Allergic dermatitis in dogs and cats

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Summary

Allergic dermatitis is a common clinical condition in dogs and cats. In this paper the ethiology, diagnosis and management of atopic dermatitis and food allergy will be reviewed with special focus on the nutritional management of allergic dermatitis.

Nutrients as fatty acids play an important role in the maintenance of the epidermal barrier function. Furthermore, certain fatty acids from fish oil and borage oil can exhibit multiple anti-inflammatory and immunomodulating properties and have the potential to affect skin inflammation. Adequate diets for management of food allergy contain uncommon ingredients or hydrolysed proteins to reduce the risk on clinical signs of food allergy.

Abbreviations

- Arachidonic acid AA
- AD Atopic dermatitis
- AFR Adverse food reaction
- ALA α-linolenic acid
- APC Antigen presenting cell
- Cutaneous adverse food reactions CAFR
- COX Cyclooxygenase
- Dihomo-y-linolenic acid DGLA
- DHA Docosahexaenoic acid
- EFA Essential fatty acids
- EPA Eicosapentaenoic acid
- GALT Gut associated lymphoid tissue
- GLA y-linolenic acid
- IBD Inflammatory bowel disease
- LOX Lipoxygenase
- LT Leukotrienes
- PG Prostaglandins
- ТΧ Thromboxane

Allergic dermatitis

Dogs and cats are susceptible to a wide range of inflammatory skin diseases. In dogs, these include allergic disorders, parasitic infestations, bacterial infections and adverse reactions to food. Cats show the same disorders with the addition of miliary dermatitis and eosinophilic granuloma complex. Allergic skin disorders are among the most common dermatological conditions in dogs and cats. Allergic skin disorders in dogs include atopic dermatitis (AD), food hypersensitivity (or allergy, FA) and flea-bite hypersensitivity. In cats, allergic skin disease also manifests as miliary dermatitis¹⁻⁴.

Atopic dermatitis

Atopic dermatitis is defined as a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features, associated with IgE antibodies most commonly directed against environmental allergens as such as mites (house dust, storage), pollens (trees, grasses, weeds), moulds and danders⁵. The pathogenesis of AD is not completely understood, susceptibility to clinical disease is determined by genetic and environmental factors. Sensitisation to environmental allergens and/or allergens from food, microbial or insect sources can lead to infiltration of the skin by inflammatory cells, activation of resident cells and local production of inflammatory mediators (Figure 1). Epidermal barrier dysfunction, cutaneous bacterial and yeast infections, psychogenic factors, and concurrent skin diseases are contributing factors to sensitisation⁶.

There are breed predilections, but the prevalence within a breed largely depends on the genetic pool and region. Breeds predisposed to development of AD include Chinese Shar-Pei, Wirehaired Fox Terrier, Golden Retriever, Dalmatian, Boxer, Boston Terrier, Labrador Retriever, Lhasa Apso, Scottish Terrier, Shih Tzu, and West Highland White Terrier. Purebred cats may have a higher risk than domestic shorthaired cats6.

Dogs normally show signs of the disease between 3 months and 6 years of age, though atopic dermatitis can be so mild during the first year that it does not become clinically apparent before the third year. In cats the age of onset is variable but generally is under 5 years old.

Pruritus is the characteristic sign of AD. The feet, face, ears, flexural surfaces of the front legs, axillae, and abdomen are the most frequently affected areas. Primary lesions consist of erythematous macules, patches, and small papules. Lesions that develop secondary to selftrauma include alopecia, erythema, scaling, salivary staining, haemorrhagic crusts, excoriations, lichenification, hyperpigmentation, superficial staphylococcal pyoderma, Malassezia and bacterial overgrowth, perianal pruritus⁹ and allergic otitis externa. In cats, clinical presentation includes miliary dermatitis, symmetric alopecia, eosinophilic granuloma complex and head and neck pruritus.

Skin has only a limited number of ways in which to react. Thus, a variety of dermatological and other medical disorders can be manifested by the same clinical cutaneous abnormalities. Thus, diagnosis of atopic dermatitis in pets is based on exclusion of other possible pruritic dermatoses after thorough physical examination and testing to exclude other causes including parasites (flea, mites...), infections (bacteria, Malassezia...), other allergies (flea bite, contact allergy...) and other pathologies (endocrine, neoplasic, psychogenic disorders...) and meeting the diagnostic criteria for AD. Allergy tests should only be used once a clinical diagnosis of AD has been made with the primary purpose being to identify potential causative allergens that may be avoided or treated by immunotherapy.









Later Exposure

At later exposure to the same allergen, allergens may penetrate the epidermis and cross-link IgE on the surface of the dermal mast cells, leading to degranulation and immediate release of inflammatory mediators including histamine and, in a late phase a de novo synthesis of inflammatory mediators: leukotrienes, prostaglandins and various cytokines that recruit inflammatory cells into the skin⁷.

