

ATOPIC DERMATITIS IN THE 21ST CENTURY: It's a brave new world

Valerie A. Fadok, DVM, PhD, Diplomate, ACVD
North Houston Veterinary Specialists
Spring, TX
fadokv@aol.com

Atopy represents the inherited tendency to mount a skewed and flamboyant immunological reaction to environmental antigens such as pollens, molds, danders, and mites. If one ascribes to the "danger" hypothesis for activation of the immune response, then these are people and animals who mistakenly perceive environmental antigens as perilous! One of the key features is the development of reagenic antibody, which in mammals is represented by the immunoglobulin IgE. The simple model based on Th1 vs Th2 reactions, so elegantly described in the allergic mouse, is probably too simple for dogs and humans! The pathogenesis of the IgE-mediated immunologic response involves both early and late phase reactions. The allergen binds to IgE on the surface of mast cells to trigger degranulation of preformed mediators, as well as the activation of inflammatory pathways. It is the later phases that result in the sustained inflammatory response we see in our patients, and pruritus is the major complaint!

While IgE plays a role, it is only the tip of the iceberg. Much more is going on with cellular infiltrates, and the cytokines known to accompany atopic states. Furthermore, the interaction of cytokines with the nervous system promotes the intractable itch that patients with atopic dermatitis often experience. Repressing these cytokines is the goal of therapy, and this is done using allergen specific immunotherapy, along with medications such as steroids or cyclosporine to reduce itch and inflammation. Next year, oclacitinib (Apoquel) will be released in the United States. It is a Janus kinase inhibitor that blocks the ability of cytokines to stimulate a response. It is more focused than cyclosporine, and appears to have fewer side effects. It looks very promising because itch is reduced quickly.

There has also been great interest in the contribution of the skin barrier to atopic dermatitis. It is clear that in humans there are genetic mutations associated with various structural proteins in the stratum corneum and other proteins as well. One of these proteins, filaggrin, seems to have some abnormalities in distribution, although the presence of mutations is not well explored yet. Lipids in the stratum corneum have been shown to be abnormal in humans as well as dogs, and emphasis is being placed on trying to repair the barrier with topical lipid preparations as well as oral fatty acids. The dysfunctional barrier in the stratum corneum allows for penetration of allergens, as well as toxins from microbes such as *Staphylococcus* spp and *Malassezia*. Certainly infections will also contribute to the impaired barrier as well.

CLINICAL PRESENTATION: Classical clinical signs of atopic dermatitis in the dog include face rubbing, foot chewing, and axilla and belly scratching, lending support to the idea that most atopic dogs experience their allergenic exposure through their skin, rather than through the mucus membranes of the nasal passages. Dermatologic syndromes appreciated in atopic cats include military dermatitis, eosinophilic plaques, and hair pulling. However, there is a small but important group of dogs and cats whose major manifestation of atopy is respiratory. Dogs may present with allergic rhinitis and/or conjunctivitis, and sometimes an asthma-like disease in the

absence of dermatological signs. This is not usual, so it is important to rule out other causes of persistent rhinitis or cough first. Cats may present with upper respiratory signs or with asthma-like conditions as well. Atopic patients often are afflicted with secondary infections. These infections increase their discomfort and contribute significantly to the difficulties in managing their disease.

DIAGNOSIS: The diagnosis of atopy and/or atopic dermatitis is based on appropriate history and clinical signs, and ruling out other causes of itch, including occult scabies, flea allergy dermatitis, and in some cases, food allergy. Intradermal skin testing and/or blood allergy testing are used to select allergens for immunotherapy. Conceptually, skin testing is appealing, as we examine the organ directly affected in most of our veterinary patients. However, blood testing remains a valid choice for those animals who cannot be skin tested or whose skin test cannot be interpreted. The choice of the diagnostic lab should be based on the judicious balancing of sensitivity with specificity. Several companies offer serum allergy testing including Veterinary Allergy Reference Laboratory (VARL), Heska, Greer (now via IDEXX), Biomedical Services, Spectrum, and Nelco. It is important to keep in mind that neither skin testing nor serum testing are perfect tests. Clinical knowledge must always be correlated to the results in order to make an effective allergy vaccine.

