clinical sign in dogs with CARF. Dogs with combinations of allergies may be pruritic throughout the year, but the level of pruritus may intensify on a seasonal basis. This is most commonly seen in dogs that get worse in the warm months because of concurrent reactions to seasonal pollens, fleas or other insects.

Dogs with CARF generally will not respond as well to conventional anti-inflammatory doses of glucocorticoids as dogs with other allergic diseases. However, about 40% will still show an excellent response with regard to a decrease in pruritus (Rosser, 1993-A). Dogs with CARF respond poorly to antihistamines, essential fatty acids and cyclosporine. Lack of response to these medications in a dog with pruritus would make atopic dermatitis a lower differential and elevate CARF, canine scabies and other parasitic hypersensitivities to the top of the list of considerations.

The clinical lesions of CARF are secondary to the pruritus (which may be variable in intensity) and self-trauma. The lesions consist of erythema, alopecia, excoriations, hyperpigmentation, lichenification and pyotraumatic dermatitis. A papular eruption, urticaria and angioedema have also been reported but are rare. The distribution is usually similar to that seen in atopic dogs with facial, ear, extremity and ventral involvement. Rosser (1993-A) reported the following body site involvement in a study of 51 food allergic dogs: ears (80%), feet (61%), inguinal region (53%), and axilla, anterior foreleg, muzzle and periorbital (31-37%). Twenty-four percent of dogs had only ear involvement without any other parts of the body affected. Some patients with CARF will present with localized perianal pruritus (Loeffler et al., 2004), clinical lesions which are identical to those associated with flea allergy dermatitis or canine scabies, or seborrheic dermatitis. Dogs with CARF may have secondary staphylococcal pyoderma (35% in Rosser, 1993-A) or Malassezia dermatitis. In a more recent study (Loeffler et al., 2006), bacterial pyoderma and Malassezia dermatitis were present in 32% and 24% of dogs, respectively. A recurrent cutaneous infection with minimal pruritus as the only clinical manifestation of CARF is seen but is rare. Additionally, there are rare or anecdotal reports of paronychia, symmetric lupoid onychodystrophy, vasculitis and erythema multiforme responding to elimination diets.

The most common differentials for CARF in dogs include atopic dermatitis, flea allergy dermatitis and canine scabies. As described above, the clinical features of CARF and canine atopic dermatitis are very similar, suggesting a common pathogenesis (Favrot et al., 2010). Thus, the term food-induced atopic dermatitis (FIAD) has been proposed to describe dogs with food hypersensitivity and clinical features typical of atopic dermatitis. Although poorly defined in dogs, oral allergens may cross-react with aeroallergens, resulting in similar clinical disease in sensitized individuals. However, it should also be remembered that dogs with CARF may manifest clinical signs not typically associated with canine atopic dermatitis. It has been suggested (Favrot et al., 2010) that atopic dermatitis be divided into food-induced atopic dermatitis (FIAD) and non-food-induced atopic dermatitis (NFIAD).

It is uncommon to see other organ systems involved with CARF. However, supportive evidence includes vomiting, diarrhea, borborygmus, flatulence and an increased frequency of defecation.
Loeffler et al., 2004). The prevalence of gastrointestinal signs in dogs with CAFR varies between 10% and 31% (Favrot et al., 2010; Gaschen et al., 2011).

Cats

CARF is an important cause of pruritus and self-trauma in cats. As in dogs, non-seasonal pruritus is the most common clinical sign in cats (White and Sequoia, 1989) and age of onset has been reported from 3 months to 11 years (Carlotti et al., 1990; White and Sequoia, 1989; Rosser, 1993-B).

Since cats tend to be fed a more variable diet, the pruritus may wax and wane over time. Therefore, it is even more important in cats than in dogs to get as detailed a dietary history as possible in order to select an appropriate protein-restricted diet for a diagnostic trial. Additionally, cats that are allowed free access to the outdoors will have more exposure to a variety of potential allergens such as garbage, birds, mice and fish. It is virtually impossible to conduct a good dietary elimination trial in cats that are allowed to roam.

Although CARF may be steroid-responsive, lack of response, partial response or only short-term steroid response should alert one to the possibility of food as a serious differential.

