

Adverse Food Reactions in Dogs and Cats

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KEYWORDS

- Adverse food reaction • Food allergy • Food intolerance
- Dog • Cat • Chronic enteropathies

Adverse food reactions (AFRs) are defined as reactions to an otherwise harmless dietary component, which are experienced by certain individuals on ingestion.¹ These reactions encompass disorders with an immunologic basis (food allergy [FA], also called dietary/food hypersensitivity), nonimmunologic reactions (food intolerance), and toxic reactions (intoxications) (**Fig. 1**).^{1,2} Although intoxications, such as garbage can gut gastroenteritis, are encountered frequently in dogs, they are not discussed in this review. Food intolerance may be caused by a metabolic problem such as digestive enzyme deficiency (eg, lactase deficiency in adult cats) or by a pharmacologic reaction (eg, vasoactive amines such as histidine in spoiled fish that is transformed into histamine by the intestinal flora) or can be idiosyncratic (eg, reaction to food additives, gluten-sensitive enteropathy in Irish Setter dogs).² FA is defined as an aberrant adverse immune response elicited by exposure to a particular food substance, most often a protein.^{1–3} In general, these responses are characterized as IgE antibody dependent, cell mediated, or mixed.^{1–3} In dogs and cats, all AFRs can be associated with similar inciting foods, gastrointestinal (GI) clinical signs, diagnostic test results, and responses to treatment. Thus, it may be difficult to distinguish between food intolerance and FA in the patient with primarily GI signs. Cutaneous disease is seen only in the truly FA patient.^{4,5} In people, it is believed that food intolerance represents most AFR.¹

In recent years, the importance of diet in the management of dogs and cats with chronic idiopathic intestinal disorders has received much attention.^{6–8} A new term of diet-responsive or food-responsive chronic enteropathy (CE) has been coined, and it encompasses AFR as well as mild intestinal inflammatory conditions that benefit

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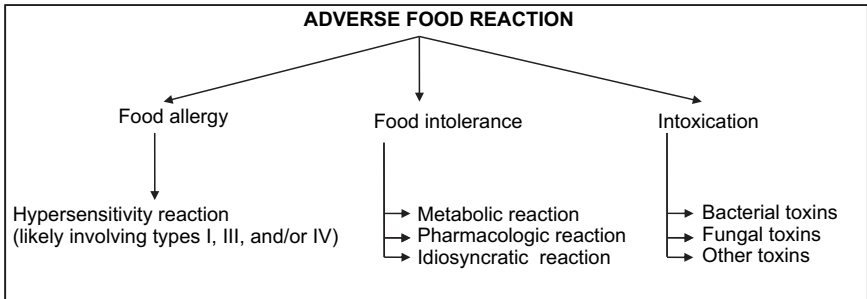


Fig. 1. Classification of AFRs in dogs and cats.

from the properties of the new diet. Dietary elimination trials are now recommended in most dogs and cats with chronic idiopathic GI signs of mild to moderate severity.^{6–8}

In veterinary dermatology, further discussion has centered on the role that cutaneous AFR (CAFR) plays in canine atopic dermatitis (AD).⁵ The concept that food allergens might trigger flares of AD in some dogs has been discussed in the literature. The International Task Force on Canine Atopic Dermatitis supports the concept that CAFR might manifest as AD in some canine patients.⁵ However, dogs with CAFR may also experience clinical signs that are not typically associated with AD, such as GI signs. It has recently been suggested that AD be divided into food-induced atopic dermatitis (FIAD) and non-food-induced atopic dermatitis (NFIAD) or canine atopic dermatitis *sensu stricto* for cases that are not responsive to an elimination diet.⁹

Besides the GI tract, other organ systems may be affected by AFR. These systems include the central nervous system (seizures, personality changes), respiratory system (asthmatic syndrome) and lower urinary tract (cystitis). However, these organ systems are rarely involved, and subsequent clinical signs are rare.¹⁰ One of the authors (S.R.M.) has seen young dogs in poor general condition with failure to thrive and GI signs mimicking hypoadrenocorticism, which have, in fact, FA. This misdiagnosis is usually compounded by blunting of the cortisol response to adrenocorticotrophic hormone stimulation test by previous low-dose glucocorticoid administration for control of pruritus. In addition, AFR is also recognized as a cause of vasculitis with associated cutaneous manifestations.¹¹

This article reviews pathophysiologic, epidemiologic, and clinical aspects of AFR in dogs and cats with added emphasis of diet-responsive chronic enteropathies.

PATHOGENESIS

GI Mucosal Barrier

The GI mucosa represents the largest surface area in contact with the external environment.¹² Although the main function of the GI mucosa is to process the ingested food into nutrients that can be absorbed and used by the body, GI mucosa is also responsible for preventing the entry of harmful pathogens into the body. The GI barrier consists of several anatomic, physiologic, and immunologic components. The single layer of mucosal epithelial cells joined by tight junctions offers an important physical barrier. It is covered by a thick mucous layer that is able to trap particles and microorganisms.^{3,12} Changes in luminal pH across the different parts of the digestive tract, luminal and brush border digestive enzymes, and bile salts all contribute to destroying potential pathogens, breaking down ingested food, and rendering dietary antigens less immunogenic.^{3,12} Cells and factors from the innate and adaptive immune

system are additional obstacles to foreign antigens and contribute significantly to the mucosal barrier.^{3,12}

