An allergic response is defined as a hypersensitive immune reaction to a substance that normally is harmless and would not cause an immune response.

Before performing diagnostic tests for allergic skin disease or pursuing therapy, always be sure to rule out other causes of pruritus such as ectoparasites (Fleas, Sarcopes, Cheyletiella, Notoedres), secondary infections (bacterial or Malassezia), Demodecosis (D.canis, D.cati, D.irjai, D.gatoi), dermatophytosis etc. Diagnostic tests should include cytology (swabs versus tape preparations), skin scrapings (deep and superficial), flea combing, parasiticidal trials (Revolution®, Advantage Multi®) and potentially a fungal culture, pending clinical signs.

Cats are fastidious groomers therefore finding ectoparasites on scrapings may present a challenge. Consider scraping regions the cats cannot easily access, such as between the shoulder blades, or consider performing a fecal examination for ectoparasites (e.g. Demodex gatoi). Regardless of a lack of positive identification of ectoparasites on dermatologic or fecal examination, aggressive ectoparasiticidal trials for lice, fleas and mites is an essential part of a diagnostic and therapeutic approach to any pruritic cat. If minimal to no response is noted, then consider environmental or food allergies as one of your primary underlying etiologies.

Food Allergies

The term “Food allergy” is often used incorrectly in veterinary medicine to describe any adverse reaction following food ingestion. The term “Food allergy” should be reserved for immunologic-based hypersensitivities. The ACVD classifies any abnormal reaction after ingestion of food or additive as an Adverse Food Reaction (AFR). AFRs have been further classified as follows:

1. Food hypersensitivities (immunologic adverse reactions)
   a. Food allergies - IgE-mediated reactions or Type I hypersensitivity
   b. Non-IgE mediated hypersensitivity - Type III and/or IV hypersensitivity

2. Food intolerance - non-immunologic adverse reactions
   a. Food-dependent factors - toxins / poisoning or contaminants
   b. Host-dependent factors - enzyme deficiencies, drug reactions, idiosyncrasies

The major food allergens are heat-stable, water-soluble glycoproteins of molecular weights between 10 to 70 kilodaltons. We know that peptides as small as 3 to 5 kd may be allergenic in dogs. Proteins greater than 70 kd are too large to be absorbed through intact enteric mucosa and therefore are not considered allergenic.

Food allergies are the third most common allergic skin disease in dogs following flea allergic dermatitis (FAD) and atopic dermatitis (AD) and account for 32.7% of all allergic conditions. Food allergies are the second most common allergic skin disease in cats following FAD, accounting for 10-23% of allergic conditions in cats.

Signalement

There appears to be no sex predilection for AFRs in dogs and cats. Top breeds associated with food allergy include Labrador retrievers and cocker spaniels, along with others described in the literature including, but not limited to, the Soft-Coated Wheaton terrier, dalmatian, West-Highland white terrier, Bichon Frisee, collie, Shar Pei, Lhasa apso, Dachshund, miniature schnauzer, boxer, springer spaniel, Cairn Terrier, Irish / English setter, Golden retriever, German shepherd dogs, along with Siamese and
Birman cats.

Age at presentation is typically less than one year (2 months to 16 years; 33–52%) in dogs; in fact one third to one half of dogs with AFR develop clinical signs prior to one year of age. In cats, typical age at presentation is less than 2 years of age (4 months to 15 years; 38.5%). In general, an underlying AFR should be considered in any pet that develops pruritus / clinical signs prior to 6 months and after 6 years of age, with no previous history of skin disease.

**History**

The most common clinical sign of food allergy is non-seasonal pruritus. In rare cases there may be a direct correlation of onset of pruritus with a dietary change or indiscretion, but this is most often an exception to the rule. The majority of dogs who develop an AFR have been on a diet containing the offending allergen for years. Pets can also be allergic to more than one antigen in a diet. Food allergy is often associated with other pruritic skin conditions including atopic dermatitis, flea allergy, superficial pyoderma and *Malassezia* dermatitis. When food allergy is noted along with atopic dermatitis, the patient may present with year round pruritus with seasonal peaks (i.e. a worsening during the warmer months of the year).

Food allergic patients may respond temporarily to antimicrobial therapy as secondary infections are treated, but pruritus will return, +/- lesions, at the termination of therapy. Greater than 60% of patients with food allergies have a minimal to absent response to anti-inflammatory doses of glucocorticoids.