Figure 1. Skin inflammatory allergy condition sensitization.

Since several factors appear to contribute to the cutaneous inflammation and pruritus of AD patients, the therapeutic strategy should focus on the control of those factors that can be identified and, for which, interventional measures are feasible. Treatment should include control of ectoparasites, particularly fleas, which can exacerbate pruritus. Bacterial and yeast infections primary or secondary to AD lesions should be properly treated by systemic and/or topical therapy, followed by regular topical treatment for preventing relapse. Concurrent dietary hypersensitivity should be investigated and treated if present as is explained below. Depending on the severity of the clinical signs of atopic dermatitis and the willingness and expectations of owners, symptomatic treatment and/or specific interventional therapy for environmental allergy (allergen avoidance, allergen-specific immunotherapy) may be implemented. Symptomatic treatment includes: the use of glucocorticoids (systemically or topically), cyclosporine and oclacitinib. Other treatment modalities of sometimes lower or less proven efficacy include antihistamines, dextromethorphan, fatty acids, feline interferon-omega, misoprostol, pentoxifylline, specific serotonin re-uptake inhibitors and tricyclic antidepressant drugs¹⁰.

The therapeutic approach of atopic dermatitis should be reviewed at regular intervals and tailored to the individual's needs. A successful long-term outcome can usually be achieved by combining the various treatment approaches in a way that maximises their benefits and minimises their drawbacks⁶.

Food allergy

An adverse food reaction (AFR) is described as an abnormal response to ingested food components. If it involves immune mediated mechanisms, it is defined as a FA whereas in all other cases it is defined as food intolerance¹¹. Food intolerance can be further categorized into metabolic, pharmacologic, toxic, and idiosyncratic reactions. The most frequent clinical signs associated with AFR are dermatological (cutaneous adverse food reactions, CAFR) and gastrointestinal^{11,12}. The term AFR includes multiple pathophysiological mechanisms that result in similar clinical signs for both FA and food intolerance.

The pathophysiology of FA in dogs and cats is poorly understood, although it is assumed that there is an alteration in the normal processing of food antigens and the development of oral tolerance^{11,12}. Although there is little data, both IgE and non-IgE mediated mechanisms are believed to exist in veterinary medicine, most notably type III and IV responses¹¹. With type I hypersensitivity reactions, IgE-sensitized mast cells are triggered by a specific allergen. When the mast cell releases its pharmacological mediators, an inflammatory response will follow in the tissue leading to dermatological, respiratory, or gastrointestinal signs or a combination.

A food allergy can arise when an allergen induces an abnormal immunological response. Normally, an antigen will induce oral tolerance, which is an active response and is designed to limit the unnecessary and wasteful activity of the Gut Associated Lymphoid Tissue (GALT) in response to non-dangerous luminal antigens, such as those from endogenous microbiota or food. If this normal tolerance is not well established, the antigen induces an inappropriate immune response to endogenous flora (resulting in Inflammatory Bowel Disease; IBD) or to food allergens resulting in FA^{11,12}. Several mechanisms ensure the conflicting functions of tolerance and exclusion of antigens: the mucosal barrier, the regulation of the immune response and the elimination and tolerance of antigens reaching the mucosa.

During the oral tolerance development mechanisms, the wall of the digestive tract is the largest surface of the body exposed to the environment. The digestive tract must differentiate between nutrients and unharmful microbiota which must be tolerated and potential harmful organisms as some bacteria, viruses and, parasites which must be avoided. Gut Associated Lymphoid





Tissue (GALT) oversees this differentiation. GALT encloses different lymphoid tissues all along the intestine. Tolerance of antigens reaching the mucosa starts with the interaction of specialized M-cells within the epithelium who report antigens to B-cells, macrophages, and dendritic cells. Those specific intestinal antigen presenting cells (APCs) lack co-stimulatory molecules, which allows a lack of reaction against antigens as it would happen in other lymph tissues in the body. Further presentation of the antigen to those unresponsive APCs leads to tolerance to the antigen.

Loss of tolerance to dietary antigens will produce a conventional but detrimental immune response against the dietary antigen that may produce inflammation locally, or at another anatomical sites such as skin. The response may include (alone or in combination) a local cell mediated inflammation (which may result in a lymphocytic intestinal infiltrate, as in IBD), a local antibody production of IgE that may lead to mast cell priming with histamine release and intestinal hypersensitivity (as in FA with gastrointestinal signs) and a systemic IgE production (Figure 2). Systemic circulating IgE will lead to priming and degranulation of mast cells at sites distal to the intestine such as dermal hypersensitivity (as in food allergy with pruritus).



Figure 2. Pathophysiological mechanisms of clinical signs in food allergies.

