Allergic dermatitis (AD) is a complex, multifactorial disease, involving connections between the immune system, epidermis, and the nervous system. Speaking at the Ontario Veterinary Medical Association (OVMA) Conference on January 29, Douglas J. DeBoer, DVM, DACVD, a professor of dermatology at the University of Wisconsin School of Veterinary Medicine, outlined 10 treatments and considerations veterinarians need to know about allergic skin disease, and shared some tips for effective treatment of dogs that present with this condition. He explained that more than half of allergy cases in dogs are caused by environmental or flea allergies. Allergic skin reactions cause pain, itching, and discomfort to the pet, and can be a challenge to diagnose due to unreliable diagnostic tests, and symptoms that can mimic other problems. Veterinarians are moving away from treatment with antibiotics due to resistance issues. Topical therapies are being used more, and there are various new immunotherapies on the horizon. As well, prescription diets that reduce the signs of environmental allergy are now available. Still, there is no single solution to treating skin allergy in pets. Rather, veterinary practitioners must use a multimodal, individualized approach to achieve optimal results.

1. JAKs: key cytokine in pruritus

Aimed at treating a variety of neoplastic, inflammatory and immunologic diseases, kinase inhibitors, (Kis) are advancing rapidly. The most recent molecular targets to receive attention are the Janus Kinases (JAK). The JAKs function to communicate a signal from a cell surface receptor to the nucleus, and many inflammatory pathways (especially cytokines and their receptors) use JAKs for signaling. In particular IL-31 has recently been identified as a key cytokine in pruritus, and uses the JAK pathway.

Dr. DeBoer said that oclacitinib (Apoquel, Zoetis), a JAK inhibitor administered orally, has shown the ability to suppress pruritic responses rapidly and effectively, in some cases better and more quickly than prednisolone. It is indicated for control of acute or chronic pruritus in dogs over 12 months of age. Overall, it appears that at least 60-70% of allergic dogs receiving the drug have rapid, substantial, and prolonged relief of their clinical signs. He noted that currently it is unavailable in Canada.

2. Monoclonal antibodies

Dr. DeBoer explained that an important characteristic of therapeutic monoclonal antibodies (mAbs) is that they must not be recognized by the patient's immune system as foreign proteins – therefore, they must undergo some process to render them identical to naturally occurring antibodies of the host. In veterinary medicine, mAb treatment products are referred to as “cananized” or “felinized.”

Considerable research has been done with a monoclonal antibody directed against the cytokine IL-31, a key molecule in causation of allergic pruritus in dogs. Recent studies reported the production of a “cananized” version of monoclonal anti-IL-31. This mAb binds to IL-31 and eliminates it from tissues. In preclinical laboratory models, the mAb was capable of reducing pruritus in dogs for more than 3 weeks after a single injection. Field trials next demonstrated that this mAb therapy was highly effective at controlling atopic pruritus in dogs. Dr. DeBoer said the treatment (now called Canine Atopic Dermatitis Immunotherapeutic) currently has a limited licence and is available at specialty dermatology clinics in the United States.

3. Trend towards use of topical solutions

Over the past 10 years, there has been a substantial increase in the prevalence of antibiotic resistance in canine staphylococcal infections. Many strains are now multidrug resistant, leaving the practitioner with few good options for treatment.

Dr. DeBoer said that most dermatologists are now advocating that topicals be used instead of antibiotics wherever possible to help minimize the development of antimicrobial resistance. Topical products will still kill even highly antibiotic-resistant strains. Chlorhexidine is an excellent choice, noted Dr. DeBoer. Mild to moderate superficial pyoderma responds very well to daily topical application of 2-4% chlorhexidine for 3-4 weeks. The keys here are daily application with a spray or mousse product to make frequent chlorhexidine application easy, with weekly whole-body chlorhexidine shampooing of the pet.