If a patient is thought to have food allergies, part of the history taking should include questions regarding previous diets fed, treats and table scraps given, flavoured medications such as monthly flea preventatives, flavoured toys/chews, pillling vehicles and flavoured toothpastes. Often these questions will need to be phrased multiple ways to receive the desired response. For example, "What do you feed your dog?" may precede a reply of "Diet X". This answer does not eliminate the fact that the dog may also receive certain treats and "the bit of cheese to get their pill in"! It is also advisable to ask "does your pet receive any treats, table scraps?" and "do you use anything to give Fluffy her medication?". I also include fruits and vegetables on my checklist, as a condition called Oral Allergy Syndrome has been documented in humans, whereby ingestion of oral antigens from various food items may have similar antigenic proteins (e.g., Bet v1 in birch and apple; cedar pollen and raw tomato) or may cross-react with environmental allergens to escalate clinical signs of the patient's atopic condition.

Questions should also be directed to any gastrointestinal disturbances occurring such as stool consistency, flatulence, number of bowel movements etc. Coprophagic dogs may obtain undigested material that could affect a food allergy.

**Clinical Signs**

**Cutaneous Findings**

The most common clinical sign of food allergy is pruritus, although not every patient will present with this sign. Erythema, scaling, crusting, alopecia, hyperpigmentation and papular eruptions are other common clinical signs. Urticaria and angioedema are less common but can occur. Malodor might be a client’s primary concern and can occur when a secondary bacterial or *Malassezia* dermatitis is present.

In dogs with AFR, the ears are most consistently involved (80%) followed by the feet (61%) and the inguinal / perineal region (53%) (think ears, feet and rears). In 24% of dogs, the ear may be the only affected region of the body. Otitis can be bilateral or unilateral. The frequency of perianal pruritus in dogs with atopic dermatitis and/or AFR was significantly higher than that in dogs with other diagnoses. 52% of dogs with atopic dermatitis and 51% of dogs with AFR had perianal pruritus. Axillary, anterior foreleg and periorbital regions were nearly equal in occurrence (31–37%). Many dogs will also have dorsal pruritus and if this pruritus extends past the thoracolumbar region, this will increase the suspicion of an AFR in this author’s opinion.

AFR in cats can present similarly to dogs. However, cats may also present with manifestations of the eosinophilic granuloma complex, symmetrical alopecia and miliary dermatitis. Studies have previously tried to document regions on the cat most commonly affected by AFR and it does appear that the head and neck are more commonly affected than the ears, feet and rear end.

Other cutaneous conditions that may be attributable to or triggered by AFR include Cocker Spaniel idiopathic seborrhea, symmetric lupoid onychodystrophy, sterile interdigital cysts, chin acne, pemphigus complex, perianal fistulas, pinnal vasculitis, recurrent generalized demodicosis, and food-induced
cutaneous vasculitis.

**Gastrointestinal (GI) Signs**
Up to 32% of patients with AFR will present with concurrent gastrointestinal signs, as well as cutaneous signs. These include vomiting, changes in the stool consistency, increased frequency of bowel movements, halitosis, borborygmus, flatulence, tenesmus, eosinophilic or lymphocytic-plasmacytic colitis / IBD, anal gland impaction & scooting, pica and/or coprophagia.

**Other Related Signs**
- **Neurologic / behavioral** signs such as malaise, seizures, behavior changes, dominance aggression, attention deficit disorders and difficulty in training, have either been proposed, documented or are currently being researched.
- **Respiratory** signs associated with AFR include asthma, rhinitis and sinusitis.
- **Musculoskeletal** conditions potentially attributable to food allergies include sterile polyarthritis and masticatory muscle myositis. Concurrent conditions noted with frequency include environmental, flea, intestinal parasite and insulin hypersensitivities, secondary recurrent pyoderma and *Malassezia pachydermatis* infection (may be the only sign).

**Diagnosis**
Based on our current knowledge that 35-50% dogs and cats have an adverse food reaction to more than one food item, finding a test to identify the food items causing allergic reactions in dogs/cats is appealing. However, to date, there is a lack of correlation between food allergy, RAST or ELISA results, gastroscopic food sensitivity testing, colonoscopic allergen provocation studies (COLAP) and *in vivo* intradermal allergy test results. Positive predictive values were recently determined to be 40% whereas the negative predictive values were 60.9%. The advantage of these tests is obvious but the correlation to actual food hypersensitivity is not known. There have been reports in humans with good correlation between *in vitro* test procedures, skin testing and food allergy. This has not been documented in veterinary medicine. The overall consensus of most dermatologists is that **dietary trials** are a more effective method of diagnosis.

More recently a saliva test for food sensitivities has become available. There is a lack of published data in regards to the sensitivity and specificity of this test. Patch testing for food allergies is currently being investigated as an alternative method to diagnose a food allergy.

