Managing Canine Atopic Dermatitis: Are We Any Better Off Now Than 10 Years Ago?

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Atopic dermatitis is a chronic, inflammatory, and pruritic allergic skin disorder that affects about 10% of the canine population. Dogs with atopic dermatitis have characteristic clinical signs and develop IgE antibodies primarily against environmental allergens (e.g. house dust, house dust mites, pollens of plants, trees and weeds, etc.) but, also food antigens. In a subpopulation of dogs with clinical features identical to those with atopic dermatitis, an IgE response to environmental or, other allergens, cannot be documented by serum or intradermal allergy tests. These dogs are referred to as "atopic-like" or, as having "atopic-like dermatitis". Because the clinical signs of these two subpopulations are indistinguishable, we will only use the term "atopic dermatitis" in this brief review.

Dogs with atopic dermatitis experience a life-long, seasonal or year-round pruritus that can vary in intensity from mild to severe and, eventually, leads to various self-induced skin lesions and chronic inflammatory changes. These dogs are very prone to develop secondary superficial bacterial skin infections and malassezia dermatitis, which typically significantly aggravate their clinical signs.

When planning the management of this non-curable skin disease the following should be taken into consideration: (i) to identify and appropriately treat any secondary skin infection; (ii) to modulate the immune system in disfavor of an allergic response; (iii) to reduce the pruritus to a comfortable level without causing concerning side effects from the medications; (iv) to find treatment strategies that will maintain life-long control of the disease.

Identifying and treating secondary skin infections

This is an important aspect of the treatment plan of any patient with atopic dermatitis because these patients are highly predisposed to skin infections which often aggravate their allergic condition.

Most superficial bacterial skin infections and malassezia overgrowth can be identified by performing very simple cytological tests such as, direct impression smears or acetate tape preparations. The presence of intra- and extra-cellular cocci-shaped bacteria and neutrophils (mostly degenerated) will indicate a staphylococcal infection. The presence of large numbers of cocci and yeast organisms without inflammatory cells, will indicate staphylococcal and Malassezia spp. overgrowth, respectively.

Depending on the extent and severity of the infection, the treatment can be solely topical or topical combined with systemic antimicrobials. The latter approach is most commonly used because the large majority of dogs will have an infection extending to areas with hair which impedes an adequate administration of topical medications, limiting their effect.

Topical antimicrobials can be applied in the form of shampoos, lotions, sprays, rinses, wipes, gels, creams, and ointments. Common antibacterial ingredients in shampoos, sprays, wipes and lotions include: chlorhexidine, benzoyl peroxide, ethyl lactate, acetic acid, lactic acid, malic acid, and triclosan. Common ingredients present in gels, ointments, and creams include: novobiocin, bacitracin, gentamycin, neomycin, silver sulfadiazine, fusidic acid (only in Europe), and mupirocin. Ideally, only use topical antibiotics based on culture and sensitivity tests (C&S). Mupirocin and fusidic acid should be avoided, if at all possible, because they are frequently used for cases of methicillin-resistant Staphylococcus aureus (MRSA) infections in humans. Common antifungal ingredients in shampoos, sprays, rinses, wipes, creams and/or ointments include: chlorhexidine, miconazole, clotrimazole, ketoconazole, selenium sulfide (main ingredient in Selsun Blue or Head & Shoulder Intensive Care shampoo), acetic acid, and boric acid. The various commercial formulations can contain one or more of these ingredients.

The choice of which topical antimicrobial to use and its frequency of administration should be based on the following: (i) extent and severity of lesions, (ii) location of the lesions (area with hair vs area without hair), (iii) owner's ease of application, and (iv) history of previous adverse reaction to the product. When prescribing shampoos, it is important to tell owners to massage the shampoo gently into the skin for about 10 minutes and, then rinse it off thoroughly. It is also important to dry the skin well.

The question clinicians should always ask at the time of choosing systemic antibiotics to treat patients with bacterial infections is: Should I perform C&S or, can I choose the antibiotic empirically to treat my patient? If you are practicing in a geographic area where methicillin-resistant and multidrug resistant staphylococcal infections are frequent, you should always consider performing C&S to select the appropriate antibiotic. The following are common situations where this test is indicated: (i) lack of response to appropriate empirical treatment (e.g. less than 50% improvement and/or appearance of new lesions 2 weeks or more after initiating therapy), (ii) history of methicillin or multidrug resistant infections, (iii) presence of rod-shaped bacteria on cytology, and (iv) history of recurrent infections or frequent antibiotic use. An empirical antibiotic selection can be considered for mild and non-recurrent infections when the clinician is not practicing in a geographic area where antibiotic resistance is a concern. In these circumstances, first-tier antibiotics (i.e. first generation cephalosporins [e.g. cephalexin, cefadroxil], amoxicillin-clavulanate, trimethoprim/ormetoprim potentiated sulfas, clindamycin, and lincomycin) should be used. Most dermatologists will first select cephalexin or cefadroxil for empirical treatment of

superficial bacterial folliculitis, with the second choice being typically amoxicillin clavulanate. Make sure to treat the infection for at least 7 days past complete clinical resolution, which should be assessed by the clinician, not the owner.