Although the mechanisms that lead to loss of oral tolerance, or prevent it from developing are not fully understood, suggested initiating mechanisms include an increase in mucosal permeability, following, for example a mucosal injury, or the immature neonatal intestine, the co-administration of a mucosal adjuvant that activates and changes the phenotype of intestinal dendritic cells, and for example bacterial enterotoxins and intestinal parasitism which leads to an exaggerated systemic humoral response that includes increased production of IgE^{8,13}.

Dietary antigens are commonly glycoproteins that require a minimum size to trigger a reaction. This size has been defined in human medicine as 10-70 kD, but there are no data for dogs or cats¹⁴. As for food intolerance, the pathophysiological mechanism varies depending on the reaction. In these cases, other non-protein ingredients can be responsible for the clinical signs (such as food additives).

The CAFR is the third most common allergic skin disease in dogs after flea allergy dermatitis and atopic dermatitis. CAFR in the cat is reported to be second in frequency to flea allergy dermatitis. Nevertheless, the exact prevalence in dogs and cats of FA is unknown, in part due to the difficulty in diagnosing and the variety in clinical signs. It has been reported as 1% of all skin disease and 10% of all allergic skin disease⁶.

There is no age, sex, or breed predilection described, although first symptoms often arise before 1 year in dogs, and Siamese cats have been suggested to be at higher risk¹².

The most common dermatological sign is non-seasonal pruritus, which can be generalized or localized^{15,16}. Common skin lesions include erythema, papules, excoriations, pododermatitis and otitis externa in dogs^{16,17} and miliary dermatitis, eosinophilic plaques, self-induced symmetrical alopecia and head and neck excoriations in cats¹⁸. Gastrointestinal signs include vomiting, diarrhea and abdominal pain^{12,19}.

The coexistence of skin and gastrointestinal signs, usually reported as 10-15% of the cases^{20,21}, is considered very suggestive of AFR, at least in cats¹⁹.

An elimination diet trial is the most important and only reliable diagnostic test to evaluate for and diagnose a FA in a dog or cat¹⁰. Figure 3 summarizes the steps to perform properly a diagnostic elimination trial. The trial consists in feeding a chosen diet for at least 8 weeks based on avoiding ingredients previously fed and then challenging the patient with the ingredients of the original diet²². Neither serology nor intradermal testing should be used for diagnosing food allergy. These tests do not provide clinically relevant information about which food proteins an animal is allergic to^{11,23,24}.





Elimination phase

- Owner's commitment is required to successfully complete an elimination and challenge diet trial, so owners and family should understand that an elimination and challenge trial is the only way to conclusively identify clients with FA.
- The diet should include ingredients (or at least protein sources) that the patient has never been exposed to. This is only possible with an exhaustive diet history of the patient which include all the products fed during his life.
- An elimination diet should be administered exclusively during the trial. Other antigen sources should be eliminated (treats, flavoured medication, flavoured toothpaste, unmonitored sources of food).
- The duration of this trial should be of at least 8 weeks.
- The elimination trial can give false results if the ingredients used were not novel to the patient, so if possible, two or more elimination diets should be tested before ruling out FA.

Challenge phase

- Animals that improve clinically to the elimination phase should then be challenged with individual ingredients suspected of eliciting the adverse reaction for 1-3 weeks.
- It is also possible to challenge with the previous diet, but then the individual offender might never be identified.
- If the clinical signs recur the patient is diagnosed with FA. Patients with CAFR will have a recurrence of exacerbation of their pruritus within hours to days, with most having a recurrence within 3 to 7 days.
- Therapy for any concurrent dermatologic diseases should be continued during the challenge phase of the trial so that infections do not recur that could exacerbate pruritus and lead to erroneous interpretations of the challenge phase.

Figure 3. Elimination diet trial protocol for food allergy diagnostics in dog and cat.

A percentage of canine patients (35%) may react to more than 1 ingredient²⁵. The patients whose clinical signs do not recur with the challenge cannot be diagnosed with FA. In one study it was reported that 20% of cats with chronic diarrhoea responded to elimination but not to the challenge¹⁹. The authors hypothesized that the offending ingredient might not have been correctly identified, the challenge phase might have been too short, the disease might have spontaneously resolved or other aspects of the elimination diet might be responsible for the improvement, such as digestibility or fat content. Also other changes besides the diet during the elimination phase may have resulted in an improvement of the condition. Partial response may occur when concurrent allergies are present (up to 75% of dogs with CAFR will concurrently have other allergies⁶) or in atopic patients that go through a fluctuation in severity¹². Elimination trial response may also be hampered by the influence of infections (bacterial, mycotic) or a simultaneous started treatment for pruritus. Those factors may lead to a false diagnosis of FA. Figure 4 summarizes the decision options during FA diagnostics.

Long-term treatment of FA is based on allergen avoidance, using food that lacks those dietary components that trigger an allergic response. Similarly, as in AD, skin health and symptomatic treatment should be also considered according the patient's situation.