**Dietary Restriction**
Confirmation of food allergy can only be determined by a **novel protein restriction diet trial**. The diet is changed to one with a combination of ingredients to which the animal has no previous exposure. The diet is then restricted to exclude ALL OTHER treats, table scraps, pilling vehicles, flavoured medications and toothpaste and flavoured toys. Protein sources are more often to blame than grains for AFR, so selecting a novel protein with no history of exposure is paramount. Food items most commonly causing food allergy include beef, milk, lamb, wheat, corn, chicken egg, soy, chicken in dogs, adding tuna and salmon to the list in cats. When selecting a novel protein source, cross-reaction between protein sources must also be considered. Some studies demonstrate that bovine IgG in milk can confer cross-reactivity to beef and also proteins in other ruminants such as lamb; therefore if an animal has been fed a beef diet previously, lamb should not be considered a novel protein. There are also some current concerns about cross reactivity between chicken and other poultry species; therefore animals fed chicken should not receive duck/turkey etc during a diet trial.

The gold standard of performing a restricted diet trial is to use a home-prepared diet. The preferred diet should include a protein source and a carbohydrate (1:2). Novel protein sources currently available for home-cooking include kangaroo, camel, ostrich, emu, bison, elk, venison, rabbit, duck, fish, as well as lamb. Old world grains such as spelt along with oatmeal, quinoa, rutabaga, sweet potato and white potatoes can be used as the carbohydrate source. Restricted raw food diets may also provide some benefit to dogs with AFR although concerns re bacterial contamination/overgrowth should be identified. Supplementation with a multivitamin is not necessary for the length of the trial. If concerns arise about young growing dogs or cats placed on a home-prepared elimination diet, an option is to select one of the commercial foods. Any vitamin / mineral supplement used during an elimination trial should be of the non-
flavoured variety. Consulting with nutritionists for advice about specific breed requirements may be helpful. Once improvement is noted the diet is then balanced accordingly using supplements/nutritionist input etc.

Cats can be more finicky than dogs and can become bored with a restricted diet after it is fed for a prolonged period of time. Cats should also be kept indoors during the diet trial to prevent hunting, which may also pose a difficulty for some owners.

Multi-pet households are another issue when performing a restricted diet trial if animals are fed different diets. Ideally, during the period of the diet trial, animals of the same species would be all transitioned onto the same diet. Alternatively animals should be isolated when fed and bowls/plates removed from the floor in between meals to prevent the animal on the restricted diet having access to other food items.

Owners often want to continue to give treats during the elimination diet. Treats with the same ingredients as the selected diet can be given without invalidating the diet trial. For example, if the diet contains sweet potato, pure sweet potato treats can be given. The most difficult part of the trial is avoidance of any other food. Table foods fed by children (or other family members) is a concern since it would invalidate the dietary restriction. It should be stressed to the client that previous studies have demonstrated that a single tablet of a flavoured oral medication given to a dog with AFR can result in a prolonged reaction.

Diet trials should be undertaken for a period of 8–12 weeks to determine response. This prolonged duration often leads owners to abandon home cooking and seek an easier alternative. When selecting a commercially available diet for the trial, the selection of the single protein and carbohydrate source should be based on the dietary history of the animal, as previously described. The selection of a food with limited ingredients is the next priority. A large variety of limited ingredient foods exist based upon different novel and hydrolyzed protein sources. The use of a commercial food provides a conservative way of evaluating food allergy although it has some compromise compared to a home-prepared fresh food because of multiple ingredients and additives present. Veterinary diets are preferable over diets obtainable from a pet store based on concerns regarding ingredient contamination and the cleaning process. In one study, three of the four over the counter (OTC) venison canine dry foods with no soy products named in the ingredient list were ELISA positive for soy; additionally one OTC diet tested positive for beef protein with no beef products listed as an ingredient list. In fact, none of the four OTC venison diets could be considered suitable for a diagnostic elimination trial as they all contained common pet food proteins, some of which were readily identifiable on the label and some that were only detected by ELISA. The conclusion was that, if the four OTC venison products selected in this study are representative of OTC products in general, then the use of OTC venison dry dog foods should not be used during elimination trials in suspected food allergy patients.

Whether to select a novel protein diet or a hydrolyzed diet is a common question this author is asked when a diet trial is started. In multiple studies analyzed, up to 50% of dogs with AFR enrolled exhibited increases in clinical signs after ingesting partial hydrolysates from foods to which they were hypersensitive. Although limited studies are available there is evidence to suggest reduced immunological and clinical allergenicity of hydrolysate-based commercial diets. However, a proportion of dogs with AFR will exhibit a worsening of clinical signs when fed partial hydrolysates. This author greatly prefers the use of novel protein diets over hydrolyzed diets unless the patient has GI signs along with cutaneous.