Pruritus is the predominant clinical sign of CARF in cats, especially with involvement of the head and neck. Head and neck pruritus was the predominant sign in 42% of cats in one study (White and Sequoia, 1989) and in 65% of cats in another report (Guaguère, 1993). The intense pruritus and self-trauma result in erythema, alopecia, scales, erosions, ulcerations and crusts. Many of these cats have such intense pruritus, that physical restraint with an Elizabethan collar is necessary to keep patients from excessively damaging the skin at the same time as the restricted diet is instituted. Other signs include more generalized pruritus, miliary dermatitis, eosinophilic granuloma complex lesions and symmetrical alopecia caused by excessive grooming. Concurrent gastrointestinal signs are rare.

The most common differentials for CARF in cats include feline atopic dermatitis, flea allergy dermatitis, feline scabies, cheyletiellosis, dermatophytosis and ear mites.

DIAGNOSIS

Before starting a dietary trial, it is recommended that sarcoptic mange, other ectoparasites and flea allergy dermatitis be eliminated from the list of differentials with appropriate therapy. Additionally, secondary bacterial and yeast infections should be adequately controlled with systemic antibiotics and topical antiseptics.

Client Education

Lack of client compliance is the major reason for failure of dietary trials. Compliance is often directly related to the amount of client education in the clinic during the visit and the follow-up after the visit. Client education handouts with simple bullet-point instructions are strongly
advised. Follow-up phone calls to clients on a weekly basis to provide motivation and address problems and questions are very helpful. A daily food diary kept by the owner will document patient progress, provide valuable observations for the clinician at rechecks and keep the client engaged in the process. A recheck is strongly advised at 3-4 weeks into the diet to be sure the prescribed plan is followed. After palatability of the prescribed diet has been established, it is important to prescribe an adequate quantity of food to last until the recheck visit in order to avoid a diet change when the owner runs out of the test diet.

Test Diet Trials

The best way to make a diagnosis of CARF is by feeding a prescription single protein limited ingredient test diet or a prescription diet containing protein hydrolysates, and subsequent challenge with the patient’s original diet. Prescription is highlighted because a recent study (Raditik et al., 2011) determined that three out of four venison OTC therapeutic diets for food allergy contain undisclosed soy, beef and/or poultry protein.

Other commercial or experimental diagnostic methods include prick testing, intradermal testing, patch testing, serum testing and gastroscope testing, but none have proven to be reliable or practical for establishing a diagnosis in a clinical setting.

Single Protein Limited Ingredient Dietary Trial

A single protein limited ingredient diet contains a single protein and a single carbohydrate source not previously fed to the patient. Although any molecule in the diet has the ability to induce a CARF, proteins are more likely to cause reactions than are other nutrients. The selection of a trial diet depends on the patient’s previous dietary history. Information should be collected about previous commercial diets, table foods, treats, chewable medications, vitamins and exposure to other outside food sources. The test diet is selected to avoid the protein sources in the previous diet. In many if not most cases, it is not possible to get a complete dietary history. For these patients, the author will select diets containing single protein sources not commonly found in over-the-counter commercial foods or consider using a hydrolyzed protein diet. The dietary trial must also exclude all other food sources including table scraps, chew toys, treats, chewable and flavored medications (oral heartworm and flea preventatives, antibiotics, etc.), flavored toothpastes, vitamins and access to other animals’ foods. Confinement of a dog or cat that is normally allowed to roam is required during the dietary trial to eliminate possible ingestion of other foods.

If the patient has a history of recurrent pyoderma or flea allergy dermatitis along with suspected CARF, then systemic antibiotics and flea control should be used throughout the dietary trial and during challenge with the original diet. Additionally, glucocorticoids and an Elizabethan collar may be needed for the first 3-4 weeks of the trial in a dog or cat with severe pruritus and dermatitis. This will allow the skin to heal as the restricted diet takes effect. Concurrent medications should be discontinued for 2 weeks before the recheck visit at the end of the dietary trial.
The length of an elimination dietary trial is variable and controversial and ranges from 3 to 12 weeks or longer. Most dermatologists recommend that the single protein limited ingredient diet be fed for at least 8 weeks before a decision is made regarding efficacy. A beneficial response is usually manifested by a decrease in pruritus and cutaneous inflammation. If no response is seen in 8 weeks, then it is unlikely that food is playing a major role in the patient’s dermatitis and the diet is discontinued. However, if even a partial response is noted then the diet should be continued for an additional 4 weeks since some cats and dogs may take 10 weeks or more for a maximum beneficial response (Rosser, 1993-A). Even a 30-40% improvement is enough to warrant continuation of the diet indefinitely as the patient may have concurrent CARF, atopic dermatitis and/or flea allergy dermatitis.