Figure 4. Diagnostic algorithm for adverse reaction to foods.



Other hypersensibilities

Flea allergic dermatitis is caused by an allergic reaction to allergens in flea saliva and is the most common hypersensitivity encountered in the dog and cat. Flea allergy is not age-specific and might occur as early as 3 months of age. Flea allergy normally affects the caudal part of the body (lumbosacral area, base of tail, caudomedial thighs and abdomen) in both cats and dogs⁶. Diagnosis of flea allergy can be made based on clinical signs, presence of fleas and flea excrements or based on treatment results.

Contact dermatitis can be allergenic or irritant in origin, which cannot be distinguished in clinical cases. It is a rare disease. It might be induced by contact to carpets, plastic feeding bowls, collars, shampoos or medications used for local treatments.

Concurrent allergies

Concurrent hypersensibilities are not uncommon. The combination of atopy, FA and flea allergic dermatitis is well known^{25,26}. In 20–30% of the cases of FA, simultaneous allergic skin diseases have been reported¹². In specific studies with dogs diagnosed to suffer from adverse food reactions, 44% to 59%^{27,28} of them had concurrent atopy. As mentioned above, concurrence of hypersensibilities may complicate diagnoses in some patients. Optimal management of concurrent allergies requires a combined approach taking into account all relevant allergies.

Nutritional management of allergic dermatitis in dogs and cats

Epidermal barrier dysfunction

Dog and cat epidermis has an important role to provide a protecting barrier to the body from potentially damaging environmental effects. These effects include a desiccating atmosphere, physical trauma as well as constant contact with allergens, irritants and toxic agents. The skin, and specifically the epidermis, has a stratified structure. Of the constituent layers, it is the outermost 'cornified' stratum corneum (SC) which plays the principal role of barrier defence. The SC is formed via the terminal differentiation of the main skin cell, the keratinocyte, which differentiated by multiple steps to flat, protein-rich cells called corneocytes. The corneocytes are one of the two main components of the SC, the other being a specialized lipid matrix that surrounds the cells (Figure 5). The composition and conformation of these lipids are a key point determining the qualities and efficiency of the epidermal barrier²⁹. In addition to the corneocytes and the lipid compartment, unique tight junctions also contribute to the integrity of the skin barrier³⁰.

The importance of an intact and effective epidermal barrier to the overall health of the skin is essential; indeed many skin conditions have been related to altered epidermal barrier. Thus, ensuring that the barrier remains intact may ameliorate many of the skin diseases.

Defective skin barrier function is present in skin of allergic dermatitis affected dog and cats. It can occur because of inflammation and self-trauma. A defective skin barrier function is associated with perturbation of lipid metabolism and dysfunction of proteins with skin integrity functions as filaggrin, keratins and, intercellular adhesion molecules^{31,32}. Studies in AD canine patients have found an abnormal composition of the SC lipids, and more specifically ceramides, which lead to compromised barrier function by a los of continuity and overall thickness of the SC intercellular lipid.

Epidermal barrier defects may lead to dry skin which aggravates pruritus and allows an increased penetration and sensitization to environmental, bacterial or fungal allergens as well as irritants³¹.

Restoration of the epidermal barrier function is an important part of the therapeutic approach in dogs and cats with allergic dermatitis¹⁰.







Figure 5. Epidermal barrier defects in allergic dermatitis patients.

Epidermal barrier defects may lead to dry skin, which aggravates pruritus and allows increased penetration and sensitization to environmental, bacterial or fungal allergens as well as irritants.^{33,34}

Skin barrier defects facilitate penetration of the SC by allergens⁷. This may trigger antigenpresenting cells in the epidermis^{7,32}. Immune cell derived inflammatory mediators then activate keratinocytes, which in turn release additional cytokines and chemokines³¹. At the same time, there is an IgE-mediated degranulation of cutaneous mast cells and an immigration of granulocytes, T lymphocytes and dendritic cells (Figure 1). The resulting dermal and epidermal damage in combination with self-trauma and secondary infections contribute to self-perpetuating inflammation and chronic skin lesions³¹.

Some key nutrients involved in lipid matrix and epidermal barrier structures integrity have been suggested to be beneficial to assure barrier functions and limit skin alterations in dogs and cats. Nutrients suggested enclose pantothenic acid, nicotinamide, histidine, choline, inositol³⁵, as well as essential fatty acids⁶.

The role of fatty acids

Essential fatty acids (EFA) have been used in veterinary dermatology for many years due to its beneficial effects on skin health and integrity and its anti-inflammatory effects.

Figure 6. Structure and nomenclature of omega polyunsaturated fatty acids.

What is a fatty acid? - Fatty acids are molecules composed of long chains of carbon and hydrogen atoms (referred to as hydrocarbon molecules) containing a carboxylic acid moiety at one end (a carboxylic acid is written –COOH). See the structure in the Figure 6a. Most naturally occurring fatty acids have an unbranched chain of an even number of carbon atoms, from 4 to 28.