TREATMENT: Treatment of atopic dermatitis can be a complicated affair! One must take into account not only the animal's threshold of tolerance for itch but the owner's! One must also take into account how much work the owner is willing to do to get the disease process under control and their acceptance of the notions that the disease is not curable and that there is no quick fix! It is my belief that success increases exponentially if we combine multiple therapeutic approaches, including topical. This is the multimodal approach to which we all allude when talking about allergy management. This multimodal approach requires a dedicated owner, and I am always impressed with the devotion of most of our clients toward their animal companions. Basically we avoid allergens if we can (usually foods, fleas), use immunotherapy to modify the immune response, control infections and ectoparasites, repair the skin barrier, and control itch.

Avoidance: Whenever possible we want to avoid the allergens or infections that are typical flare factors for pets with atopic dermatitis. Practically speaking, foods and ectoparasites such as fleas are the only allergens we can practically avoid in allergy management. Food allergy or adverse reactions to foods can be part of the atopic problem so it is always worth considering what role diet plays in an atopic patient. We can help reduce exposure to environmental allergens as well. For dogs with pollen allergens, reducing their time outside during the high pollen counts, along with wiping their faces and feet when they come inside, reduces the ability of the pollen proteins to absorb through the skin. For dogs allergic to house dust mites, frequent vacuuming of the carpets (or even removal of the carpets) will help. For dogs that sleep in the bed with their owners, we can recommend the hypoallergenic bedding that is recommended for people with similar allergies.

Immunotherapy: Specific immunotherapy remains the treatment of choice for the atopic patient. It is a biologic long term plan for management. The notion that we can retrain the immune system to perceive the environment differently is a powerful one. The observation that this is a difficult process speaks to the fact that injection therapy has to be given frequently and for long periods of time. The success of this

therapy will depend on the accuracy of the diagnostic testing, the formulation of the vaccine, and the realization that “one size fits all” will not work. Each program will need to be tailored to the specific needs of the patient with regard to frequency of injections and number of allergens used. In the old days, we generally used one vaccine containing 10-12 antigens and encouraged the owners to believe that eventually one injection every 3-4 weeks would be sufficient to control their allergens. Now we are finding that many patients can benefit from two vaccines. This enables us to hyposensitize against 20 or more allergens without diluting the vaccine. These can be given at the same time, although some dermatologists prefer to separate them. I think we are finding that many dogs in the Houston area seem to do better with weekly injections rather than monthly injections. We can encourage our clients to experiment with the frequency. Those dogs who have specific seasons in which their signs exacerbate might do well with weekly injections during their bad times and less frequent injections during the off seasons. This individualized approach requires a lot of communication back and forth between clinician and client. We are the cheerleaders for the client-pet team. Using the basic principles of behavioral analysis, we must come up with the positive reinforcement each client needs to continue what can be a difficult regimen. Alternative approaches to traditional immunotherapy include rush immunotherapy and sublingual immunotherapy.

Rush immunotherapy is done by hospitalizing the patient for a day, and giving the injections every 30 - 60 minutes until the maintenance dose is achieved. Both dogs and cats seem to tolerate this approach quite well. It does have increased risk, though, so the patients have to be watched carefully for side effects. Rush immunotherapy is used in humans, and it results in a faster and better response to immunotherapy. We do not know if these benefits are seen with dogs and cats that experience rush. It is used to help get animals up to maintenance therapy quickly to help simplify the protocols for injections.