**Challenge with the patient’s original diet is always recommended to be sure that the improvement was not coincidental with other factors.** For example, if a dog is pruritic due to seasonal atopic dermatitis, it will show improvement with the first freezing temperatures in the fall. If the dietary trial was started in the fall, improvement could be due to either the diet or change in season. The challenge will help to determine the cause of improvement.

Ingredients incorporated into restricted diets include lamb, pinto beans, soy, oats, kelp, barley, lentils, flax, alfalfa, pork, venison, rabbit, duck, ostrich, emu, kangaroo, goat, horse, donkey, moose, elk, camel, potatoes, sweet potatoes, rutabagas, pumpkin, whole-grain rice, green peas and a variety of different types of fish. Although protein cross-reactivity has not been studied well in dogs and cats, it would still be advisable to select a protein source as taxonomically distinct as possible from previous diets. Common allergens have been detected in avian meats (Kelso et al., 1999) so the use of duck-based diets may not be optimal for patients previously fed chicken.

A home-prepared elimination diet is still the gold standard for diagnostic purposes. From a practical standpoint, such diets are rarely utilized because of owner reluctance, poor compliance and difficulty in formulating complete and balanced diets. Calcium, vitamins and essential fatty acids are generally required for home-cooked diets to be nutritionally complete. Private practice and university nutrition services and commercial nutrition websites may be helpful in providing complete and balanced special diet recipes. Two of the most commonly used are:

- [www.balanceit.com](http://www.balanceit.com)
- [www.petdiets.com](http://www.petdiets.com)

One should realize that by not utilizing home-prepared diets, some food allergic patients will undoubtedly be missed. Although conducted many years ago with the older commercial elimination diets, there is some scientific evidence which shows that dogs and cats may improve on a home-cooked diet but experience recurrence of signs when fed the commercial diet containing the same ingredients (White, 1986; White and Sequoia, 1989; Jeffers et al., 1996). More recently, a study (Leistra et al., 2001) was conducted using sequential commercial elimination diets and three of these were required before 95% of cases improved which had previously responded to a home-cooked, single-protein-source elimination diet. Ultra-hydrolyzed diets picked up 80-85% of the cases. Based on this work, some have suggested using
sequential venison-based, poultry-based and fish-based elimination diets, a regime which would have minimal compliance.

The author has most commonly used commercial venison (Royal Canin, Hill’s), rabbit (Royal Canin) or kangaroo-based (Iam’s) diets in dogs, and venison (Royal Canin, Hill’s) or rabbit (Royal Canin, Hill’s) diets in cats. Occasionally, a vegetarian diet (Royal Canin) containing oat flour, rice, tomato pomace, beet pulp, flaxseed and carrot pomace has been utilized. I generally do not use fish-based diets because fish is ubiquitous as an inexpensive source of protein in many diets and treats. However, I have not seen problems with fish oils added to diets. These diets offer the advantage of increased levels of omega-3 fatty acids that may help reduce proinflammatory eicosanoids in the skin and help with any type of allergic dermatitis.

Palatability will be a problem in some patients on commercial diets used to diagnose CARF. Some options recommended by dermatologists in these patients include adding: cooked meat (rabbit, venison, ostrich, goat, etc.) corresponding to the protein source or another unique source in the diet, some of the corresponding proteins from the Rayne Clinical Nutrition Peel-and-Serve diets, canned pumpkin, canned yams and vegetarian refried beans.

**Diets Containing Protein Polypeptide Hydrolysates**

The process of protein hydrolyzation involves cleavage of peptide bonds. The theory is that protein hydrolysates of appropriately low molecular weight (generally ≤ 10 kD) will not elicit an immunologically mediated response. Theoretically, because of the low molecular weight, protein hydrolysates need not be novel or unique protein sources. Polypeptide hydrolysates in veterinary diets include chicken, poultry liver and soy.