Gut-associated Lymphoid Tissue

The gut-associated lymphoid tissue (GALT) is the largest and most complex part of the immune system.¹³ This system can be divided into organized tissues and effector sites. Peyer patches, mesenteric lymph nodes, and intestinal lymphoid follicles are the organized tissues in charge of the induction phase of the immune response. The effector sites consist of epithelial and lamina propria lymphocytes.¹³

Oral Tolerance

Despite the large extent of exposure to dietary antigens, only a small percentage of people, dogs and cats develop FA. Oral tolerance to dietary proteins and commensal microorganisms is an active immunologic process that results in inhibition of the immune response to an antigen after prior exposure through the oral route.^{12,13} Oral tolerance requires the presence of an intact GI barrier.^{12,13} Antigen-presenting cells (APC), such as enterocytes and dendritic cells, and regulatory T (T_{reg}) cells are essential for the development of oral tolerance.^{12,13} Several types of T_{reg} cells have been described in the GI tract of rodents and people. The T_H3 regulatory cells produce transforming growth factor β that has been shown to enhance the production of IgA in response to luminal antigens. Once released on the mucosal surface, IgAs form a complex with the antigens they bind to and prevent further interaction with the immune system.¹² Moreover, enterocytes may process luminal antigen and present it in association with major histocompatibility (MHC) class II complex, but they lack the second signal to activate the T cells.¹³ Thus, antigen presentation by enterocytes results in anergy and may contribute to oral tolerance.¹³ These results do not apply to cats, however, because feline crypt and villus epithelial cells do not express MHC class II complex on their surface.¹⁴ In rodent models, priming of T cells by APC in the intestinal mucosa seems more likely to elicit a tolerogenic response, whereas priming of T cells in the mesenteric lymph node, either by migrating APC or by antigen present in the lymph, is more likely to elicit an immune response.¹³

Two mechanisms of oral tolerance are recognized that depend on the dose of GI mucosal antigen exposure. High-dose tolerance results from lymphocyte anergy, and low-dose tolerance is mediated by T_{reg} cells. Abnormalities in the development of low-dose tolerance are thought to be an important cause of FA in people.¹² Other factors that may influence oral tolerance include the normal intestinal microbiota and the genetics of the host.¹²

In FA patients, this complex balance is disrupted. Oral tolerance may be breached directly by an inflammatory process that increases mucosal barrier permeability, causing absorption of allergenic antigens and sensitization.¹ Alternatively, oral tolerance may be bypassed by presentation of antigens via the respiratory tract or the skin. In mice, epicutaneous application of food proteins may elicit a strong allergic response and inflammation.^{1,3} In people, reduced exposure to microorganisms (hygiene hypothesis), increased consumption of n6 fatty acids and decreased consumption of n3 fatty acids, reduced dietary antioxidants, and excess or deficiency of vitamin D may favor a T_H2 -biased immune reaction in response to antigen exposure and lead to sensitization.^{1,15}

Allergens

Most allergens are water-soluble glycoproteins that are 10 to 70 kDa in size and relatively stable to heat, acid, and proteases.³ However, many of the allergens that

are inhaled or ingested are glycosylated with oligosaccharides. These carbohydrate moieties can be present on multiple different types of protein and are prone to extensive cross-reactivity. Recent data suggest that IgE antibodies to carbohydrate epitopes can be an important factor in anaphylaxis in people.¹⁶ There is currently no data about the existence of IgE against carbohydrate epitopes in canine and feline patients.

In dogs, the most common documented food allergens originate from beef meat, dairy products, wheat, eggs, and chicken meat.¹⁷ Bovine IgG heavy chain found in cow's milk and meat was determined to be the target of IgE in a group of dogs with CAFR.¹⁸ The muscle enzyme phosphoglucumutase was another target of circulating IgE in these dogs. Cross-reactivity was suspected between molecular targets of bovine and ovine origin.¹⁸ Bovine serum albumin was the target of antibovine IgE in another dog.¹⁹ This may have implications for vaccination of these patients because commercially available vaccines for dogs contain a large amount of bovine serum albumin. Vaccinating a dog with this molecule could sensitize the patient to this bovine allergen. In cats, the most common food allergens are beef meat, dairy products, fish, and lamb.¹⁷

Although type I (IgE mediated) hypersensitivity reactions are the most common mechanism associated with FA in people,³ the situation is less clear in dogs⁴ and cats. The exact mechanism leading to FA in dogs is unknown, and type I (immediate), III, and IV (delayed) hypersensitivities have been postulated to occur.¹⁷ The clinical phenotype in small animals is, however, different from the immediate, sometimes life-threatening, reaction observed in people. In dogs, the clinical phenotypes of CAFR and AD may be remarkably similar. Although canine AD is typically associated with IgE against environmental antigens, dogs with AD frequently also exhibit high levels of food antigen-specific IgE.²⁰ Moreover, in a subset of dogs with skin lesions suggestive of AD, clinical remission can be induced after a food elimination trial (FIAD).⁵ Thus, the division between AD and CAFR is less clear than what was previously thought.⁵