Sublingual immunotherapy has been shown to be as effective in dogs as injection therapy. In some dogs, it seems to work faster, and it has been successful in a subset of dogs who have failed injection immunotherapy. The advantages are that no injections have to be given; a potential disadvantage is that the drops have to be given at least twice daily. In humans, the goal is to use the allergy drops (or injections) for 3-5 years with a goal toward permanent tolerance and stopping the vaccine. We don't know if dogs will be able to stop allergy drops, but a few dogs who have been started on injections early in life have been able to stop immunotherapy after several years. These are aspects of canine atopic dermatitis about which we know very little.

If immunotherapy is the long term plan, it is clear that we need a short term plan to control the pruritus and clinical signs while we get immunotherapy underway. The **short term plan** will involve a detailed analysis of the individual's skin condition. These are the questions I like to ask myself.

Controlling ectoparasites and infections

What role do insect hypersensitivities play in this patient's skin disorder? In most of the United States, insects, particularly fleas, really complicates the response to immunotherapy. Fortunately, flea control is much more pleasant than it ever used to be! Whether we can successfully use immunotherapy in the management of insect

hypersensitivities, particularly those to fleas, remains controversial. In general, our approach has been to put most of our atopic dogs with flea allergy on vigorous flea control throughout the year. In the past, we utilized Capstar given every Monday, Wednesday, and Friday. In my part of the country, I use Comfortis given every 2-3 weeks or Vectra 3D every 3-4 weeks. For dogs being bathed frequently oral flea control may be preferred, as bathing more than once weekly reduces efficacy of topical flea control. For cats, we have used some Comfortis, although we have relied on Capstar orally or Revolution topically. We do not seem to bathe our atopic cats as frequently. The key is to treat atopic patients with the flea control product of your choice every 30 days throughout the year. In some cases, flea control may need to be used every 2 weeks, particularly with the spring and fall flea surges we have in places like Houston. The release of Seresto collars (Bayer) is exciting and I am eager to see how well this collar works in areas with high flea and tick pressure.

What role do infections play in this patient's skin disorder? Bacterial and yeast infections of the skin contribute significantly to the allergic animal's discomfort. Even if these organisms merely sit on the surface of the skin, they produce toxins and metabolites that are significantly irritating or in some cases, allergenic. Nuttall and Halliwell have shown that atopic dogs have significant levels of anti-Malassezia IgE and IgG in their blood. Although not well documented in our canine patients, superantigen reactions contribute greatly to atopic dermatitis in humans, and I believe they do in dogs as well. Creative approaches to infection control really help our atopic patients. Look carefully for the presence of superficial and deep pyodermas, but also be aware that the mix of bacteria and yeast on the skin surfaces of the muzzle, feet, perianal and perioral areas, and ventrum may manifest as erythematous greasy patches. Cytologies are indicated in almost all atopic patients. A subset of dogs with recurrent pyodermas associated with their allergies will benefit from the use of Staphage Lysate in addition to their allergy vaccine. These dogs are likely allergic to the Staph itself.

Once the fauna inhabiting the skin has been identified, one must determine the need for systemic and/or topical therapy. Certainly the presence of folliculitis and deeper pyodermas warrant the use of systemic antibiotics. My average treatment period has been 20 - 30 days. Regrettably we have little evidence to support what we do in pyoderma. There is a tendency in human medicine to use higher doses of antibiotics for shorter periods of time and this needs to be evaluated in canine pyoderma. I still like cephalosporins with the caveat that if a good response is not seen, methicillin resistance may need to be considered. Cefovecin has become my preferred drug because of its excellent pharmacokinetics and because it takes compliance out of the hands of the owner. It reaches high levels in the skin to kill bacteria quickly and maintain levels above the MIC for extended periods (two weeks). Cefpodoxime (Simplicef) is an excellent choice as well; the notion of once a day treatment is a beautiful one and may improve compliance! This medication should be used at a minimum dose of 5 mg/kg/day but we often use it at 8-10 mg/kg/day. Underdosing should not be done with this antibiotic or any other. We have to remember too that these antibiotics are time-dependent, meaning that there is no post-antibiotic effect, and that the bacteria are only susceptible when the levels in the tissue are above the MIC.