Although a diet trial should last 8–12 weeks, it is important to receive updates from your clients every few weeks while on the trial. I always tell my clients "It should only get better, it should not get worse" during the trial. If clinical signs deteriorate any time before the initial recheck, the owner should discontinue the diet, allow the reactions to calm and switch to a different diet. During the dietary trial, it is important to control coexistent factors that may increase pruritus and obscure the results such as flea allergy dermatitis, *Malassezia* dermatitis and superficial pyoderma. I often begin anti-inflammatory glucocorticoid therapy for 30–45 days of the dietary trial to control pruritus and self-mutilation. After this time, the steroids are tapered, the restricted diet is continued, and the patient continues to be evaluated.

Up to 75% of dogs with AFR will have other allergies so there may only be a partial improvement during the food trial. To prove a decrease in pruritus was due to the diet trial, a re-challenge needs to be performed with the original diet. Relapses typically occur within 15 minutes to 14 days (12–48 hrs most commonly). If a relapse occurs during the challenge, the pet should be returned to the elimination diet for a period of time to allow inflammation and pruritus to decrease. Return to pre-challenge level of control takes much less time than the original response noted during the original trial.

Many clients are not interested in performing this re-challenge due to the improvement noted on the restricted diet. Dietary challenges with one food item at a time can then be undertaken as necessary.
Conclusion
Adverse food reactions are common reason for pruritus and an AFR should not be overlooked when diagnosing the cause of pruritus in our patients. Multiple conditions may have an underlying food allergy as a trigger factor for clinical signs, therefore a novel protein restriction diet should also be undertaken in these cases to attempt to minimize the use of medications.

Suggested Reading


Rosser EJ. Diagnosis of food allergy in dogs. JAVMA. 1993;203:259–262.


Environmental Allergies (Atopic dermatitis)

Atopic dermatitis (AD) is defined as a genetically predisposed inflammatory and pruritic skin disease with characteristic clinical features associated with IgE antibodies directed against environmental allergens. In most cases, the veterinarian is dealing with an allergic etiology whereby the offending allergen cannot be avoided or eliminated from the patient's environment.

Epidermal barrier defects, such as decreased levels of skin ceramides in allergic individuals, are thought to facilitate percutaneous absorption of environmental allergens. During sensitization, the allergens are processed by antigen presenting cells within the skin which then carry these antigens to regional lymph nodes. T cells are activated and stimulate the release of cytokines such as IL-4 and IL-13 and consequent production of allergen specific IgE. The activated T cells then migrate back to the skin. On subsequent exposure, Langerhans cells with allergen specific IgE can rapidly trigger the activation of T-cells, which in turn release pruritogenic cytokines. One of these cytokines, IL-31, has recently been identified as a pruritogenic cytokine and has become the focus of much research and discussion. A thorough review of the pathogenesis of atopic dermatitis is beyond the scope of these notes.

An excellent explanation along with video of the pathomechanism of allergic dermatitis can be found at http://www.itchcycle.com (Zoetis).

Signalment

Atopic dermatitis (AD) is a common diagnosis in veterinary dermatology affecting between 3-10% of the entire canine population. 80% of patients with atopic dermatitis will develop non-seasonal signs and require long-term therapy. Most animals with atopic dermatitis will present with clinical between 6 months to 3 years of age. A slightly older onset between 3-5 years is also recognized. There is no known gender predisposition. Breed and geographic region can determine the age of onset with dogs living in warm climates with pollen present year round, more likely to develop signs at a younger age. Definite breed predispositions are noted including, but not limited to Beauceron, Boston Terrier, boxer, Cairn terrier, Shar-pei, cocker spaniel, dalmation, English bulldog, English setter, fox terrier, Irish setter, Labrador retriever, Lhasa apso, schnauzer, pug, Scottish terrier, West Highland white terrier, wire-haired fox terrier and Yorkshire terrier.

History

Certain patients with AD may present with a seasonal pruritus during the warmer months. More commonly patients will present with a non-seasonal pruritus that waxes and wanes over the year. Clinical signs can also start seasonally, then become year round as the disease progresses. It is important to document whether seasonality is noted to determine whether clinical signs worsen over the next year.

Atopic dermatitis is often associated with other pruritic skin conditions including food allergies, flea allergy, superficial pyoderma and Malassezia dermatitis which should be identified and treated.

Atopic patients may respond temporarily to antimicrobial therapy as secondary infections are treated, but pruritus will return, +/- lesions, at the termination of therapy. Patients with atopic dermatitis often have a complete response to glucocorticoids, if secondary infections are not present.

Another factor influencing the development of AD is the month of birth. Animals born during a high pollen count season, therefore exposed to multiple pollens from birth, appear to be at increased risk for AD. Studies have previously documented certain factors associated with a lower risk of developing AD. These include: living in a rural environment, living in a household with multiple animals and walking in a forest.