Two recent studies investigated the types of immune cells and cytokines that prevail in the skin and duodenal mucosa of dogs with well-documented CAFR and no GI signs when they were fed a challenge diet that elicited clinical signs, as well as during a successful elimination trial. The study results show a lack of changes in the expression of T_H1-, T_H2-, and T_{reg}-related genes in the duodenal mucosa, suggesting that it is not the primary site of T-cell activation that ultimately leads to cutaneous inflammation.²¹ The same studies also looked at T-cell phenotypes and cytokine gene expression in the lesional and nonlesional skin of the same dog population and found that CD8⁺ T cells were increased in lesional skin of dogs with CAFR when compared with controls. Expression of cytokines revealed a T_H2-skewed environment with increased interleukin (IL)-4, IL-13, SOX-3, and Foxp3 genes expression in lesional skin. Remarkably, these changes were not reversed during resolution of clinical signs after dietary therapy. Moreover, IL-4 and Foxp3 expression was also increased in nonlesional skin, indicating a generalized process.²²

It is unsure why some dogs and cats with AFR develop cutaneous signs, whereas others show GI signs or a combination of both. One possible explanation is that activated T cells home to different target organs. Upregulated T cells with the skin-homing receptor cutaneous leukocyte-associated antigen are increased in people with food-responsive AD, and T cells with the $\alpha_4\beta_7$ integrin molecule are associated with the GI phenotype.²³ In dogs, T-cell homing also depends on the expression of $\alpha_4\beta_7$ ligand on mucosal lymphocytes that binds to MADCAM-1 in the GALT endothelial cells. Other ligands are associated with intraepithelial lymphocyte localization.¹⁴

A gluten-sensitive enteropathy has been studied in families of Irish Setter dogs and is an example of a canine AFR with GI manifestations. This enteropathy is inherited as

an autosomal recessive trait, and affected animals show chronic intermittent diarrhea and poor weight gain or weight loss between 7 and 10 months of age when fed a diet containing gluten.²⁴

Many, if not most, small animals eat processed food (canned or dry). Heat treatment changes the tertiary (3-dimensional) structure of protein. This change in structure may destroy some epitopes but may also uncover previously hidden epitopes.²⁵

Diet-responsive CE

Dogs and cats that respond to an elimination trial but do not relapse after provocation with their original diet or components thereof do not have true AFR, such as food intolerance or FA. It is likely that these animals have mild to moderate enteritis, colitis, or enterocolitis as a result of other causes and benefit from other advantageous properties of the special diet (**Fig. 2**). Higher bioavailability of the nutrients decreases the amount of undigested/unabsorbed substances that are otherwise metabolized by the intestinal flora and may cause changes in its composition. Likewise, prebiotics such as fructooligosaccharides also modulate the intestinal microbiome. Also, a higher n3:n6 fatty acid ratio may increase synthesis of less inflammatory eicosanoids and decrease intestinal inflammation.

EPIDEMIOLOGY

Prevalence of FA in people is thought to be between 1% and 10.8%, and children are more frequently affected than adults.^{1,3} Many but not all pediatric FAs resolve before age 16 years.^{1,3} There are no comparable data for dogs and cats with AFR. Based on published studies, the prevalence of AFR among dogs presented to a dermatology center with cutaneous signs is estimated between 7.6% and 12%.^{26,27} Among allergic dogs, 9% to 36% are diagnosed with CAFR.^{26–29} The proportion of dogs with CAFR that show GI signs varies between published case series. In a cohort of 63 dogs from Switzerland with FIAD, 20 (31%) had chronic diarrhea and/or vomiting.²⁹ However, earlier studies report a lower prevalence rate of 10% to 20%, with many dogs having mild GI signs, such as tendency to develop loose stool and flatulence,

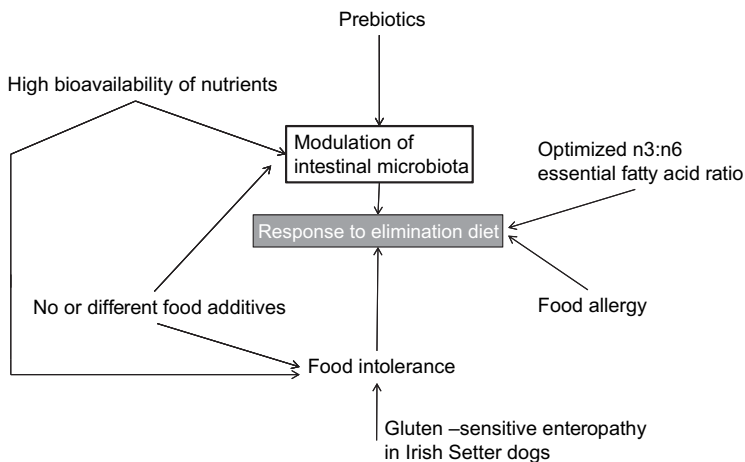


Fig. 2. Canine and feline diet-sensitive enteropathy. Possible mechanisms for positive response of the inflamed GI mucosa to an elimination trial with a commercial veterinary prescription novel protein diet or a hydrolyzed diet.

whereas few had overt diarrhea and vomiting.²⁶ A recent large multicenter prospective study of dogs with AD reports a GI signs prevalence of 26.3% among dogs with FIAD, whereas it was only 10.5% in dogs with NFIAD.⁹