More severe cases, or cases of deep pyoderma, still require antibiotic treatment. Upon first diagnosis, empirical treatment with a cephalosporin antibiotic is reasonable if the patient has not received multiple courses of antibiotics previously.

4. Food hypersensitivity and diet trials

Food hypersensitivity is considered the third most common allergic disease diagnosed in dogs and cats after flea allergy and AD, explained Dr. DeBoer. It can be seen alone or in combination with these other allergies. The controversies surrounding diagnosis of food allergy illustrate our inability to make evidence-based statements about this disease.

Dr. DeBoer highlighted the following facts based on recent studies on diet trials:

- Serum allergy tests are NOT reliable for diagnosis of food allergy.
- The only accurate test for food allergy is a carefully-performed, strict, dietary restriction-provocation trial
- Diet trials should never be performed with “pet store brand” diets, as these diets often contain trace amounts of important allergens not listed on the label

He added that he frequently gets asked, “Which diet is the best to use?” His answer is that there is no convincing evidence that for a given patient, a home-cooked or commercially-prepared diet is better, though compliance is paramount and may be better with a commercial diet.

Dr. DeBoer said that his diet of choice is a hydrolyzed commercial diet, such as Hills® Prescription Diet® z/d®, because diets based on hydrolyzed protein sources have less chance of containing clinically relevant allergens. Hydrolysis breaks down the proteins into very small particles, in an effort to prevent recognition by the immune system of the intact protein. Ensuring the client fully understands the reasoning behind an elimination diet, and the need for continuous vigilance during this process to eliminate any other sources of edible allergens, will ensure best success during this period of diagnostic trial.

5. The news on cyclosporin

The calcineurin inhibitors work by inhibiting production and action of cytokines, and through other mechanisms as well. Clinical trials of cyclosporin modified (CsAM) is remarkably free from long-term adverse effects, due to slow onset of action, many dermatologists begin a 2-week tapering course of oral prednisolone alone with CsAM for faster patient relief, and this appears safe.
Allergic skin disease therapy should be individualized and multimodal

6. EFA: multiple benefits
Dr. DeBoer explained that essential fatty acid (EFA) supplements remain a cornerstone of conservative management. Their effects may occur through their weak anti-inflammatory effects, or through possible effects on epidermal barrier function. Studies demonstrate they may have improved efficacy with antihistamines and with glucocorticoids (dose-sparing effect). Recently, it has been demonstrated that they also have synergistic effects with cyclosporin, allowing the dose of the latter to be substantially tapered over time. He noted that because they are relatively inexpensive, safe, and easily administered, many dermatologists advise that ALL atopic pets should receive enhanced levels of EFA. EFAs can be administered as a capsule or oil supplement or as a component of the dog food, as long as the dog receives more than 25 mg/kg/day. Feeding a diet high enough in the correct fatty acids (such as Hill’s® Prescription Diet® Derm Defense™, among others) is often a cost-effective way to provide the EFAs with better client compliance.

He stressed that clients must be warned that many over-the-counter supplements (such as “salmon oil”) have only very small amounts of the desired EFA. There is little evidence that the ratio of omega-3 to omega-6 EFA is important in skin disease. It is also important to advise clients that beneficial effects take at least 1-2 months to be seen.

7. Epidermal barrier function
Historically, AD was viewed as a disease that began on the “inside” – the immune system – and that following this, “outside” influences such as allergens, irritants, bacteria, and yeast would cause development and worsening of symptoms.

More recently, this “inside-outside” view has come into some question, and a different view is evolving. It was noted that perhaps AD might begin first as a defect in the “outside” – and following this the barrier function problems result in development of an altered immune response and inflammatory cascade.

It was later determined that not only the permeability barrier, but also the antimicrobial barrier was defective – the skin of atopic people produces much less antimicrobial peptide than normal. The more the concept of “barrier dysfunction” is examined, the more it becomes obvious that barrier function is abnormal in AD, and this is a critical part of the pathogenesis of the disease.