I try to avoid the use of fluoroquinolones for superficial pyodermas; they do not seem to be as effective and there is some evidence in the human literature that these

antibiotics may encourage the development of resistance mechanisms in bacteria. Given the rather rapid increase in methicillin resistance, we find we use much more ormetoprim-sulfa (Primor) again, if culture and sensitivity supports it. I used 27.5 to 30 mg/kg once daily of this medication. We are also using doxycycline if the C/S results indicate sensitivity, although being a bacteriostatic antibiotic it may not be as effective in vivo as we would like. Dr. Mark Papich recently told us that the CSLI standards for *S. pseudintermedius* for doxycycline are being revised. Currently 4 ug/ml is considered sensitive, but the newer standard may be as low as 0.25 ug/ml. If you choose doxycycline, have a look at your MIC; if it is higher than 1 ug/ml, don't use the doxycycline. Minocycline is advocated for use in MRS in people and can be used for dogs as well. Chloramphenicol, amikacin, and rifampin are also being used with increasing frequency. For cats, I think that secondary pyodermas are less common. If cytologies show bacteria, then we often use Clavamox or cefpodoxime suspension or tablets. MRS, including MRSA, has reared its ugly head in cats too, so if response is not what is expected, consider a culture and sensitivity. For topical use, you can mix amikacin to 5 mg/ml in Tris EDTA and use it as a spray for MRS, when culture indicates that the organism is sensitive. It is a nice way to use amikacin without the risk of renal damage when it is used systemically.

The presence of *Malassezia* is always a complicating factor. Daily bathing with an imidazole-containing shampoo (DOUXO chlorhexidine with climbazole, Malaseb, Mal-A-Ket, KetoChlor) will reduce yeast numbers without having to resort to systemic therapy but not many people are willing to bathe their dogs daily. Therefore, we use a combination of ketoconazole 5 mg/kg once daily or fluconazole 5 mg/kg once daily with once to twice weekly bathing with Malaseb or one of the other shampoos. Itraconazole (5 mg/kg/day) and terbinafine (30-40 mg/kg/day) can also be used. In particular, terbinafine has been useful for canine Cushing's disease patients being treated with trilostane. For cats, fluconazole has been a wonderful treatment for yeast dermatitis. It is safe, well-tolerated, and rarely causes side effects. The use of pledgets or pads impregnated with chlorhexidine and an antifungal agent (e.g. DOUXO chlorhexidine pads, Mal-A-Ket pads, TrisChlor 4 pads) on feet and focal areas of bacterial/yeast colonization has been a wonderful addition to allergy management! Some dogs are allergic to their yeast, and for these dogs we can add *Malassezia* allergen to their allergy injections or drops.

What role does otitis play in this patient's skin disorder? Many canine and some feline atopic patients have otitis externa associated with their disease. This issue should be addressed as part of the whole package. Ear cytologies are routinely performed and treatment based on the findings. I most commonly see patients with mixed infections of bacteria and yeast. I advocate weekly flushing with EpiOtic Advanced or DOUXO Micellar once the infections are cleared. These flushes can prevent recurrence of infection if done regularly. Many dogs with atopy will do well except for some residual pruritus in their ears. Rather than utilize an oral steroid, I like to use an otic steroid. We will often ask the clients to use HB101 daily (e.g. Bur-otic or Hydro-Plus) or sometimes Synotic applied 2-3X per week.

Repairing the skin barrier.

There are two ways in which we can help repair the skin barrier. The first is by using oral fatty acid therapy. The recommended dose has been 180 mg eicosapentaenoic acid per 10 lbs of dog. There is good evidence, though, that diets such as Iam's Response FP and other fatty acid enriched diets improve the skin and coat quality of

atopic dogs. The second way to improve the skin barrier is by using topical therapy. The choice of shampoos and rinses will be determined by the individual. Evidence has accumulated that shampoos containing chlorhexidine are the most effective against *Staphylococcus pseudintermedius*, *Pseudomonas aeruginosa*, and *Malassezia*. There is also some evidence that miconazole can enhance the anti-staphylococcal effects of chlorhexidine. Thus, a shampoo like Malaseb or Miconahex-Tris EDTA are very useful. In addition, the latter has ceramides which may help to restore the barrier. Shampoos containing miconazole are also ideal for yeast dermatitis as well. DOUXO chlorhexidine with climbazole and phytosphingosine is another good shampoo for long term use.