Systemic antifungals to treat malassezia overgrowth should be considered in cases of generalized disease (in these cases it is typically used in combination with topical therapy) or when topical treatment is impractical or ineffective. The following antifungals can be used: ketoconazole (5 to 10 mg/kg/ day), itraconazole (5 to 10 mg/kg/day), or terbinafine (30 mg/kg/day).

Modulating the patients' immune system to disfavor an allergic response

The only treatment that specifically addresses the allergic response of patients with atopic dermatitis is the allergen-specific immunotherapy (known by clients as "allergy shots"). Its mechanism of action is not completely understood but, it is believed to be associated with the following: (i) production of allergen-specific IgG that blocks the circulating serum IgE and prevents its binding to high-affinity IgE receptors on the surface of mast cells avoiding their degranulation; (ii) shifting the predominance of Th-2 lymphocytes (typical of atopic patients) in the skin and serum of atopic dogs to a Th-1 prevalence which does not promote an allergic response; (iii) stimulation of T-regulatory cells that secrete IL-10 and TGF-beta which have anti-inflammatory effects.

The selection of allergens that will compose the immunotherapy is typically based on the patient's history and results of the serum and/or intradermal tests. For example, if the patient only reacts to house dust mites or house dust but, has strictly seasonal clinical signs, immunotherapy will not be initiated. The allergen-specific immunotherapy can be administered subcutaneously or orally (sublingual). The sublingual route has only recently been tried in veterinary medicine and, at this time, there are few studies (no randomized, double-blind, and controlled trials were performed) demonstrating its efficacy and, it is not known if this route is more efficacious than the subcutaneous one. The sublingual administration can be an option for clients that do not like to give injections but, it has to be giving once or, ideally, twice daily for the life of the patient (if it is working), in contrast to the typical maintenance schedule of every 21 days associated with the subcutaneous route.

The success rate of allergen-specific immunotherapy is on average 60% to 70%, independent of the route of administration. Success is typically defined as at least 50% reduction in clinical signs. It is important to educate clients that it may take up to 1 year before significant improvement can be noticed (some dogs improve in 2 to 4 months). If the owner perceives that the pet's allergies are better than before adding immunotherapy to the treatment regimen, it should be continued for the life of the patient. However, if no improvement is noticed after 1 year of treatment, the immunotherapy should be discontinued. Side effects associated with allergen-specific immunotherapy are typically mild and rare, and may include: pruritus or pain at the injection site if administering it subcutaneously, worsening of clinical signs (primarily pruritus) for a few hours to a few days after administration, lethargy, diarrhea (noticed with the sublingual administration), and rarely anaphylaxis. The administration of an antihistamine 30 minutes to 1 hour before the injection (mainly if the patient is receiving more than 12 allergens per injection) may prevent or minimize more severe side effects. The reader should refer to veterinary dermatology textbooks or scientific papers for additional information regarding the use of allergen-specific immunotherapy.

Reducing the pruritus

Traditionally, antihistamines have been used solely or in combination with essential fatty acids and/or immunomodulatory drugs (e.g. glucocorticoids, cyclosporine, or oclacitinib) to help control the pruritus associated with atopic dermatitis. To this date, there is no scientific evidence supporting its use for the management of canine atopic dermatitis; nevertheless, clinicians often prescribe antihistamines as adjunctive therapy, because they are safe and many clients believe they are beneficial. Ideally, a trial using 4 to 5 antihistamines should be performed to select the best one because the individual's response to each antihistamine can be variable. Each antihistamine should be tried for 7 to 14 days and, the owner should determine which one, if any, is more efficacious in reducing the pet's itching level. The ones commonly used in trials include: hydroxyzine (2.2 mg/kg every 12 h), diphenhydramine (2.2. mg/kg every 12 h), cetirizine (1 mg/kg every 24 h), chlorpheniramine (0.4 mg/kg every 8-12 h), cyproheptadine (0.3-2 mg/kg every 12 h), and loratadine (1 mg/kg every 12 h). Do not start an antihistamine trial and a treatment for superficial pyoderma concurrently because most likely the pyoderma resolution will decrease the pruritus level which will confound the trial interpretation. The sedative effect associated with first generation antihistamines has some benefit since the dog will not itch when sleeping. It is a good practice to prescribe an antihistamine at the high end of the dose range, before bedtime. Use antihistamines with essential fatty acids to optimize the pet's response to these drugs. Unfortunately, there is no consensus on the ideal dose and ration of omega-6/omega-3 fatty acids or, the best formulation. Omega-3 sources are more efficacious for reducing inflammation and pruritus. If a capsule contains at least 180 mg of eicosapentanoic acid (EPA) and 120 mg of docoisahexanoic acid (DHA), the author uses 1 capsule per 10 pounds. Another option is to use a total (i.e. EPA + DHA) dose of 66 mg/kg/day. Treat a patient for 8 to 12 weeks before assessing the response.