Although there are no epidemiologic studies of canine CE, the proportion of dogs that responded completely to a 10-day elimination trial in a recent series of 70 dogs with CE from Switzerland was very high (56%). Surprisingly, 79% of these diet-responsive dogs could be switched back to their original diet after receiving a salmon, trout, and rice novel protein diet for 14 weeks. The remaining 8 dogs (21%) relapsed when the novel protein diet was discontinued and improved again when the elimination diet was resumed. These dogs were diagnosed with AFR, and 2 of them reacted to challenge with beef, lamb, chicken, or milk, suggesting FA. One dog with FA could not be successfully managed and was euthanized. This dog had initially presented with chronic GI signs and pruritus.⁷ Pruritus is a parameter included in one of the scoring systems for dogs with chronic enteropathies.⁷ A Dutch study published in 2010 included 26 dogs with idiopathic CE and small intestinal diarrhea. A response to an elimination trial with a hydrolyzed diet was seen in 16 of 18 dogs (complete in 12, partial in 4). Seven of 8 dogs receiving a highly digestible control diet also responded. A dietary challenge with the original food was performed in 22 of 23 responders, and 15 relapsed (65%). There was no difference in the relapse rate between dogs that received the hydrolyzed diet and those that received the control diet. Ninety percent of dogs continuously receiving the hydrolyzed diet remained in remission for up to 3 years, whereas only 12% of those on the control diet remained in remission.⁸

The prevalence of diet-responsive disease in feline CE is comparable. In a study from New Zealand, 27 (49%) of 55 cats with idiopathic CE and diarrhea and/or vomiting responded to a switch to a novel protein diet.⁶ The clinical presentation of diet responders and nonresponders did not differ significantly. Challenge with the original diet triggered a recurrence of clinical signs in 16 cats (29%) that were diagnosed as food sensitive. Of these cats, 12 underwent a more detailed dietary challenge that included protein sources tailored to the cats' history. Beef, corn gluten, and wheat were the food ingredients most commonly associated with FA. Four cats had concurrent cutaneous signs, which were attributed to FA in 3 animals.⁶ AFR was also diagnosed in 8 cats from a feline research colony, which exhibited vomiting and dermatitis and were responsive to an elimination trial. Dietary challenge with the original diet elicited recurrence of clinical signs within 4 weeks in 4 of 8 cats.³⁰

Even though numerous canine breeds are predisposed to develop AD,³¹ no definitive breed predisposition for FA has been reported in dogs, with the exception of soft-coated wheaten terriers³² and a colony of Maltese-beagle crossbreds.³³ However, CAFR seems to occur frequently in American cocker spaniel, English springer spaniel, Labrador retriever, collie, miniature schnauzer, Chinese shar-pei, poodle, West Highland white terrier, boxer, dachshund, dalmatian, Lhasa apso, German shepherd, and golden retriever.^{34,35} Specific lineages of Irish setter dogs may be at risk for gluten-sensitive enteropathy, a disease with autosomal recessive transmission.²⁴ In cats, Siamese and Siamese crosses may be at increased risk.^{34,36}

CLINICAL SIGNS

CAFR

Dogs

Although there is no age or sex predilection for AFR, many cases occur in dogs younger than 1 year.³⁷ CAFR-associated allergic dermatitis is much more common than environmental allergy (AD) in dogs 6 months of age or younger. The most

common clinical sign is nonseasonal pruritus. However, in some cases, a recurrent staphylococcal folliculitis with no pruritus or resolution of the pruritus when the infection is resolved may be the main clinical manifestation. Cutaneous signs may be nonspecific and may mimic any other allergic dermatosis, such as canine AD with facial, ear, extremity, and ventral distributions as the foci of pruritus (Figs. 3–5). Pruritus of the ears and licking of the perianal area, “ears and rears,” is a pattern attributed to AFR (Figs. 6 and 7). Perianal pruritus may also be seen alone. In a published case series, the ear region was involved in 80% of the cases of AFR; paws in 61%; inguinal region in 53%; and axillary, anterior foreleg, and periorbital regions in 31% to 37% of cases.³⁸ However, otitis externa with erythema of the pinnae and vertical canal with minimal horizontal canal involvement was the only cutaneous manifestation of AFR in 24% of dogs.³⁸ Otitis externa may even occur unilaterally only.

Secondary yeast/bacterial infection of the skin is a common sequel leading to a more generalized dermatitis and pruritus. A clinical presentation comparable with that of canine scabies with generalized papular pruritic dermatosis has also been associated with AFR and may be more common in Labrador retrievers (personal observation, S.R.M.). Although tail head pruritus is the classic clinical sign associated with flea allergic dermatitis in the dog, on rare occasions, tail head dermatitis may be AFR related. Secondary changes resulting from chronic pruritus to include keratinization abnormalities, lichenification, hyperpigmentation, and extensive alopecia are not uncommon. AFR dogs may show a papular dermatitis or only secondary lesions resulting from pruritus and complicating microbial infections.

Uncommon clinical signs may be the result of food-induced vasculitis,¹¹ food-induced urticaria,³⁹ and even food-induced erythema multiforme.⁴⁰ Signs consistent with vasculitis include poorly healing ulcers located in the center of the footpads, erosion, ulceration and crusting of the pinna margin, elliptical lesions on the concave aspect of the pinna, and urticarial vasculitis.¹¹ Urticarial vasculitis presents as urticarialike lesions that do not blanch with diascopy and do not pit with pressure, distinguishing them from a true urticaria.³⁹ Erythema multiforme is a clinically distinct lesion usually consisting of erythematous polycyclic or target-shaped macules that are nonpruritic or slightly elevated papules that spread peripherally and clear centrally.⁴⁰ In rare cases, primary pustules that are associated with bacteria may be noted.