Bathing is absolutely critical when dealing with methicillin resistant staphylococcal infections. When the infections are superficial, daily bathing with chlorhexidine shampoos will resolve infection if done for 30 days or until all the lesions are resolved. A new shampoo product, Top Vet Splash Plus has been very useful in the management of infections in atopic dogs. The active ingredient is sodium hypochlorite (www.vetsplash.com). Additional topical remedies that can be helpful include Vetericyn VF spray, if used 2-3 times per day, and nisin wipes (Wipe out dairy wipes and Bayer's Preva wipes), used 1-2X per day (<http://immucell.com/wipe-out.htn>). Dilute bleach rinses (6-30 cc/gallon water), 2% chlorhexidine rinses, and lime sulfur dips can also be used.

For dogs with itch but no infection, then we can use shampoos containing fatty acids, phytosphingosine, or ceramides. It is critical to remember that with shampoo therapy, formulation is a critical part of its efficacy. All of the above can be followed with a soothing crème rinses or leave-ons such as Resicort.

Topical barrier repair: Some newer approaches in addition to bathing include the use of topical lipids to stimulate repair of the skin barrier. There is some evidence to show that the topical application of ceramide, phytosphingosine stimulate the keratinocytes to repair the barrier and to resume production of their own lipids. Ceramide and fatty acids are contained in the new product by Virbac, Allerderm Spot-on. Phytosphingosine is contained in the DOUXO line of products by Sogeval. Their DOUXO Spot-on contains highly purified phytosphingosine. Dermoscent makes a line of products containing essential oils which supply fatty acids to the skin. Time will tell how useful these products will be, but we have seen very encouraging results so far. Coat quality and skin quality are enhanced, with perhaps a reduction in the frequency of pyoderma recurrences. In mild atopics, we have noted that these products may even reduce itch. Dechra has begun to add ceramides to their shampoo products, and so these products would be expected to help with barrier repair as well.

Control of itch. Itch is the most common sign that drives the owners of atopic dogs into our clinic. We must control itch to buy us the time we need to utilize immunotherapy effectively. Up until recently, the only good evidence we have is for steroids and cyclosporine; however, recently oclacitinib (Apoquel, Zoetis) has been approved, and it will be released after the first of the year.

Antihistamines: Frankly, I don't find antihistamines as sole agents that helpful for most patients, and evidence for their efficacy is fair to poor. They may be worth trying for some dogs and cats with mild disease. I often start with recommendations

for over-the-counter antihistamines, asking that the owners give each a try for a couple of weeks. If none of the over the counter products work, I like to prescribe either hydroxyzine or amitriptyline. For dogs that don't respond to antihistamines alone, the veterinary product Temaril-P (Zoetis) can be helpful. The combination of trimeprazine and prednisolone (2 mg per tablet) allows good control for many dogs while keeping the total dose of steroids

Steroids: Glucocorticoids have profound effects on inflammatory pathways, and they are very effective in reducing itch. The potential side effects can be divided into two groups: short term and long term. The short term side effects include polyuria, polydipsia, polyphagia, and behavioral changes, which are offputting to many clients. The long term side effects include liver enzyme elevations, muscle loss, weakening of the ligaments, thinning of the skin, reduced coat quality, and increased susceptibility to infections. While these side effects do not occur in all dogs, they occur with enough frequency to make the routine use of glucocorticoids less desirable. For some dogs, however (at least prior to Apoquel), glucocorticoids were the only medication that was effective.