In animal tissues, fatty acids are usually found as part of triglycerides of fat or as part of phospholipids of bilayer membrane of cells.

a. Structure of fatty acids

Carbon atoms can form covalent bonds to four other atoms. In some cases, the C or O atoms bound to a C are bound via a double bond (written -C=C- or -C=O; see Figure 6a). Fatty acids that contain no carbon-carbon double bonds are termed saturated fatty acids because the carbon atoms are "saturated" with four single covalent bonds. Fatty acids that contain carbon-carbon double bonds are termed saturated fatty acids that contain carbon-carbon double bonds. Fatty acids with multiple double bonds are termed polyunsaturated fatty acids (PUFAs). The presence of double bonds changes carbon chain conformation and causes the chain to bend (see Figure 6b). When a chain has many double bonds, it becomes quite curved. This may affect its properties, such as when fatty acids are part of a phospholipid in a lipid bilayer, or triglycerides in lipid droplets, double bonds limit the ability of fatty acids to be closely packed, and therefore can affect the fluidity and stability of the membrane or of the fat.



Figure 6a.



b. Saturated and unsaturated fatty acids

Nomenclature of unsaturated fatty acids – Although other nomenclatures exist, omega (ω or Ω) is the most widely used in medical literature. The term omega refers to the position of double bonds in relation to the hydroxyl group on the end of the fatty acid. The designation of a PUFA as an omega-3 fatty acid, for example, defines the position of the first double bond position counting carbons from the hydroxyl group as shows Figure 6b. Thus, an omega-3 fatty acid, has a double bond between the third and fourth carbons from the hydroxyl end. An omega-6 fatty acid, has a double bond between the sixth and seventh carbon of the carbonated chain.

Essential fatty acids - The majority of fatty acids found in the body are acquired in the diet. However, some of the body fatty acids can be synthetized by the body. Two key exceptions to this are the PUFAs known as linoleic acid and alpha-linolenic (α -linolenic) acid, abbreviated ALA. These two fatty acids cannot be synthesized from precursors in the body, and are thus considered the essential fatty acids; essential in the sense that they must be provided in the diet. These two essential fatty acids are also referred to as omega fatty acids. Linoleic acid is an omega-6 PUFA and ALA is an omega-3 PUFA.



Figure 6b.

c. Enzymatic desaturation and elongation of omega-6 and omega-3 fatty acids.

Fatty acid sources – Linoleic acid and ALA can be modified (elongated and desaturated) by means of enzymes to form other omega-6 or omega-3 fatty acids (respectively) with important functions in the body (see Figure 6c). Due to a lack of activity of the enzyme delta-6 desaturase, cats are not able to form arachidonic acid (omega-6) from linoleic acid, making arachidonic acid also an essential PUFA for cats. When discussing omega-3 and -6 fatty acids, it is important to note that their dietary origin is quite important. Omega-3 fats from plants, such as those in flaxseed oil, are enriched in ALA. As indicated in Figure 6c, ALA must first be converted to EPA (requiring three independent reactions) and then to DHA (requiring an additional four reactions). Omega-3 fats from fish are enriched in EPA and DHA and thus do not need to undergo the complex conversion steps as required for ALA. In addition, the conversion of ALA to EPA and then EPA to DHA is very inefficient in dogs, and even more in cats. Therefore, direct dietary intake of omega-3 fats rich in EPA and DHA are of the most clinical benefit.

Similarly, linoleic acid is the precursor for arachidonic acid (AA) (Figure 6c). The significance of arachidonic acid is that it serves as the precursor molecule for the synthesis of a family of bioactive lipids called the eicosanoids (see the text). Except the cat that should consume AA, upon consumption, linoleic acid is converted to gamma-linolenic acid (γ -linolenic acid, GLA). GLA can be also directly consumed. GLA is then converted to dihomo- γ -linolenic acid (DGLA) and then to arachidonic acid. The activity of the enzyme that converts linoleic acid to GLA (Δ 6-desaturase, see Figure 6c) is slow and can be further compromised due to nutritional deficiencies as well as during inflammatory conditions.



Figure 6c.

Anti-inflammatory effects of polyunsaturated fatty acids

EFA (Figure 6) are key nutrients for maintainance of skin health. Indeed, deficiency in linoleic acid (omega-6 EFA) leads to coarse, dry hair, and desquamation that evolves to a greasy, pruritic skin. The epidermis becomes thick and oedematous and parakeratosis appears with time. Skin infiltrates of monocytes and neutrophils and ulceration have been also observed³⁶.

Supplementation of EFA exhibit multiple anti-inflammatory and immunomodulating properties. They have the potential to affect allergic and other forms of skin inflammation through modulating cytokine production, inhibiting cellular activation and cytokine secretion and altering the composition and function of the epidermal lipid barrier⁷.