Fig. 3. Young Newfoundland with severe weight loss, lethargy, and a very poor body condition, which was later diagnosed as having FA.

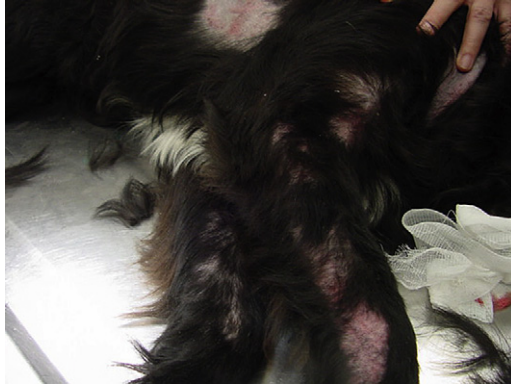


Fig. 4. Same dog as in **Fig. 3**. Papules, erythema, and alopecia were present on the distal extremity.

Cats

In cats, the mean age of onset of CAFR is 4 to 5 years.^{34,36} The most consistent clinical sign is pruritus, which was reported to be present in 100% of cats with FA.^{34,36} Pruritus may be localized or generalized. Miliary dermatitis is a common cutaneous reaction pattern that can be associated with AFR in its local or generalized form. Self-inflicted alopecia, the fur-mowing cat, can be observed in some cases. Pruritus most commonly affects the head and face region. Head and neck pruritus can be severe and lead to extreme self-trauma (**Figs. 8 and 9**). Some cats develop an exfoliative dermatitis. In addition, AFR may be the cause of eosinophilic plaques; indolent ulcers; and, rarely, angioedema, urticaria, and conjunctivitis.³⁶

Diet-responsive CE

Dogs

Dogs with diet-responsive CE are usually relatively young. In a Swiss study describing 70 dogs with CE, the median age of dogs with diet-responsive CE was 3.4 years (range 0.6–7.6 years), whereas it was 4.8 years (range 2.1–13.0 years) in dogs that required steroid treatment.⁷ Of the 38 dogs with diet-responsive CE, 27 (71%) had exclusively large bowel diarrhea (with signs such as frequent defecation, tenesmus, mucoid feces and/or hematochezia), whereas 9 dogs (24%) had mixed small and large bowel



Fig. 5. Same dog as in **Figs. 3 and 4** after a successful elimination trial.



Fig. 6. Significant ear and facial pruritus with self-inflicted alopecia on a Labrador retriever.

diarrhea and 2 (5%) had only small bowel diarrhea (**Fig. 10**). Using a clinical scoring index (canine inflammatory bowel disease activity index [CIBDAI]), the severity of signs was insignificant to mild in 30%, moderate in 62%, and severe in 8% only. By comparison, most dogs requiring steroid treatment and those with protein-losing enteropathy had small bowel diarrhea, and 52% had severe clinical manifestation of disease.⁷ A Dutch study that enrolled exclusively dogs with small intestinal diarrhea showed that almost 90% of dogs responded to either a highly digestible or a hydrolyzed diet over 2 to 3 months.⁸

Cats

The median age of 16 cats from New Zealand diagnosed with food sensitivity was 5 years (0.5–14.0 years). Their clinical signs included vomiting (56%), diarrhea (25%), or both (19%). Vomiting was usually infrequent (less than once a day in most cats). Nature and timing of vomitus were variable. More than half of the cats with diarrhea had large bowel signs. Weight loss was present in 69% and flatulence, in 38%. Four cats had concurrent cutaneous signs.⁶

DIFFERENTIAL DIAGNOSIS

The differential diagnoses for AFR with cutaneous and GI signs are listed in **Boxes 1–3**.



Fig. 7. Significant perianal pruritus with alopecia on the Labrador retriever in **Fig. 6**.



Fig. 8. Self-inflicted erosions and ulceration of the head and neck of a cat.

DIAGNOSTIC APPROACH

Diagnosis is intimately intertwined with therapy because in most cases, diagnosis is based on response to therapy. The gold standard for diagnosing AFR is abatement of clinical signs while the animal is being fed an appropriate restricted/novel diet and recurrence of clinical signs when the patient is challenged with previous food items. Other tests such as intradermal skin testing, skin patch testing, and measuring circulating food allergen-specific serum IgE are of no diagnostic value because of their low sensitivity and specificity.^{41–43}

Cutaneous Form

For CAFR, a few steps should be taken before embarking on a food trial; it is preferable to treat for possible sarcoptic mange if clinical signs are suggestive. If tail head pruritus is seen, adequate flea control should be initiated and the dog should be observed for 6 to 8 weeks. Secondary bacterial and yeast infections should be appropriately treated previously. In many instances, one or more of these treatments resolve the dermatitis. If pruritus or other clinical signs persist after the earlier-listed treatments have been instituted, a food trial should be considered. Similarly, if bacterial and/or yeast dermatitis recurs after discontinuation of antimicrobial therapy, a food trial may be warranted.



Fig. 9. Self-inflicted dorsal cervical ulcerations on a cat.