It is also worth note that up to 30% of patients with AD will have concurrent adverse food reactions so food should be considered a potential flare factor during periods of increased clinical signs.

Clinical Signs

Cutaneous Findings

Pruritus is the most common clinical sign associated with AD. Pruritus can manifest as actual scratching but is also present when an animal licks excessively, chews or rubs a part of their body. Many cat owners will not believe their cat is pruritic, even in the presence of symmetrical alopecia, purely because they do not see the cat overgrooming as this will occur away from the owner.

The most common clinical signs of AD are erythema and pruritus, although not every patient will
present with this sign; rare cases will not be pruritic but will present with recurrent secondary infections. Acute cases may also present with scaling, crusting, alopecia and papular eruptions. As the case becomes more chronic, other clinical signs noted can include hyperpigmentation, lichenification, excoriations and ulcerations. As is the case with food allergies, malodor might be a client’s primary concern and can occur when a secondary bacterial or *Malassezia* dermatitis is present.

Regions on the body commonly affected in cases of AD are the ventral abdomen, inguinal region, axillae, muzzle, periocular region and the flexural surfaces of the forelimbs (patients can often be seen “corn-cobbing” up and down their front limbs). Otitis externa is another common finding.

Cats with AD can present with any of the major reaction patterns documented: symmetrical alopecia, the eosinophilic granuloma complex, head and neck erosions/ulcerations and miliary dermatitis. Studies have not documented specific body regions on the cat that are consistently involved in an individual with atopic dermatitis.

**Other Related Signs**

**Respiratory Signs** - Owners of animals with AD may also report episodes of reverse sneezing along with recurrent rhinitis and/or sneezing.

**Ocular abnormalities** can include increased lacrimation during “allergy season”, ocular congestion and conjunctivitis.

Some patients may have mild gastrointestinal disturbances during periods of increased allergen load within the environment and occasional reports have documented alterations in estrus cycle in affected individuals.

**Diagnosis**

The diagnosis of atopic dermatitis is one of exclusion, as no definitive test for AD exists to date. Diagnosis is based on history, clinical signs and exclusion of other pruritic diseases via cytology, superficial and deep skin scrapings, fungal cultures etc. In non-seasonal pruritic patients, the differential diagnosis list should include scabies, demodecosis with a secondary infection, dermatophytosis, food allergies and atopic-like dermatitis. In patients with seasonal pruritus the differential diagnosis list should include seasonal ectoparasites such as fleas and lice, atopic-like dermatitis and mosquito bite hypersensitivity. **Allergy testing**, either intradermal or serologic should not be used as a definitive diagnostic test for atopic dermatitis, but rather as an aid to select appropriate allergens for immunotherapy.

In 2010, Favrot documented eight criteria that are often observed in individuals with AD. It was noted that fulfillment of 5/8 of these criteria met with a high sensitivity (85%) and specificity (79%) in the diagnosis of AD. The criteria are as follows:

1. Age at onset <3 years
2. Mostly indoor animal
3. Corticosteroid-responsive pruritus
4. Chronic or recurrent yeast infections
5. Affected front feet
6. Affected ear pinnae
7. Non-affected ear margins
8. Non-affected dorso-lumbar area

However, up to 20% of cases would be missed if clinicians rely on these criteria alone. In cats, similar criteria were suggested.

1. Presence of at least two body sites affected
2. Presence of at least two of the four following clinical patterns:
   a) Symmetrical alopecia
   b) Miliary dermatitis
   c) Eosinophilic dermatitis
d) Head and neck erosions/ulcerations
3. Presence of symmetrical alopecia
4. Presence of any lesion on the lips
5. Presence of erosions or ulcerations on the chin or neck
6. Absence of lesions on the rump
7. Absence of nonsymmetrical alopecia on the rump or tail
8. Absence of nodules or tumours

Fulfilment of 5/8 of these criteria gives a sensitivity of 75% and a specificity of 76% for the diagnosis of non flea induced hypersensitivity.

**Therapy**

Based on the many components of the immune system involved in an allergic response, treatment of atopic dermatitis often involves a MULTI-MODAL approach. A combination of therapeutic approaches will often lead to minimization of the need for more potent medications such as steroids. Ectoparasite control, epidermal repair products, shampoo therapies, essential fatty acids, antihistamines, cyclosporine, oclacitinib (when available) and immunotherapy all work slowly to control and prevent allergy flares with minimal side effects. Due to the number of individuals who have concurrent food allergies and atopic dermatitis, dietary restrictions can aid in the treatment of AD as dietary indiscretions can act as flare factors for these animals.