Dr. DeBoer explained that manipulating the diet by altering its fatty acid composition affects the composition of skin lipids. A series of studies has demonstrated convincingly that modifying barrier function is an important and effective part of treatment in human AD, and may become a mainstay of therapy in animals in the near future. Some of these studies suggested that by modifying epidermal composition, there was a relief of allergy clinical signs.

Topical modification of barrier function is an active area of research in veterinary medicine. Initial research has shown that application of topical lipid emulsion preparations can result in “normalization” of the intercellular lipid lamellar structure and composition. Dr. DeBoer said that if these therapies result in remission of clinical signs, they would become an important and necessary part of the therapy of AD.

8. Antihistamines still don’t help much
Dr. DeBoer said that antihistamines may benefit 5-20% of pets, and they are always worth trying, though there has been little or no medical evidence to prove that they are beneficial, and they are most likely only effective in mild cases. Recent, better-designed and controlled studies have shown some success in dogs with the antihistamines dimetindene, fexofenadine, and a combination of hydroxyzine and chlorpheniramine.

9. Cats: is it allergy?
Before deciding that allergy is the cause of a cat’s pruritus, all other common causes of itch should be ruled out, such as parasites and infections, explained Dr. DeBoer. Unfortunately, even recent and extensive studies show that there is no specific set of clinical signs that indicates feline allergy. Allergy, he said, remains a diagnosis of exclusion in cats.

Initial “allergy evaluation” typically begins with a dietary restriction-provocation trial in cats. Dr. DeBoer stressed that the most important factor is that compliance with the dietary restriction is complete; therefore choose a diet that the owner is happy to feed, and the cat is happy to eat. The initial trial should be for 4 weeks, with an additional 4-8 weeks if improvement is occurring. If response is apparent, challenge with the original food to prove the food is responsible and not some other coincident factor.

Allergy testing, in particular, is problematic, explained Dr. DeBoer. Intradermal tests are difficult to perform and interpret in cats. Most important for the practitioner to understand is the use of serologic IgE tests – in both dogs and cats. Studies generally demonstrate that normal cats, or pruritic but nonallergic cats (for example, cats with fleas) are positive on these tests just as often as “truly allergic” cats. Therefore, serologic tests must never be used to make a diagnosis of allergy. Rather, their only benefit is to attempt to determine what the relevant sensitivities may be in preparation for immunotherapy treatment.

10. Sublingual immunotherapy
Sublingual immunotherapy (SLIT) involves administration of allergen extract into the oral cavity, under the tongue. Dr. DeBoer described it as an easy to administer, safe, and potentially faster way to treat allergies. He said that most dogs accept administration easily as a “treat” because the formulation is sweet tasting, which increases compliance.

SLIT formulations are typically supplied in 3 bottles of increasing concentration. Concurrent medications do not appear to interfere with efficacy. Many SLIT formulations use glycerin-based extracts, which purport to stabilize the allergens and/or facilitate uptake through the oral mucosa. SLIT formulations are typically administered every day, often several times per day, for the duration of therapy with no tapering.

Studies have shown that approximately 60% of dogs with AD that have not had prior immunotherapy attempts will have substantial improvement of their clinical signs with this formulation. Also, about half of dogs that are “shot failures” due to lack of efficacy, difficulty with administration, or anaphylactic reactions can be successfully treated with SLIT.

Anaphylactic reactions to SLIT are rare to nonexistent, and SLIT can be used in dogs with a prior history of reaction to allergy shots.

Summary
Allergic skin disease is a multifactorial disease with a complex pathogenesis. As there is currently no cure or “magic bullet” for treatment of this condition, it is important that therapy be multimodal and individualized. Veterinarians need to determine the optimal combination of treatments, diet, and supplements that work best for individual dogs that present with allergic skin disease. New treatments and therapies, already available or on the market soon, are allowing for more effective and safer long-term management.