Their mechanisms of action, are likely to be explained by a combination of effects. Unsaturated fatty acids have an impact on numerous cells involved in the pathogenesis of AD, including keratinocytes, dendritic cells, T lymphocytes and mast cells (Figure 1). It appears that dietary PUFA are readily integrated into cell membranes, whereby modulating the properties of the lipid bilayers leading to cell functional changes, as has been suggested for down-regulation of exaggerated mast cell degranulation³⁷.

The most commonly proposed mechanism of action of EFA in the treatment of inflammatory skin diseases is the modulation of cutaneous production of prostaglandins (PG) and leukotrienes (LT), which are inflammation mediators synthesized from omega-3 and -6 fatty acids (Figure 7)³⁸.

Arachidonic acid (Figure 6c) is the major PUFA in cell membrane phospholipids. The normal response of injured tissue is inflammation, a tissue protective mechanism. Under these circumstances, phospholipases are activated and act on phospholipids of cell membranes to release constituent fatty acids (Figure 7). Arachidonic acid, the fatty acid in greatest concentration, is released and converted into eicosanoids, which mediate inflammation (Figure 7).

Arachidonic acid derived LT (series 4) and PG (series 2) play a central role in the inflammatory process. The 4-series LT stimulate neutrophil and eosinophil chemotaxis and increase vascular permeability and 2-series PG inhibit T and B lymphocyte proliferation, reduce cytokine production and limit natural killer cell activity. However, these proinflammatory eicosanoids can result in pathologic conditions when produced in excessive amounts and/or prolonged periods of time³⁹. In many chronic inflammatory diseases increased production of 4-series LT and 2-series PG has been reported⁴⁰. Synthesis of AA derived eicosanoids are targets of numerous pharmacological agents such as the non-steroidal anti-inflammatory drugs, COX-2 inhibitors, and leukotriene antagonists.

Nevertheless, different series of eicosanoids (PG and LT) are also derived from DGLA and EPA (Figure 6c). Generally, omega-3 fatty acids are thought to produce less inflammatory cytokines³⁹. Increased consumption of long-chain omega-3 PUFAs, such as eicosapentaenoic acid (EPA; 20:5 omega-3) and docosahexaenoic acid (DHA; 22:6 omega-3), results in increased proportions of those fatty acids in inflammatory cell phospholipids⁴¹. The incorporation of EPA and DHA into inflammatory cells occurs in a dose-response fashion and is partly at the expense of AA. Because less substrate is available for synthesis of eicosanoids from AA, the synthesis of 4-series LT and 2-series PG by inflammatory cells decreases⁴². When EPA is available in phospholipids, eicosanoids derived from EPA are synthetized. These EPA-derived eicosanoids have a slightly different structure from those formed from AA (Figure 7) and result in the production of 5-series LT and 3-series PG^{42,43}. The functional significance of this is that the mediators formed from EPA are less potent than those formed from AA and some exert anti-inflammatory actions (Figure 7), leading to attribute to omega-3 long chain PUFAs anti-inflammatory properties⁴³. Long chain



Figure 7. Synthesis of eicosanoids from polyunsaturated fatty acids. COX: cyclooxygenase, LOX: lipoxygenase

PUFAs EPA and DHA are found in marine sources as algae, krill or fish. Main source of EPA and DHA in pet food is fish oil.

A similar effect is proposed for the use of GLA, an omega-6 derivative of linoleic acid. Consumption of GLA increases the content of DGLA (derived from GLA, see Figure 6c) into membrane phospholipids competing with AA. Release of membrane DGLA occurs in response to the same signals that lead to release of AA or EPA, and the same enzymes (COX, Figure 7) synthesized eicosanoids. DGLA results in production of 1-series thromboxane (TX) and PG, which are anti-inflammatory, induce vasodilation, and inhibit platelet aggregation⁴³ (Figure 7). Borage oil and evening primrose oil are the main sources of GLA.





Effects of omega-3 and -6 polyunsaturated fatty acids on dog and cat skin diseases

Effect of PUFAs on pruritus - The use of omega-3 fatty acids as antipruritic agents in dogs and cats has been the subject of numerous studies. The inflammation and dermatitis associated with allergic skin disease may be partially caused by abnormal EFA metabolism and inappropriate eicosanoid synthesis7.

Fatty acids have been reported to be beneficial in managing pruritus particularly in atopic dermatitis, feline eosinophilic reaction patterns (i.e., eosinophilic plaque, eosinophilic granuloma), cornification disturbances from a variety of causes, improving coat quality, and for symmetric lupoid onychodystrophy⁶.