**Epidermal barrier repair** products that contain ceramides, free fatty acids, essential fatty acids, phytosphingosine, and essential oils are used to repair and maintain an intact epidermal barrier. This helps to prevent percutaneous absorption of allergens across this epidermal barrier and also prevents adherence of microbes to the skin surface. I often describe the abnormal skin barrier noted in atopic individuals to my clients as, a “crumbly brick wall, with crevices that allergens, bacteria and yeast can get into”. These epidermal barrier repair products help to “fill in the gaps” in the wall! These products should be considered for use as a preventative as well as a topical adjunct to treatment of active clinical signs. I advise clients to apply these products to/next to active lesions as well as following the directions on the packaging.

**Topical therapy** such as bathing. Studies have shown that weekly bathing with a 10-minute contact time with shampoos containing lipids, antiseptics etc can lead to a 25% decrease in pruritus within 24 hrs. If shampoo therapy is possible, appropriate selection of shampoos, based on active ingredients, used with COOL water on a weekly basis will help to treat secondary infections, mechanically remove any allergens on the skin and help repair the epidermal barrier. There is not much evidence in the literature to support the use of specific shampoos containing oatmeal, antihistamines, lipids or glucocorticoids but the benefit stems mostly from the mechanical action of bathing. Many studies document the benefit of using antimicrobial shampoos to treat secondary infections in our AD patients. 0.0584% hydrocortisone aceponate spray (Cortavance®, Virbac) has been shown to reduce pruritus in atopic individuals. With long term use skin thinning might be noted. Topical tacrolimus 0.1% is used in human medicine for atopic dermatitis refractory to glucocorticoids applied topically or in those individuals where topical steroid therapy is not preferable. This is another alternative for topical therapy of AD dogs (caution in cats based on their ability to lick the product).

**Omega-3 fatty acids** (EPA - 180 mg/10lbs body weight for dogs) may provide relief for the pruritic individual. Reliable VETERINARY sources should be recommended to achieve optimal responses. Many veterinary products contain a mixture of omega 3 and omega 6 fatty acids. These products may have a lag time of 1-2 months to see the full anti-pruritic effect. Oral fatty acids should not be used during a food trial due to fish based proteins.

**Antihistamines** have variable efficacy in atopic individuals and one size does not fit all. Cetirizine (0.5-1.0 mg/kg q24h in dogs and 0.5-2.0 mg/kg q 24 hrs in cats) is my first choice, based on the availability of pharmacokinetic data in dogs and its action of decreasing influx of eosinophils into affected sites; useful
for cats with eosinophilic granuloma complex. Second generation antihistamines tend to cause less sedation when compared to first generation antihistamines such as diphenhydramine. Trials with antihistamines are continued for 14 days to assess efficacy. Antihistamines have minimal side effects or contraindications for long-term use.

Cyclosporine (Atopica®) is a non-steroidal alternative for treatment of atopic dermatitis in cats and dogs. Cyclosporine is a calcineurin inhibitor that prevents the release of Interleukin-2 and therefore changes the T lymphocyte immune response. It is useful as a long term symptomatic treatment for AD without the long term side effects of glucocorticoids. Cyclosporine will also decrease IL-3, IL-4, IL-5, tumour necrosis factor (TNF)-α, and interferon (IFN)-α production and serves to inhibit antigen presentation, histamine release from mast cells, neutrophil adherence and growth and differentiation of B lymphocytes. Cyclosporine is dosed at 5 mg/kg once daily for dogs and 7 mg/kg once daily for cats with both capsules available and liquid (Atopica for Cats®). At these doses it has been documented as being effective for controlling pruritus and also treating the eosinophilic granuloma complex seen in cats. It may be up to 4 weeks until maximal response is noted. Diarrhea, anorexia and vomiting are the most common side effects and are often transient. In cats, weight loss has also been documented in 20% of cases so monitoring of weight is recommended. Testing for FeLV and FIV should precede therapy with cyclosporine in cats. Fatal systemic toxoplasmosis has been reported rarely, hence caution should be exercised if considering use in cats at high risk for toxoplasmosis, such as outdoor hunters. Cats on cyclosporine should not be allowed to hunt and should be fed cooked or processed food. Pets in general should not be fed raw food diets while on cyclosporine. Long-term side effects are minimal but gingival hyperplasia is rarely noted in canines on cyclosporine. When dosing cats using the liquid version (Atopica for Cats®), the syringe in the bottle is dosed by body weight.