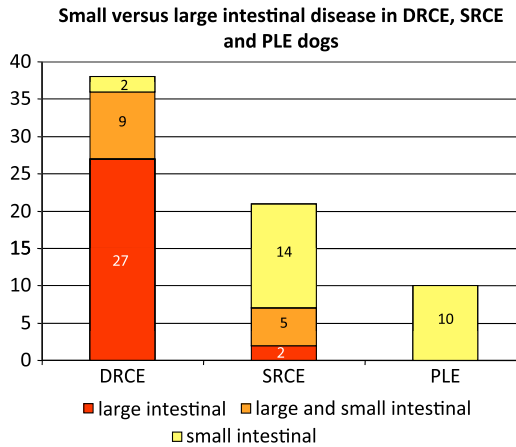


Fig. 10. Study of 70 dogs with chronic enteropathies. Numbers of dogs in each group presenting with signs of predominantly small intestinal, large intestinal, or mixed clinical signs. DRCE, diet-responsive CE; PLE, protein-losing enteropathy; SRCE, steroid-responsive CE. (From Allenspach K, Wieland B, Grone A, et al. Chronic enteropathies in dogs: evaluation of risk factors for negative outcome. *J Vet Intern Med* 2007;21(4):704; with permission.)

GI Form

In dogs and cats with CE, a systematic elimination of all possible diagnoses is required. However, a food elimination trial is usually recommended very early in this process because of the large proportion of responders. The first step consists of ruling out the presence of intestinal parasites and includes repeated ($n = 3$) fecal examinations, including fecal smears and fecal floatation. Fecal enzyme-linked immunosorbent assay (ELISA) delivers the most accurate results for *Giardia* infestation.⁴⁴ A 3- to 5-day course of fenbendazole is generally empirically prescribed (50 mg/kg once daily by mouth).

It is impossible to unequivocally differentiate dogs with diet-responsive CE from other dogs with CE by physical examination and routine laboratory investigations. However, recent studies have shown that a high percentage (62%) of dogs with diet-responsive CE had circulating antibodies against neutrophils (pANCA, perinuclear antineutrophil cytoplasmic antibodies) when compared with dogs with CE requiring steroid treatment (23%), and pANCA may therefore be a marker for diet-responsive CE.⁴⁵ The prevalence of pANCA in soft-coated wheaten terriers with

Box 1

Differential diagnoses of CAFR in the dog

- Nonseasonal AD
- Parasitic otitis externa or other causes of otitis externa if ear involvement only
- Drug reaction, which is a differential for any dermatosis
- Sarcoptic mange if significantly papular
- Bacterial and yeast dermatitis/hypersensitivity
- Contact dermatitis if clinical signs primarily ventral in distribution
- Flea allergy; tailhead disease is a rare manifestation of FA

Box 2**Differential diagnoses of CAFR in the cat**

- Nonseasonal AD
- Flea allergy dermatitis
- Psychogenic alopecia
- Dermatophytosis
- Otodectic mange
- Other causes of otitis externa
- Other external parasites
- Drug eruption
- Feline acne

protein-losing nephropathy and enteropathy and AFR is high, and the test may allow early detection of the disease in this breed, although large-scale investigations are still underway.⁴⁶

Although abdominal ultrasonography is useful to examine the GI tract of dogs and cats with CE, the technique does not distinguish diet-responsive animals from those that require other treatments. However, evaluation of blood flow through the cranial mesenteric artery and celiac artery using Doppler ultrasonography was found to be a valuable technique to document abnormal dynamics of GI perfusion after a meal. Postprandial vasodilation leads to decreasing Doppler indices and increasing diastolic blood flow velocity, which indicates decreased resistance to flow in the

Box 3**Differential diagnoses of chronic idiopathic enteropathies in the dog and cat**

- Intestinal parasites (nematodes and protozoa)^a
- Diet-responsive enteropathy^a
 - AFR: food intolerance, FA
 - Mild form of IBD
- Antibiotic-responsive enteropathy [d]
- Inflammatory bowel disease (IBD)^a
- Granulomatous colitis [d]^a
- Protein-losing enteropathy [d]
 - Intestinal lymphangiectasia [d]
 - Enteropathy of soft-coated wheaten terriers [d]
- Gluten-sensitive enteropathy of Irish Setters [d]
- Histoplasmosis [d>c]
- Alimentary lymphoma [c>d]
- Chronic idiopathic large bowel diarrhea [d]^a
- Other neoplasia

Abbreviations: d, dog; c, cat.

^a Often associated with large bowel diarrhea

downstream capillary bed of the GI tract. In a colony of soft-coated wheaten terriers with FA, dietary provocation with the allergen resulted in prolonged vasodilation at 90 minutes postprandially compared with nonallergenic food (**Fig. 11**).⁴⁷ These hemodynamic changes occurred before the dogs developed clinical signs, such as diarrhea, in response to the dietary challenge.⁴⁷ This noninvasive ultrasonographic method shows promise for early detection of dogs with AFR and GI signs at the time of dietary provocation. Early detection of allergenic protein sources before the onset of GI signs may increase the acceptability of the dietary challenge among pet owners. However, in a preliminary study, the technique was not found to be as reliable for dogs with CAFR.⁴⁸ These results support the finding that no significant GI mucosal inflammation is observed in dogs with CAFR.²¹

GI endoscopy with collection of mucosal biopsy samples may be indicated in dogs and cats with CE. Dogs with diet-responsive CE could not be differentiated from those with disease requiring steroid therapy based on the severity of endoscopic or histologic lesions.^{7,49} Moreover, histologic scoring was not different before and after clinically successful treatment.^{7,49} Gastric or colonic antigen provocation test may be of interest in identifying the substances to which a dog is allergic, even though both tests have their limitations.⁵⁰ Moreover, these tests are not widely available at present.