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<th>Diet</th>
<th>Protein Ingredients</th>
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<tr>
<td>Hill’s Prescription Diet z/d Ultra Canine Dry</td>
<td>Hydrolyzed chicken and chicken liver</td>
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<tr>
<td>Hill’s Prescription Diet z/d Low Allergen Canine Dry</td>
<td>Hydrolyzed chicken and chicken liver, potato</td>
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<tr>
<td>Hill’s Prescription Diet z/d Ultra Canine Canned</td>
<td>Hydrolyzed chicken liver</td>
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<tr>
<td>Hill’s Prescription Diet z/d Ultra Feline Canned</td>
<td>Hydrolyzed chicken liver</td>
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<tr>
<td>Hill’s Prescription Diet z/d Low Allergen Feline Dry</td>
<td>Hydrolyzed chicken and chicken liver, rice</td>
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<tr>
<td>Purina HA Canine Dry</td>
<td>Hydrolyzed soy</td>
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<tr>
<td>Purina HA Feline</td>
<td>Hydrolyzed soy, rice starch, hydrolyzed chicken and chicken liver</td>
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<tr>
<td>Royal Canin Hypoallergenic HP Canine Dry</td>
<td>Hydrolyzed soy, rice</td>
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<tr>
<td>Royal Canin Hypoallergenic HP Feline Dry</td>
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There is documentation that dogs allergic to the parent protein can tolerate the corresponding hydrolyzed product. When Purina HA was fed to a laboratory population of food allergic Maltese-beagle dogs, 11 of 14 (79%) with soy and/or corn allergy showed no adverse effects (Jackson et al., 2003). Twelve (12) dogs with cutaneous manifestations of allergic dermatitis following exposure to chicken meat were fed a hydrolyzed chicken or hydrolyzed soy diet 14 days in a blinded crossover design. Global scoring was significantly reduced in 11 of the 12 dogs when fed hydrolyzed chicken compared to those fed whole chicken (Ricci et al., 2010).

Thirty-four (34) of 36 food allergic dogs improved during an 8-week test period with the Royal Canin Hypoallergenic HP Canine Dry diet (Biourge et al., 2004). Twenty dogs had uncomplicated CARF and in 18 dogs signs completely regressed or were very mild with a significant reduction in pruritus scores. The other two did not respond to the diet but did respond to a home-cooked soy-based diet and a rice and rabbit commercial novel protein diet. The 16 remaining dogs had partial improvement on the diet and were ultimately diagnosed with CARF and concurrent atopic dermatitis.

In spite of the above-referenced studies, a systematic review of 11 studies on polypeptide hydrolyzed protein diets concluded that they should be avoided when the native protein is suspected as an allergen since dogs may still show signs of CARF when fed hydrolyzed protein diets containing a known allergen (Olivry et al., 2010).

**Oligopeptide and Amino Acid Hydrolysates: Royal Canin Anallergenic Canine**

A new therapeutic diet has been formulated with single and very short chains of amino acids which may be considered too small to initiate allergic reactions but are still absorbed like “normal” protein. The hydrolysate is essential amino acids extracted from poultry feathers with 88% of the protein in the form of single amino acids and 95% of the total protein content with a molecular weight lower than 1 kD. The diet has shown high palatability and contains protein-free palatability enhancers. A field trial conducted in Spain and France revealed excellent palatability, improvement in skin scores and overall satisfaction in 22 dogs with confirmed or suspected CARF (Anallergenic Product Literature, Royal Canin). An additional palatability study in Japan involving 41 dogs found that 89% of the dog owners reported a good to very good palatability score.

Long-term (26 week) feeding trials have been conducted with this diet in accordance with AAFCO protocols and it was found to be complete and balanced for canine maintenance.

**Confirmation of Food-Related Dermatosis**

The best way to definitively confirm CARF is by demonstrating that the clinical signs recur when the patient is re-challenged with the previously fed diet. A relapse will usually occur within 24-72 hours although one study (Leistra et al., 2001) has indicated this may take up to 21 days in some dogs. In Jackson et al. (2003), 38% of owners reported relapse of signs within 24 hours of challenge and 57% between 1 and 6 days. In Loeffler et al. (2006), 92% of dogs relapsed within 3 days after challenge. Improvement should again be seen after re-instituting the elimination diet.
For owners who are interested in finding specifically what their food allergic pet can tolerate in the diet, sequential provocation can be done with single protein and carbohydrate challenges, each being fed for 7-14 days.

References and Recommended Readings