Apoquel® (oclacitinib) is a new treatment for canine AD currently licensed in the US. This medication is the first Janus Kinase (JAK) inhibitor approved for veterinary use that targets itch and the inflammation pathway. It is a selective inhibitor of the JAK-1 enzyme. JAK-1 is involved in the signal transduction of pro-inflammatory cytokines including IL-31. Oclacitinib also inhibits function of IL-2, IL-4, IL-6 and IL-13 (all pro-inflammatory cytokines). Oclacitinib is currently licensed for the treatment of dogs at a dose of 0.4-0.6 mg/kg, orally, twice daily for up to 14 days and then once daily as maintenance. The medication can be given with or without food. In trials with dogs with AD, treatment success, defined by a decrease in pruritus and veterinarian-assessed dermatitis was noted in 67% of dogs treated with oclacitinib after one week of treatment. Continuous improvement was documented past one week of therapy. The type and frequency of adverse events were similar between oclacitinib treated and placebo treated dogs in the short-term trials and minimal adverse effects were documented in multiple long-term trials. The most common side effects observed in treated dogs were vomiting and diarrhea. Other reported side effects included lethargy, decreased appetite, skin and ear infections. The proportion of dogs achieving a >50% reduction in pruritus is comparable to or better than dogs with AD that improve following treatment with systemic glucocorticoids. In further studies the mean reduction in pruritus and dermatitis was not significantly different between dogs receiving oclacitinib and those receiving prednisolone, except for on day 14, when reductions were more pronounced for oclacitinib than prednisolone. Oclacitinib appears to be comparable in speed of onset to prednisolone also.

Allergen-specific immunotherapy (ASIT)
Allergen-specific immunotherapy (ASIT; also known as allergy shots, hyposensitization) is the practice of administering gradually increasing quantities of an allergen extract to an allergic subject to improve clinical signs associated with exposure to the causative allergen. In an allergic patient there is an exaggerated response to antigens. This exaggerated response is multifactorial and is due to abnormalities of the skin barrier, lipid abnormalities, environmental triggers and genetic predisposition. Dendritic cells of the immune system present antigen to CD4+ T helper cells. Effector T helper 2 cells are then produced and secrete interleukins. This causes B cells to produce IgE as opposed to IgG. IgE cross-linking on basophils and mast cells leads to degranulation and release of inflammatory mediators including histamine (type I hypersensitivity). In dogs with AD, overproduction of Interleukin 4 is due to a Th2 response.

In humans receiving ASIT, the cytokine profile is consistent with a Th1 response (increased interferon gamma). There is also an increase in T regulatory cells and cytokines with regulatory activity, such as
interleukin 10. ASIT patients show increased numbers of antigen-specific IgG that compete with IgE for binding sites ("blocking antibodies").

There are fewer studies investigating the immunologic changes that occur in an animal receiving ASIT. A potential shift towards Th1 expression has been suggested along with an increase in T regulatory cells and IL-10 concentrations. An increase in IgG after at least 6 months of immunotherapy has been documented as well as significant differences between pre and post IgG in dogs with a good response to ASIT compared to those with a fair/poor response. An increase in the ratio of Th1:Th2 cytokines following ASIT is a consistent finding in both human and veterinary literature.

Multiple studies are available outlining the success of ASIT in veterinary medicine. Studies suggest the efficacy of ASIT is anywhere from 50%-100%. This wide range could be due to differing protocols, dose, concentration etc. In cats success rates of 50-75% are noted and in horses we see a 60-71% response rate. Some studies found that dogs with non-seasonal pruritus respond better to ASIT but these results are conflicting.

The success rate on immunotherapy is based on the reliability of the environmental allergy test. Both intradermal and serologic allergy tests are available. Intradermal skin tests (IDT) are still considered by most dermatologists to be the gold standard in veterinary medicine as it tests the target organ. However, there are cases where in vitro serologic allergy testing is indicated (cases where anti-inflammatory therapy cannot be withdrawn prior to testing or sedation for the intradermal test is contraindicated). Some dermatologists perform both IDT and serologic testing and formulate immunotherapy based on both test results. Unfortunately, there are differences among the various in vitro companies both in quality and methodology. Reports documenting the efficacy of ASIT based on serological testing versus intradermal testing often show similar results. This finding, however, is not always consistent.

Intradermal allergy testing is recommended approximately 90 following the peak allergy season. In year round allergic patients this can be difficult to ascertain. Serologic allergy testing is often recommended prior to the allergy season (again difficult to determine in year round pruritic patients). Twenty percent of pets and up to 40% of humans tested with either in-vitro or intradermal tests will have negative tests. These patients are thought to have “atopic-like dermatitis”. In these cases individuals display clinical signs consistent with AD but no IgE reaction is documented.