We try to avoid using glucocorticoids for long-term management of atopy if we can, but using prednisone, prednisolone in short bursts and getting dogs to low dose alternate day therapy is necessary for some dogs during the induction phase of immunotherapy. Recent evidence suggest that steroids may actually enhance the induction of T regulatory cells, one of the mechanisms by which immunotherapy is supposed to work. Therefore steroids are NOT contraindicated in dogs on immunotherapy. Some dogs may require low dose maintenance steroids with their immunotherapy to remain comfortable. I like to start with the veterinary drug Temaril-P, a tablet containing the antihistamine trimeprazine and 2 mg prednisolone. I find this drug to be very effective in most patients, allowing us to keep the steroid use down and achieve good control of itch. I think it is important to try to use this drug and steroids in general in bursts and to stop often to see how the animal will do without it. Candace Sousa has published an easy calculation for long term steroid use that I have found very helpful. The body weight in lbs is multiplied by 15 (if kg, by 30); the resulting number is the mg of prednisone or prednisolone that the dog can take annually. This dose, based on her experiences, has been least likely to cause problems. If this dose is exceeded, the likelihood of problems may be increased.

Cyclosporine initially released as Atopica (Novartis) revolutionized the treatment of atopic dogs and cats, particularly those who had become refractory to steroids or could not tolerate them. Cyclosporine can also be used concurrently with immunotherapy and many dermatologists have said they believe this makes the immunotherapy work better. We use 5-7 mg/kg daily for 4-6 weeks, then we try to lower the frequency. When used concurrently with immunotherapy, the hope is that we will phase out the cyclosporine after several months. Many dogs can live on Atopica with good control of their allergies, but we still find they need bursts of steroid during bad times. It is not always possible to reduce the frequency, though, and some dogs and cats require daily therapy to remain comfortable. Side effects in the short term include nausea, vomiting, and diarrhea; these can often be ameliorated by using maropitant (Cerenia, Zoetis), for the first 4 days of cyclosporine therapy. Long term side effects include chronic soft stool, gingival hyperplasia,

lichenoid psoriasiform dermatitis and unusual bacterial and fungal infections. In cats, fatal toxoplasmosis has been observed.

Oclacitinib (Apoquel, Zoetis) was approved for use in dogs by the FDA in May 2013, and launched in the United States in January 2014. It can be used for short term control of itch associated with several allergic skin diseases in dogs greater than 12 months of age, and for long term use in chronic atopic dermatitis. It is a focused inhibitor of allergy cytokines that works by inhibiting Janus kinases (selectively JAK1); these kinases help transmit the signal of the cytokine to the inside of the cell, resulting in activation. In particular, interleukin 31, the itch cytokine, is very sensitive to inhibition by Apoquel. The most common side effects include vomiting, diarrhea, and anorexia (in less than 5% patients). The medication is available in 3 tablet sizes (3.6, 5.4, and 16 mg). Dosing is 0.4 to 0.6 mg/kg BID for 14 days, then once daily for chronic use. Many clients report that their dogs stop itching within a few hours of taking the medication. This rapid action corresponds very well with research in the laboratory in which Apoquel reduced the itch associated with intravenous IL-31 injection within 3 hrs, whereas steroids had little to no effect in this time. The drug has a half life of 4 hrs and is virtually gone by 24 hrs. In some dogs, there is an increase in itch when the dose is reduced from twice daily to once daily. For those dogs, it may be most effective to give the once daily dose in the early evening, so that the dogs have a comfortable night. Twenty-eight day studies have shown that itch control with Apoquel is comparable to that for prednisolone, but without the side effects. Similar findings were seen when the drug was compared with cyclosporine over 84 days. Apoquel reduced itch much more rapidly and was associated with fewer side effects. For more information, see the articles by Cosgrove et al. below. Also visit ExcellenceInDermatology.com and ItchCycle.com for access to more information about canine atopic dermatitis and downloadable resources.

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