Summary

Canine atopic dermatitis remains one of the most difficult conditions for veterinarians to manage. This presentation will focus on the most recent treatment guidelines, including topical and systemic therapies as an integrated approach, recommended by the International Task Force on Canine Atopic Dermatitis and will also highlight new treatment modalities.

Atopic dermatitis (AD) is a common, chronic, relapsing pruritic skin disease of dogs, for which treatment options are wide and have varied over time including opical therapy, glucocorticoids, antihistamines, fatty acids and hyposensitization. Some newer forms of non-steroidal therapy such as ciclosporin and pentoxifylline have also been recently utilized. Most commonly, a combination of therapies is used in clinical practice. Recent high-quality randomized controlled trials and systematic reviews have established which drugs are likely to offer benefit. In 2010, the International Task Force for Canine AD published guidelines recommending a multimodal approach to treat dogs with AD.

Canine AD: “A genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features associated with IgE antibodies most commonly directed to environmental allergens”.

Canine Atopic-like dermatitis: An inflammatory and pruritic skin disease with clinical features identical to those seen with atopic dermatitis in which IgE response to environmental or other allergens cannot be documented.

Treatment recommendations vary according to acute flares or chronic flares of AD, and whether skin lesions are localized or extensive.

Treatment of Acute Flares of Atopic Dermatitis

Identification, Avoidance and Removal of Flare Factors
When an allergy signs flare in a dog that previously had AD in remission, it is important to look for and eliminate, if possible, the flare causes. Currently known causes of flares AD in dogs include fleas, food and environmental (e.g., house dust, house dust mites, pollens) allergens.

Use of Antimicrobial Therapy
Skin and ear infections are common reasons for skin lesions and pruritus acutely worsen in dogs with AD. A very large percentage of AD cases are complicated by pyoderma and malassezia dermatitis. If bacterial or yeast infections are identified with the presence of clinical signs, cytology and/or culture, antimicrobial therapy is indicated, typically using topical therapy with or without oral medications. In many cases once the secondary infection is controlled then the signs of AD can be reduced. Some cases can be successfully managed by treating the infections without specific
treatment for the AD. The client must realize that recurrences will occur and some frequency of treating the infections will have to be maintained.

**Baths - Improvement of Skin and Coat Hygiene and Care**
Bathing dogs with AD helps reduce pruritus. This benefit appears to be due to the mechanical washing action which helps remove allergens from the skin. Weekly bathing improved pruritus score (50% improvement) in 25% of treated dogs according to one study. Outside of Allermyl®, a lipid-containing shampoo, there is currently no evidence of benefit of other shampoos or conditioners containing ingredients such as oatmeal, pramoxine, antihistamine, lipids or glucocorticoids.

**Short Term Treatment with Topical Glucocorticoids**
There is evidence for high efficacy of two medium-potency glucocorticoid sprays: triamcinolone (Genesis®) and hydrocortisone aceponate (Cortavance®) to reduce skin lesions and pruritus in dogs with AD. These sprays are mostly useful for localized skin lesions and for short treatment durations. It is important to tailor the frequency and duration of treatment to the severity of clinical signs for each patient. Caution is advised with long-term use, as adverse effects including skin atrophy are likely to occur.

**Short Term Treatment with Oral Glucocorticoids**
Oral glucocorticoids are recommended when allergy signs are too severe or extensive to be controlled with topical formulations alone. Prednisone, prednisolone or methylprednisolone can be given at 0.5-1 mg/kg daily until clinical remission occurs. Side effects of oral glucocorticoids are usually proportional to drug potency, dosage and treatment duration.

**Interventions Likely To Be of Little or No Benefit to Treat Acute Flares of Canine AD**

**Antihistamines and Essential Fatty Acids (EFA):** Antihistamines and EFA supplements are often recommended by clinicians for the treatment of canine AD, however; there is no conclusive evidence of efficacy of oral type 1 antihistamines and EFA for the treatment of active AD in dogs.

**Topical tacrolimus and oral ciclosporin:** These medications are unlikely to be of any benefit for acute flares of AD in dogs because of their slow onset of treatment effect.

**Treatment Options for Chronic Canine AD**

**Identification and Avoidance of Flare Factors**

**Performance of Dietary Restriction-Provocation Trials in Dogs with Nonseasonal AD**
Food allergens can cause flares of AD in dogs hypersensitive to such allergens. It is recommended that or more restriction-provocation dietary trials be performed in all dogs with nonseasonal or year-round AD to determine whether food allergens contribute to clinical signs in these patients. There is current no clear evidence of superior benefit of hydrolyzed versus limited ingredients versus homemade diets for elaboration of elimination diet trials.
Implementation of an Effective Flea Control Program
There is evidence that AD predisposes dogs to develop hypersensitivity to flea saliva if exposed repeatedly to flea bites. As a result, where flea infestation is endemic, all dogs with AD should be treated with year-round flea preventatives combined with relevant environmental treatment.