Careful consideration of the allergens that are to be included in the extract is critical to the outcome. Too many allergens in a vial are likely to negate the benefit of ASIT. Many allergens will cross react; not all positives need to go in the vial and most dermatologists limit the number of allergens per vial to 10 - 12. Selection of allergens should be based on the pet's exposure and a detailed history as opposed to the magnitude or “numeric value” of the reacton.

Allergy extract can be formulated in a number of ways as aqueous extracts (most common) or emulsion extracts. During the induction phase of the ASIT, the volume and concentration of the allergen extract is gradually increased over weeks-months. The maintenance phase in then started where the time interval between injections is increased. Rush immunotherapy involves hospitalization of the patient while the patient is induced over hours rather than days.

Adverse reactions documented for ASIT in animals are rare. Animals may become pruritic after an injection, which can be overcome by pre-treatment with an anti-histamine/steroid or the dose schedule can be changed. Systemic reactions (depression, diarrhea, panting, urticaria, collapse, anaphylaxis) are noted in less than 1% dogs. Localized injection site reactions are also rare. It is recommended that owners give shots when they will watch their pet for a few hours after and when the closest veterinary clinic is open, in case of emergency.

There are no specific studies documenting the use of anti-inflammatory medications during the induction phase of ASIT. Although we do not want to mask the effects of the treatment, anti-inflammatory treatment maybe warranted to prevent pruritus and secondary infection (especially as it may be a while prior to seeing improvement with ASIT). In dogs a positive response to ASIT can be seen within 3-8 months of therapy. Cats and horses tend to respond slightly faster than dogs in this author’s opinion. Note that it is the only therapy that may cure atopy or at a minimum prevent the development or progression of allergies.

The newest form of immunotherapy is sublingual immunotherapy (SLIT). This new approach has been available in the US for a while and has, more recently, become available in Canada. SLIT involves allergen administration into the oral cavity. Studies to date suggest efficacy is similar to subcutaneous administration. Some patients that fail SQ administration respond well to SLIT. It appears that anaphylaxis may be less common with this route of administration. An “induction” phase is still followed; where the
number of drops administered is gradually increased over a few weeks. The patient is then maintained on daily drops long-term.

**Glucocorticoids** are an effective method of providing immediate relief from symptoms of AD. Oral prednisone or prednisolone (anti-inflammatory doses), dexamethasone (0.05 mg/kg/d) or methylprednisolone (1-2 mg/kg/d) can all be used to decrease inflammation and pruritus and then tapered to the lowest effective dose. Once the clinical signs have abated, steroids may also be used once daily in 3-7 day bursts to “put out fires” – I often explain this to clients as a sort of epi-pen for their animals when things get really bad! Long-term inappropriate steroid use can result in recurrent secondary infections, PU/PD, polyphagia, iatrogenic Cushing’s, diabetes, ligament laxity and feline cutaneous hyper-fragility syndrome, to name a few potential side effects. Use of steroids should always be minimized in atopic patients by using the above methods to control clinical signs. **Prednisone bioavailability in cats has been estimated to be ~26% relative to prednisolone and I will use prednisolone preferentially in this species.**

**Alternative medications**

In refractory cases of AD that develop side effects associated with steroid or other anti-inflammatory medications, **chlorambucil** or **azathioprine** are sometimes used. Initial daily therapy then tapered to every other day or less. Adverse reactions include anorexia, vomiting, diarrhea, bone marrow suppression and hepatotoxicity. Regular monitoring of CBC, chemistry profile and urinalysis is recommended.

**Pentoxifylline**

This is a synthetic xanthine with some anti-inflammatory activity. It has been used successfully in previous studies to reduce pruritus but has not been found to completely eliminate this clinical sign. It is, therefore, rarely effective as a single therapy for AD but may provide some improvement when used in combination with glucocorticoids and may allow tapering of the dose of glucocorticoid.

**Gabapentin**

The sensation of itch and pain are shared by the same neurons. Gabapentin has been cited in the human literature as an option in people with poorly responsive pruritus. While the precise mechanism of action is unknown, it appears to act where the itch pathways synapse by inhibiting the release of excitatory mediators.

**Maropitant**

Substance P is a mediator of pruritus. In people, an increase in the expression of its receptor, neurokinin-1 (NK-1), has been reported on keratinocytes in pruritic skin diseases. Maropitant is a potent NK-1 receptor antagonist and has been documented to reduce the development of ulcerative lesions in mice.

**Conclusion**

Control of atopic dermatitis can be a long road so it is important to educate clients. Most clients are looking for “the cure” so it is paramount to provide the owners with the realistic expectation of management of the disease versus cure. Regular communication to minimize frustration and maximize compliance serves to increase response rates in our patients. Factors that trigger flares of AD e.g. secondary yeast infection, must also be identified and treated.

**Suggested reading**