A recent study describes the use of the lymphocyte blastogenic response (or lymphocyte stimulation test [LST]) to various food antigens to determine the inciting food allergen in a series of dogs with AFR and cutaneous and/or GI signs.⁴¹ The agreement between LST and dietary elimination and provocation trials was good while the dogs were fed the allergenic diet. However, the LST was blunted in dogs receiving an elimination diet and experiencing clinical remission.⁴¹

TREATMENT

Dietary Elimination Trial

For maximum efficiency in performing a food trial, it is important to obtain a complete dietary history from the client concerning their pet before choosing any food for the AFR elimination diet trial. Clinical signs of GI disease usually improve within 2 weeks, whereas cutaneous clinical signs may take up to 8 to 12 weeks to respond to a dietary change.

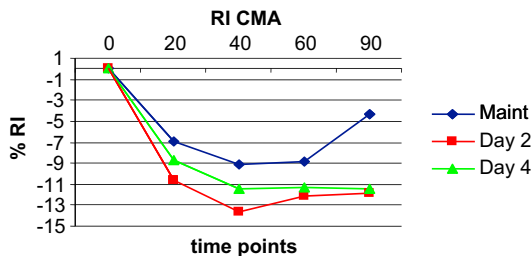


Fig. 11. Postprandial changes in the percentage of resistive index versus time in the cranial mesenteric artery in soft-coated wheaten terriers crossbreds. The dogs had been fed a meal containing an allergen that they were reactive to (see text for explanation). RI, resistive index; CMA, cranial mesenteric artery; Maint, maintenance diet that does not elicit clinical signs; Day 2 and Day 4, time between exposure to dietary allergen and examination. (From Kircher PR, Spaulding KA, Vaden S, et al. Doppler ultrasonographic evaluation of gastrointestinal hemodynamics in food hypersensitivities: a canine model. *J Vet Intern Med* 2004; 18(5):608; with permission.)

An immune response can be mounted against any substance (especially protein) to which that pet has been exposed, which has not been modified to the point of rendering it nonallergenic.

Novel protein diets

Commercially available novel protein source diets typically include proteins from venison, rabbit, duck, kangaroo, moose, elk, goose, goat, ostrich, or emu and are combined with a carbohydrate source such as potatoes, sweet potatoes, rutabagas, oats, barley for the dog, and green peas for the cat. Generally, the closer the taxonomic relationship between meat sources, the higher the risk of cross-reactivity. Allergens from beef theoretically may cross-react with those from other ruminants. Thus, lamb and venison may not be the best unique ingredient protein sources because most animals have been previously exposed to beef. However, this finding has yet to be seen as a problem in veterinary medicine. There is evidence of common allergens in avian meats,⁵¹ and the use of duck diets in patients previously exposed to chicken may not be advisable. Cross-reactivity among meats of various proveniences has not been studied yet in dogs and cats.

Controversy persists between the choices of a home-cooked diet, a commercial veterinary prescription diet, and a novel protein over-the-counter (OTC) diet for the elimination trial. The veterinary prescription diet and the OTC novel protein diet may offer the advantage of enhanced owner compliance because of minimal time in food preparation. Home-cooked diets can be unbalanced and may be inadequate in young, large breed, rapidly growing dogs if they are not carefully formulated. In addition, purchased ground meat from one animal source may be contaminated with ground meat from another meat source if the grinding machine was not completely and thoroughly cleaned between uses. However, some clients wish to home cook for their pet, and recipes for balanced formulations are available. Veterinary prescription diets or OTC novel protein diets may not be adequate for the growing puppy. Rarely, dogs have been described that tolerate home-prepared ingredients from a specific protein source but not their commercially prepared versions. This finding raises concerns that heat processing may change the food allergen configuration, substances may leech into the food during industrial processing, or food additives may be an allergen source.^{38,52} In a recent study, none of the 4 OTC venison diets was considered suitable for an elimination trial because they all contained common pet food proteins, some of which were not mentioned on the label. Of the 4 OTC venison diets, 3 tested positive for soy, poultry, and/or beef using an ELISA, even though these ingredients were not listed among the ingredients.⁵³

The existence of nonprotein allergens has been documented; however, these allergens are generally thought to be combined with protein allergens (glycoproteins, lipoproteins). Thus, attention should be paid to the carbohydrate and lipid sources chosen for incorporation into elimination diet because these sources may represent an important source of allergens, unless the food company has taken steps to remove any protein allergens from these components of the diet.