Performance of Allergen-Specific Intradermal and/or IgE Serological Tests to Identify Possible Environmental Allergen Flare Factors
Environmental allergens, such as house dust mites, have been shown to cause flares of AD in dogs hypersensitive to these allergens. The performance of allergen-specific intradermal testing (IDT) and/or IgE serological tests is helpful to identify hypersensitivity to environmental allergens in dogs with AD. Importantly, positive immediate IDT reactions and IgE serologies to environmental allergens are also common in dogs without signs of AD. As a result, these tests cannot be used to differentiate dogs with AD from normal dogs.

Use of Antimicrobial Therapy
The skin and ears of dogs with AD are commonly secondarily infected or colonized with *Staphylococcus* and *Malassezia* species. It is suspected that these microorganisms might contribute to the severity of AD outside of “classical” superficial infections (e.g., bacterial folliculitis). The systematic prescription of antibiotics and antifungal drugs to every dog with AD is not recommended; as such, routine use of antimicrobial drugs is likely to increase the prevalence of drug-resistant microbes. Mild localized pyoderma cases can be treated topically chlorhexidine (spray, shampoo, wipes and mousse), benzoyl peroxide (gel, shampoo), ethyl lactate (shampoo), mupirocin (cream, ointment), and Vetericyn® (spray), among others. Topical therapy for localized infections associated with malassezia include miconazole (lotion/ointment), chlorhexidine (spray, shampoo, mousse, wipes) and ketoconazole (shampoo). Systemic therapy for generalized cases associated with pyoderma include cephalosporins and clindamycin, and for malassezia dermatitis include ketoconazole and terbinafine.

Baths - Improvement of Skin and Coat Hygiene and Care
Weekly bathing with a mild, non-irritating shampoo and lukewarm water is likely to be beneficial for a direct soothing effect to the skin, the physical removal of surface allergens and microbes and an increase in skin hydration. At this time, there is no evidence of superiority of any particular shampoo or protocol to achieve these goals.

Dietary Supplementation with EFA
At this time, there is no evidence of superiority of any particular EFA combination, dosage, ratio or formulation (including enriched diets) to improve skin and coat quality in dogs with AD, but, in general, EFA-enriched diets provide higher amounts of EFA than oral supplements. The benefit of EFA, if seen, might not be noticed before 8 weeks of supplementation.

Treatment with Topical Glucocorticoids or Tacrolimus
There is good evidence supporting the efficacy of topical glucocorticoids for treatment of AD in dogs. Clinicians must tailor the frequency and duration of application of topical glucocorticoids to the severity of clinical signs. Such formulations are best suited for focal (e.g., foot) or multifocal lesions and for relatively short durations (e.g., less than two months).
As an alternative to topical glucocorticoids, 0.1% tacrolimus ointment (Protopic®) has been shown to be effective, especially in dogs with localized AD. The efficacy of tacrolimus ointment appears highest when used twice daily for one week with later reduced frequency of application as needed to control signs.

**Treatment with Oral Glucocorticoids or Ciclosporin**

Oral glucocorticoids are the most commonly used and abused class of drugs in the management of AD. However, long-term use is required in about 50% of the cases. When long-term use is required their use should be limited to oral administration on an alternate day basis. There is strong evidence of the efficacy of oral glucocorticoids and ciclosporin for the treatment of AD in dogs. Such oral medications are especially suited for dogs with generalized AD, and when other flare factors have been identified and eliminated. The onset of clinical benefit occurs earlier with glucocorticoids compared with ciclosporin. Ciclosporin can take up to 4 weeks to show clinical benefit.

**Treatment with Subcutaneous Interferons**

There are studies providing evidence of the efficacy of injections of recombinant canine gamma-interferon (Interdog®) and feline omega interferon (Virbagen Omega®) to treat dogs with AD.

**Interventions Likely To Be of Little or No Benefit To Treat Chronic Canine AD**

Results from clinical trials suggest that, as a group, first- (i.e., sedating) and second- (i.e., lower sedation) generation oral type 1 antihistamines are unlikely to be beneficial in dogs with chronic AD skin lesions. If veterinarians wish to use type 1 antihistamines, they should limit their prescription to those drugs with demonstrable antihistamine effect in dogs (e.g., hydroxyzine at 2 mg/kg twice daily or cetirizine 0.5–1.0 mg/kg once daily). Finally, antihistamines should be given as a preventative, which is every single day at the recommended dosage, to keep blocking histamine receptors before histamine is released.