Although many studies reporting the use of omega-3 and -6 fatty acids in AD patients are published, only some of them are properly controlled studies conclusive about its effects. In an early cross-over study, sixteen dogs with idiopathic pruritus, confirmed atopy, or flea allergy were evaluated. Each dog was supplemented EPA and DHA or linoleic acid and ALA daily for 6 weeks. Dogs receiving the DHA and EPA had significant improvements in pruritus, self-trauma, and coat character over time⁴⁴. In another clinical trial dogs with non-seasonal atopy were included in a 2 month investigation. All dogs were administered a dose of EPA, DHA and GLA. All dogs improved, and a better result was seen in the dogs with early atopy⁴⁵. In an additional double-blinded, placebo-controlled, randomized trial, 29 dogs were administered fish oil (as a source of EPA and DHA), flax oil (as a source of ALA), or a placebo every 24 hours during 10 weeks. Clinical scores improved in dogs receiving the flax oil and fish oil preparations but not the placebo⁴⁶. In a further single-blinded trial a commercial omega-6/omega-3 EFA-balanced lamb and rice dog food satisfactorily controlled pruritus in eight of 18 atopic dogs⁴⁷. A more recent, randomised, double-blind trial found that a diet supplemented with 480 mg MJ-1 EPA and 50 mg MJ-1 GLA, significantly improved erythema and pruritus in atopic dogs compared to their usual diets (non-supplemented)⁴⁸. Additionally, feeding a omega-3 EFA enriched, omega-6 EFA controlled diet for eight weeks was recently reported to result in superior improvement of pruritus and other signs in dogs with atopic dermatitis, compared with two other veterinary diets and one non-veterinary diet49.

Effect of PUFAs as medication adjuvants in AD patients - Although PUFAs are often not sufficient as sole therapy for AD, its supplementation has also an effect as drug-sparing agent. In a randomized, double blind, placebo-controlled multicentre clinical trial of 12 weeks with 60 dogs with AD fed a standardized diet, sparing effects on a steroid drug were investigated. Dogs were supplemented daily with borage seed oil and fish oil (as source of GLA, EPA and DHA) or a placebo, in addition to prednisolone tablets. At the end of the study, both the pruritus score and the total clinical score were lower in the supplemented group⁵⁰. From 3 weeks of supplementation on, required prednisolone doses were lower in the supplemented group. The results agreed with studies reported earlier⁵¹.

In another recent randomized, double blind, placebo-controlled multicentre clinical trial the cyclosporine-sparing effects of PUFAs supplementation were investigated. Thirty-six dogs with AD received ALA, EPA and DHA or a placebo daily during 12 weeks. The results showed that the median daily cyclosporine dosage decreased in a larger extend in the supplemented group than in the placebo group⁵².

Moreover, other studies reported a reduction in antihistamine dosage when concurrent PUFAs were administered^{25,53}.

According the observed effects, supplementation of omega-3 long chain PUFAs is recommended in inflammatory skin processes as AD at doses of 125 mg per kg^{0.75 38}. Fatty acids supplementation can be reached by PUFA rich supplements or by a diet enriched in PUFA. Enriched diets allow to easily administer adequate levels of PUFA to the patient avoiding the difficulties of pills administration, palatability issues and owner compliance problems.

Effect of limited allergenicity diets on dogs and cats with food allergy

The management of AFR consists of avoiding the ingredients to which the patient shows a negative response. As discussed above, the offending ingredients should be identified by means of an elimination-challenge process after other diseases have been ruled out. Diets intended for elimination trials and long term management of FA or other adverse food reactions have specific nutritional strategies to minimize the risk of triggering adverse reactions in a patient.

The source and form of protein in food is the key nutritional factor in patients with suspected FA. The ingredients most frequently implied as culprits are beef, dairy products, chicken, and wheat in dogs; and beef, fish and chicken in cats⁵⁴. These ingredients are routinely avoided in elimination diets. However, it is believed that these ingredients are often implicated due to their high frequency of use in pet foods in the past years, so the animals are repeatedly exposed to them, and not due to some inherent "allergenicity"14. Cross reactivity between antigens of related species (poultry, ruminants, etc.) may exist⁵⁵ but it has not been demonstrated in veterinary medicine as yet.

Theoretically, digestibility can be considered as an important characteristic to minimize the time and presence of undigested large peptides in the gut lumen, which could trigger an abnormal reaction.

There are two types of elimination diets: diets that use uncommon ingredients (to maximize the likelihood of the patient being unexposed to them) and diets that use hydrolysed proteins.

Diets with uncommon ingredients

Finding a diet with ingredients the patient has never eaten previously can be a difficult job. especially with the growing number of pet foods that include exotic protein sources (such as bison, salmon or venison) in their formulation. An exhaustive diet history should be obtained and evaluated including all the products the patient has been consuming during his life and the ingredients included in composed products (see WSAVA toolkit suggestions for diet history fulfilling; http:// www.wsava.org/nutrition-toolkit). There are two dietary options we can choose from: commercial or homemade. Both approaches have pros and cons which should be considered before choosing.