Hydrolyzed diets

Hydrolysates contain small peptides that are less likely to be allergenic than full size proteins. In a study by Jackson and colleagues,⁵⁴ 21% of the dogs that were hypersensitive to soy and corn reacted adversely to the hydrolyzed soy diet with return of cutaneous signs, but 79% had no problems when the diet was fed for 2 weeks. Thus, a commercially available hydrolysate soy and corn diet was tolerated by most, but not all, of the dogs sensitized to the intact compounds. In a more recent

study by Ricci and colleagues⁵⁵ evaluating 12 dogs with cutaneous manifestations of allergic dermatitis after exposure to chicken meat, clinical signs improved in 11 dogs when fed a hydrolyzed chicken diet, whereas 1 animal did not significantly improve. In another study of experimental soy allergic dogs, IgE binding to hydrolyzed soy peptides was found to be significantly reduced (but not absent) compared with binding to the native soy protein.⁵⁶ In a recent systematic review of 11 studies examining the evidence in favor of reduced immunologic and clinical allergenicity of hydrolysates in dogs with CAFR, it was concluded that hydrolysate-containing diets were probably best used in dogs with no suspected hypersensitivity to the original source of hydrolyzed peptides.⁵⁷

Oral medications

Many medications, especially OTC medications, may contain unwanted/hidden proteins. Ten of 12 dogs from a canine colony with spontaneous AFR to soy and corn displayed cutaneous signs when given a chewable tablet containing pork liver, soy, and milbemycin.⁵⁸ All flavored medication should therefore be avoided, including medication packaged in gelatin capsules. Also, coprophagic dogs may ingest undigested material that could affect a food trial. Some veterinarians even advocate the use of distilled water during the elimination trial.

Client education and compliance

Lack of client compliance is generally the biggest reason for failure of dietary trials. Often this lack of compliance is because of insufficient client education concerning expectations and especially length of the trial. It was shown that without improved client education, 52% of elimination trials would fail at the time of follow-up compared with a failure rate of 27% after better client education was instituted.²⁶ A food trial requires full investment and cooperation of the pet's owner, and cannot be adequately performed on a free-roaming pet. The client must have complete control of what their pet ingests. This is a particular challenge in trying to diagnose food-allergic cats. An indoor/outdoor cat or completely outdoor cat may need to be kept inside only for the duration of the food trial. Motivation can be improved by supplying the clients with a daily dietary log to fill out. Daily recording of itching level, GI signs, and honest recording of dietary violations on the log can provide extra motivation and good information as well.

The lengthy food trial required for dermatologic disease (8–12 weeks) benefits from regular motivational meetings in which pitfalls, accidents, and progress are discussed. Monthly rechecks to assess changes in cutaneous symptoms provide information on flea control, secondary infection, and other issues that can complicate interpretation of the diet trial results. If the pet is severely pruritic, a short course of oral short-acting corticosteroids or other nonsteroidal antiinflammatory medication may be warranted at the beginning of the food trial. To allow accurate evaluation of the response to the food trial, this medical manipulation must be discontinued 1 to 2 weeks before the veterinarian's assessment.

Dietary Provocation Test

A rechallenge or provocation is necessary to confirm AFR after the elimination diet has been fed for 8 to 12 weeks. Improvement over this length of time could also result from elimination of seasonal environmental allergens (change of season). In addition, successful treatment of scabies and bacterial and yeast infections and/or improved flea control may be the reason for improvement.

During the rechallenge, the initial food is reintroduced or individual ingredients from the initial food are fed one by one while continuing to feed the elimination diet to cover nutritional needs. To ensure a thorough provocation, it is important to challenge with all previous food stuffs, including flavored medication, rawhide chews, other flavored chewable bones, treats, flavored toothpastes, and so on. The time needed to provoke a GI reaction is generally thought to be a few days after the allergen is reintroduced.^{6,7} The time needed to provoke a cutaneous reaction to a food allergen is not clear. Most literature reports that clinical signs exacerbate between a few hours and 21 days.⁵⁹ In one study, the mean number of allergens to which dogs reacted to on rechallenge was 2.4, with 80% reacting to 1 or 2 proteins and 64% reacting to 2 or more of the proteins tested.⁵⁹

However, many clients do not elect to rechallenge with the former diet, much less individual ingredients. In this scenario, the pet can either be kept on the test diet indefinitely, or other novel protein OTC diets that may be less costly can be tried. If new foods are to be tried, including treats, it is important to introduce only one food or treat at a time, so if a reaction occurs, the food stuff responsible can be more easily confirmed.

If the results of the elimination trial are negative and further allergy testing proves unrewarding or does not completely explain the clinical signs, a second food trial using a different protein/carbohydrate source or a home-cooked recipe may need to be considered. In dogs and cats with GI signs, other causes of chronic idiopathic enteropathies should be considered (see **Box 3**).

PROGNOSIS

In dogs and cats with AFR, the prognosis is excellent once the disorder is correctly identified with an appropriate food trial. However, it is difficult for many clients to maintain a strict diet without intermittent dietary violations, either knowingly (feeding a forbidden or suspect food) or unknowingly (OTC supplement with hidden food allergen, prescribed medication with food allergen, or pet scavenging food). Elimination of the forbidden food, treat, or supplement or better control of access to other foods improves the clinical signs, but treatment of a secondary bacterial or yeast infection of the skin or ears may be necessary to restore the skin to normal. In addition, a significant proportion of animals with diet-responsive CE can be switched back to their original diet after a successful treatment with an elimination diet.

SUMMARY

AFRs are common diseases that may have various clinical manifestations, including cutaneous lesions and GI signs. A systematic diagnostic and therapeutic approach centered on a dietary elimination trial followed by a dietary challenge is necessary. The prognosis is generally excellent.

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