A systematic review of clinical trials provides evidence that EFA supplements, EFA-enriched diets and nutritional or herbal supplements are unlikely to provide meaningful benefit if given alone for relief of inflammation and/or pruritus. EFA might be useful to improve coat quality and ameliorate dry skin, but, at this time, there is no evidence of superiority of any particular EFA combination, dosage, ratio or formulation (including enriched diets) to achieve skin barrier, coat quality or anti-allergic effect.

There is some evidence of anti-allergic efficacy of oral pentoxifylline, misoprostol and tepoxalin, but because of their modest benefit, potentially high costs and adverse effects, these medications should probably not be used as first-line medications to treat dogs with AD. Pentoxifylline (Trental®) is a methylxanthine derivative and produces a variety of immunomodulatory effects and has been shown to inhibit T cell adherence to keratinocytes. A double blind placebo controlled study in dogs with AD did show efficacy though none were 100% controlled. Misoprostol (Cytotec®) is a NSAID that acts as a PGE1 analog inhibiting production of interleukin 1 and tumor necrosis factor alpha. Of particular interest in allergic disease are its effects on decreasing histamine release and inhibiting eosinophil chemotaxis and survival. It was used in an open trial for the treatment of atopic disease. In this study of 18 dogs treated with misoprostol 6 ug/kg q8h, over 50% had greater than 50% reduction from pretreatment scores for pruritus and lesions. However in none of the dogs was pruritus reduced greater than 75%.
Strategies to Prevent Recurrence of Signs

Avoidance of Flare Factors
Avoidance of known flare factors is the most optimal strategy to prevent recurrence of signs in patients with AD. As discussed in the sections above, the maintenance of the dog on a diet not containing ingredients to which it is hypersensitive, the implementation of an effective flea control and a reduction of contact with provocative environmental or microbial allergens would be ideal, whenever possible.

Implementation of Preventive Pharmacotherapy
In humans with AD, there is evidence of high benefit, low cost and low risk of proactive intermittent applications of topical glucocorticoids and tacrolimus to skin areas repeatedly affected during flares of AD. Whether or not a similar strategy would be equally effective in dogs with AD has not been established yet, but because of the possible benefit, low risk and low cost, such interventions are worth considering in dogs with recurrent moderate or severe AD.

Implementation of Allergen-Specific Immunotherapy
Allergen-specific immunotherapy (ASIT) is the practice of administering gradually increasing quantities of an allergen extract to an allergic subject to ameliorate the symptoms associated with subsequent exposure to the causative allergen. Subcutaneous ASIT appeared effective and safe to reduce signs of AD in dogs. It should be considered in any dog in which intradermal test or IgE serology have permitted the identification of allergens likely to contribute to the disease and in whom allergen contact is unavoidable. The dog's owners should be able to afford the time, expense and technical aspects of this regimen. In addition, when symptomatic anti-inflammatory therapy is ineffective, or associated with unacceptable or potentially unacceptable side effects (e.g., glucocorticoids), or is impractical to maintain for an extended period of time, then ASIT is indicated, even in dogs with seasonal disease of short duration. Finally, due to its unique mode of action, ASIT is the only intervention that has the potential to prevent the development of signs and alter the long-term course of the disease.

It is expected that between approximately 50 and 80% of dogs with AD that have been treated with ASIT for six to twelve months will exhibit an improvement in signs and/or a decrease in anti-inflammatory or antipruritic medication use. At this time, there appears to exist no clear advantage of a particular ASIT protocol (traditional, rush or low-dose). Most importantly, injection frequencies and amounts injected must be tailored to each patient depending upon the clinical improvement observed and the presence of adverse events (e.g., increases in pruritus after each injection). Because of the delay in ASIT effect, anti-inflammatory drugs should be given temporarily, as needed to maintain good quality of life until ASIT might offer clinical benefit. Immunotherapy must be continued for at least one year before considering it ineffective as results are slowly achieved with obvious benefit taking up to 12 months to occur. ASIT requires frequent follow-up visits and may require adjustments in the protocol with most patients receiving life-long therapy. Numerous protocols for hyposensitization are used.
New Therapies for Canine AD

Sublingual Immunotherapy (SLIT)