Homemade foods usually include a combination of a single protein source and a single carbohydrate source (carbohydrate sources contain some protein as well). The ingredients should be novel to the patient, which will restrict choices to ingredients that may be expensive and hard to find. Many authors propose that homemade diets are superior as elimination diets because they do not include food additives (which are suggested as a possible cause of adverse food reaction) and they are processed at lower temperatures^{56,57}. The high temperatures of pet food processing have been proposed to form new antigens that might trigger adverse food reactions and potential FA⁵⁸. However, most of the homemade foods recommended for initial management of dogs and cats with suspected adverse food reactions were nutritionally inadequate⁵⁹. Such diets should not be fed for longer than the elimination trial and never to growing animals. If a long-term diet is required a nutritionally adequate and complete recipe must be formulated by a veterinary nutritionist. Other problems of homemade foods include cost and time.

There are several complete and balanced commercial therapeutic foods with uncommon ingredients in the market that use a single protein source and a single carbohydrate source, since not one commercial diet will work for all patients. Many of them have been tested to demonstrate its efficacy. Over the counter foods with uncommon ingredients should be avoided, since some of them may contain multiple protein sources and include traces of common pet food proteins not mentioned on the label, as shown in a recent study^{60,61}.





Diets with hydrolyzed proteins

Hydrolyzation of a protein source allows the reduction of big protein molecules into small peptide fragments (Figure 8). The aim of hydrolyzing proteins is to sufficiently disrupt the protein structure to a size that does not trigger an immune response both in patients already sensitized to the intact protein and in naive individuals. Dietary antigens are commonly glycoproteins that require a minimum size to trigger a reaction. This size has been defined in human medicine as 10-70 kD, but there are no data for dogs or cats¹⁴. Hydrolysation of protein may lead to break down of allergen epitopes; thus, they are not able to bind to the IgE receptors on the mast cell surface. Furthermore, mast cell degranulation requires cross-linking of two or more IgE molecules bound to IgE receptors on the mast cell. This means that the allergen must be large enough to bind to two IgE receptors¹⁴ (Figure 9).

Therapeutic commercial diets based on hydrolysed protein sources exist in the market. These diets use either uncommon carbohydrate sources or purified starch. These diets are good options when the patient has been exposed to multiple protein sources or the diet history is incomplete. Many studies widely demonstrate effectiveness of those hydrolysates in a high percentage of patients^{14,62,63}. However, it seems that a small percentage of animals, sensitive to the intact protein, can react to the hydrolysate⁶³ or other ingredients of these diets (starch, oils, additives, or new antigens created during processing).

In the specific case of FA pathophysiology, it has been suggested that an intestinal inflammatory environment can play a role in its development⁶⁴. Patients suffering from enteritis (among others origins infectious, parasitical, as well as IBD) might be susceptible to temporary loss of oral tolerance, which may worsen clinical signs. This concern has led to the recommendation of feeding a "sacrificial protein" during recovery in these patients during the initial treatment phase¹⁴. After a few weeks, the diet can be switched to a commercial diet with novel or hydrolysed ingredients. Another option would be to feed a hydrolysed protein diet and thus avoid the formation of new FA during recovery and minimize clinical signs and complications¹⁴.

Commercial references based on hydrolysed protein sources are complete and balanced, allowing to be fed to FA patients long-term without risks of nutritional deficiencies or unbalances.



Figure 8. Diagrammatic representation of enzymatic hydrolysation of protein into small peptides.



Α

Degranulation

A. Mast cells are sensitized by IgE binding to the high affinity IgE receptor. Allergen binding to IgE cross-links the IgE receptors and induces the release of mediators such as histamine, prostaglandins, enzymes and cytokines.

Figure 9. Requirements for mast cell activation.

Adequate diets for allergic dermatitis in dogs and cats

Concurrent allergies are common in cat and dogs. This fact influences the threshold level of clinical signs and impairs treatment results. In cases of allergic dermatitis in dogs and cats a complete and balanced diet should be fed covering all their energy and nutritive requirements and including the following nutritional strategies to maximize the benefits to the patient:

- cyclosporine).
- sources should be used to minimize the risk of food reaction signs.





No Degranulation

B. If the allergenic protein is sufficiently hydrolysed, cross-linking does not occur and mast cells do not degranulate. This is the case even if some of the fragments retain the ability to bind IgE. (Based on Cave 2006¹⁴)

- To be enriched in omega-6 and omega-3 fatty acids, GLA and EPA and DHA. Those fatty acids allow stabilization of the epidermal lipid barrier, inhibits pro-inflammatory eicosanoid secretion and exert as a medication adjuvant reducing dosage of immunomodulatory drugs (steroids,

- In patients with cutaneous adverse food reactions, uncommon ingredient or hydrolysed protein



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