Short acting glucocorticoids such as, prednisone/solone or methylprednisolone are very efficacious in reducing the pruritus and inflammation associated with atopic dermatitis. Start prednisone/solone at the anti-inflammatory dose of 1.0 mg/kg once daily or 0.5 mg/kg twice daily, and methylprednisolone at 0.8 mg/kg once daily or 0.4 mg/kg twice daily. Within 7 days or, as soon as the pruritus is controlled (whichever comes first), start reducing the dosage to achieve the lowest possible dose that maintains the dog comfortable and, administer it every-other-day. It is very likely that the dog's pruritus level will increase at this point (add antihistamines, essential

fatty acids and anti-pruritic topicals to the treatment regimen), but, if glucocorticoids are given daily for long periods of time, they will induce signs of Cushing's disease in most dogs, even if given at very small dosages. Educate the client about the side effects associated with glucocorticoids and monitor for potential side effects. Do not administer injectable glucocorticoids to manage atopic dermatitis, because they are very potent and have a long and strong effect in the hypothalamic-pituitary-adrenal axis. Moreover, their desired anti-pruritic and anti-inflammatory effects are fairly short (i.e. 7-14 days).

Cyclosporine, a calcineurin inhibitor, is an immunomodulatory drug that has shown to be as effective as glucocorticoids in managing canine atopic dermatitis. The dosage is 5 mg/kg/day and the microemulsion formulation is recommended (e.g. Atopica). When combined with ketoconazole at the dose of 5 to 10 mg/kg/day, the dose of cyclosporine can be reduced to 2.5 mg/kg/day because ketoconazole inhibits its metabolism. If ketoconazole is not available, fluconazole at 5.0 mg/kg/day can be used instead. This is a common practice when owners have monetary concerns. It is recommended to give cyclosporine 2 hours before or after feeding to improve its bioavailability which is variable but, generally low in dogs (23-45%). In contrast to glucocorticoids that work within a few hours, it may take 4 weeks before any effect from cyclosporine can be noticed. After the disease is under control, try to reduce the maintenance dose. The most common side effects are vomiting and diarrhea. Other side effects include: gingiva hyperplasia (common), hypertrichosis (common), tremors (rare), lymphadenopathy (rare), viral papillomatosis (sign of immunosuppression), psoriasiform lichenoid-like dermatitis (rare – unusual presentation of pyoderma), lympho-plasmacitic dermatitis (rare), opportunistic bacterial and fungal infections (sign of immunosuppression).

Another immunomodulatory drug that was recently approved by the FDA to treat allergic dermatitis in general, and canine atopic dermatitis, is oclacitinib (Apoquel). This drug is a Janus kinase (JAK)-1 inhibitor and inhibits various pro-inflammatory and pruritogenic cytokines (e.g. (L-31, IL-4, IL-6, IL-13, IL-2). Similar to glucocorticoids, its effect is noticeable within a few hours of administration. The manufacturer's recommended dose is 0.4 to 0.6 mg/kg every 12 hours for the first 2 weeks then, once daily as maintenance. The pruritus level increases moderately to as severe as before starting treatment, when the dose is reduced to once daily. To avoid serious side effects such as, bone marrow suppression, twice a day administration should not be prescribed long-term. However, the once a day dose can be divided into twice a day administration to improve efficacy. In addition, to control severe flares, the dose protocol used during the first 2 weeks (i.e. twice daily administration) can be repeated for a few days. Common side effects include: vomiting, diarrhea, lethargy, anorexia, and polydipsia. Rare side effects include: demodicosis, viral papillomatosis, interdigital furunculosis, pneumonia, and lymphadenitis.

There are various topical anti-pruritic and skin-barrier restorer products that should be added to the maintenance treatment regimen to help control the pruritus and lesions associated with atopic dermatitis and, ultimately prevent secondary infections. The reader should become familiar with these products.

In summary, the treatment of atopic dermatitis should be tailored to each patient and owner. It may take awhile to achieve the ideal maintenance treatment regimen for an individual pet. When managing your atopic patient remember the following: (i) always try to identify and treat any concurrent allergic disease; (ii) make sure to judiciously treat any secondary infections; (iii) do not forget to control the pruritus and skin inflammation taking into consideration the individual pet and the owner and, (iv) make sure to educate owners well about their pet's disease to improve adherence to the treatment plan.