Sublingual delivery of allergen serum has been utilized in human medicine for over 60 years, but is a relatively new concept in veterinary medicine. Sublingual and injectable immunotherapy act through similar mechanisms to “desensitize” allergic animals by altering the way their immune system responds when they encounter specific allergic triggers. Sublingual delivery provides an alternative route of administration, where instead of injecting the allergen serum, it is delivered by a specialized pump dispenser, under the animal’s tongue. The allergen serum has a slightly sweet taste, and is highly palatable. In dogs, the reported success rate of immunotherapy when delivered via sublingual administration is about 60% – these animals experience a significant reduction in clinical signs of allergy (such as itching and dermatitis) and have a reduced need for medications to treat allergic symptoms or secondary skin/ear infections. SLIT might have a faster onset of action in some patients, but as with injectable immunotherapy, response time can vary among individual animals. The risk of adverse effects with sublingual immunotherapy is extremely low. In human allergic patients, sublingual immunotherapy is often recommended for patients who experience anaphylaxis with immunotherapy injections. In fact, during original research trials, dogs with prior anaphylactic reactions to injectable immunotherapy were successfully treated with sublingual immunotherapy. Additionally, this work found that about 50% of dogs who had failed to show improvement in allergic symptoms with injectable immunotherapy did improve with sublingual immunotherapy. SLIT is an option for any dog with AD, but is it is particularly indicated for patients that do not tolerate injections well, that have had allergic reactions to injectable immunotherapy, including anaphylactic reactions, and that did not respond clinically to injectable immunotherapy. Although the principles of sublingual and injectable immunotherapy are similar, there are some slight differences in therapeutic regimen. Sublingual delivery of allergen serum eliminates the need to give injections, however, it does require twice daily administration (as compared to injections given every 7-21 days) and compliance with the administration schedule is a key factor in the success of SLIT. Both types of immunotherapy have benefits and disadvantages and the client should be involved in the decision in which mode of therapy to choose for their pets.

SLIT is currently available through different commercial laboratories including: Allercept® Therapy Drops (Heska) and ACTT® Allergy Drops (BioMedical Services) and Aller-g-complete® Drops (Greer;IDEXX).

Regionally-Specific Immunotherapy (RESPIT®)
RESPIT® (SkinVet) is an immunotherapy alternative that can be prescribed without allergy testing, including the most important allergenic substances found in a geographic region, not based on an individual response. Inclusion based on aerobiology, allergenicity and cross-reactivity among allergens. The background in the development of RESPIT® was based on the following: 1. there is no consensus as to the most accurate allergy testing technique, which display significant variability and in some cases poor reliability; 2. varied testing techniques and immunotherapy protocols produce similar results; 3. studies support the role of non-specific tolerance in humans; and lastly, double-blinded study found that stock mixture immunotherapy produced the same benefit as customized immunotherapy. Dogs that may be good candidates for RESPIT® include those that do
not show any positive results on both allergy skin and serum testing and dogs where owners would like to avoid allergy testing or have financial limitations. It is available in both injectable and sublingual formulations. At this time, there are good evidence studies to support the efficacy of RESPIIT® in dogs with AD.

Oclacitinib Maleate (Apoquel®), by Zoetis
APOQUEL is FDA-approved and indicated for the control of allergic dermatitis, more specifically atopic dermatitis, in dogs at least 12 months of age. It is a selective inhibitor of the Janus kinase (JAK)-1, a protein that is integral to the signaling pathway that results in itching and inflammation. Its novel mechanism of action on the JAK enzymes is specifically designed to target the pruritogenic and pro-inflammatory pathways involved in the itch cycle (including inhibition of IL-31 cytokine), allowing control of the signs of allergic disease. It has little effect on cytokines involved in hematopoiesis that are dependent on JAK2. APOQUEL is not a corticosteroid. It is reported to have a fast mode of action similarly to oral glucocorticoids, with efficacy rates reported to be around 60-80%. Most commonly reported side effects include vomiting, diarrhea, anorexia and lethargy, which in most cases resolve spontaneously with continued dosing. APOQUEL has been safely used in conjunction with other common medications including vaccines, NSAIDs, antibiotics, parasiticides, anticonvulsants, and allergen immunotherapy. APOQUEL can be used in combination with allergy testing. APOQUEL may be used concurrently with vaccines in dogs at least 12 months of age. APOQUEL is not for use in dogs less than 12 months of age or in dogs with serious infections. APOQUEL may increase susceptibility to infection, including demodicosis, and exacerbate neoplastic conditions. It will be launched in January 2014 and will be available in 3 different tablet formulations: 3.6 mg, 5.4 mg and 16 mg. Recommended dosage is 0.4-0.6 mg per kg of body weight administered orally twice daily for 14 days, then administered once daily for maintenance therapy if pruritus is controlled. The author recommends baseline and monitoring laboratory tests including complete blood cell count and chemistry profile.

Summary
It is important to understand the acute flares and chronic aspects of canine AD and to keep in mind that AD is a non-curable disease that needs frequent recheck visits and monitoring, client education and that, although current treatment options have limitations and not all available therapies for canine AD has shown evidence of efficacy, the treatment of canine AD is best achieved on an individualized basis through a systemic approach and multimodal therapy.

References
