TREATMENT OF ATOPIC DERMATITIS IN DOGS: NEW INTERNATIONAL STANDARD OF CARE

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Atopic dermatitis (AD) is a common chronic relapsing pruritic skin disease of dogs for which treatment has varied over time and geographical location. Recent high quality randomized controlled trials and systematic reviews have established which drugs are likely to offer consistent benefit. In 2010, the International Task Force for Canine AD published guidelines recommending a multi-faceted approach to treat dogs with AD. Treatment recommendations vary depending if one is dealing with acute flares or chronic AD, and whether skin lesions are localized or extensive.

TREATMENT OF ACUTE FLARES OF AD

IDENTIFICATION AND AVOIDANCE OF FLARE FACTORS

IDENTIFICATION AND REMOVAL OF ALLERGENIC CAUSES OF FLARES

When an exacerbation of signs occurs in a dog that previously had a disease in remission, one must look for, and eliminate if at all feasible, the cause of such flares. Currently recognized sources of flares of canine AD include fleas, food and environmental (e.g. house dust mites, pollens) allergens.

EVALUATION OF USE OF ANTIMICROBIAL THERAPY

Skin and ear infections are common reasons why lesions and pruritus acutely worsen in dogs with AD. If bacterial or yeast infections are identified with some combination of clinical signs, cytology and/or culture, antimicrobial therapy is indicated, normally using topical with or without oral medications. The latter are used if infected lesions are severe or extensive.

IMPROVEMENT OF SKIN AND COAT HYGIENE AND CARE

BATHING WITH A NON-IRRITATING SHAMPOO

Bathing dogs with AD might reduce their pruritus (itch) manifestations. This benefit appears to lie in the mechanical action of washing the pet. Outside of a lipid-containing shampoo (Allermyl, Virbac), there is currently no evidence of benefit of other shampoos or conditioners containing ingredients such as oatmeal, pramoxine, antihistamine, lipids or glucocorticoids.

REDUCTION OF PRURITUS AND SKIN LESIONS WITH PHARMACOLOGICAL AGENTS

SHORT-TERM TREATMENT WITH A TOPICAL GLUCOCORTICOID

To reduce skin lesions and pruritus of canine AD, there is evidence for the high efficacy of two medium potency glucocorticoid sprays: triamcinolone (Genesis, Virbac) and hydrocortisone aceponate (Cortavance, Virbac). These sprays are especially suitable for localized skin lesions and for short durations. Clinicians must tailor the frequency and duration of application to the severity of clinical signs. Caution is advised with long-term use, as adverse effects, such as skin

thinning, are likely to occur.

SHORT COURSE OF ORAL GLUCOCORTICOIDS
If signs are too severe or extensive to be controlled with topical formulations, then oral glucocorticoids are recommended. Either prednisone, prednisolone or methylprednisolone can be given at 0.5 mg/kg once to twice daily until clinical remission occurs. Side effects of oral glucocorticoids are usually proportional to drug potency, dosage and duration of administration.

INTERVENTIONS LIKELY TO BE OF LITTLE OR NO BENEFIT TO TREAT ACUTE FLARES OF CANINE AD:
Antihistamines: When examined as a group, there is no conclusive evidence of efficacy of oral type-1 antihistamines for treatment of active AD in dogs.
Essential Fatty Acid Supplements: As their mode of action necessitates several weeks of treatment, essential fatty acids (EFA) are unlikely to be of any benefit for acute flares of AD in dogs.
Tacrolimus and Ciclosporin: Because of their slow onset of treatment effect, topical tacrolimus and oral ciclosporin are unlikely to offer any benefit for treatment of acute flares of canine AD.

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. As a result, one or more restriction-provocation dietary trials (e.g. 'elimination diets') must be performed in all dogs with nonseasonal AD to determine whether food allergens contribute to clinical signs in these patients. Normally, dietary changes should be carried out for six to ten weeks using either commercial or homemade diets employing a low number of novel or hydrolyzed ingredients. At this time, there is no clear evidence of a superior benefit of hydrolysate-based compared to non-hydrolyzed commercial diets, or of homemade over commercial diets. In theory, the main value of performing trials with homemade diets is if hypersensitivity to a minor component of a commercial diet (colorant, preservative, etc.) is suspected, but cutaneous hypersensitivity to additives has not yet been reported in dogs.

IMPLEMENTATION OF AN EFFECTIVE FLEA CONTROL REGIMEN
There is evidence that the atopic status 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 adulticides combined with relevant environmental measures.

P*ERFORMANCE 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 hypersensititive 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. Serological and intradermal tests to determine hypersensitivity to food allergens do not reliably predict food allergies, and therefore they cannot be recommended.

IMPLEMENTATION OF HOUSE DUST MITE CONTROL MEASURES

Dermatophagoides house dust mite proteins are the most common allergens in dogs with AD. Household dust mite control measures 'theoretically' should be effective for mite-allergic patients. However, even when specific products have been shown to measurably decrease dust mite allergen in the environment, this might not necessarily lead to an improvement in clinical signs in hypersensitive individuals. Nevertheless, if mite avoidance measures were to be attempted, it would seem logical to restrict this intervention to dogs sensitized to house dust mites alone, and to use a combination of measures that might include acaricides, impermeable pet mattress covers, and frequent and thorough pet mattress and environment washing and vacuuming. A benefit, if any, is likely to take some months to occur due to the long persistence of mite allergens in the environment.

EVALUATION OF USE OF ANTIMICROBIAL THERAPY

The skin and ears of dogs with AD are commonly infected or colonized with *Staphylococci* 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). Veterinarians are encouraged to: 1) identify skin lesions suggesting microbial colonization (e.g. erythema, oedema, scaling, greasiness) at particular sites, including the ears, 2) document the presence of bacteria/yeast at these lesional sites, 3) implement specific antibacterial/antifungal interventions, 4) using cytology, observe the disappearance of organisms from previously positive sites following antimicrobial interventions, and 5) document the reduction/disappearance of skin lesions at the previous sites following antimicrobial interventions. The systematic prescription of antibiotics and antifungal drugs to every dog with AD is not recommended, however, as such routine use of antimicrobial drugs is likely to increase the prevalence of drug-resistant microbes.

INVESTIGATION OF THE RELEVANCE OF OTHER FLARE FACTORS

In human patients with AD, environmental (e.g. low humidity, clothing, detergents) and psychological factors (e.g. stress) are known contributors to the severity of clinical signs of AD. At this time, there is insufficient evidence on the role of such factors as a cause of flares of AD in dogs.

IMPROVEMENT OF SKIN AND COAT HYGIENE AND CARE

BATHING WITH A NON-IRRITATING SHAMPOO

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. If the skin is greasy and scaly, antiseborrheic shampoos are indicated. If infections are deemed to contribute to clinical signs, antiseptic shampoos are preferred. In some cases, moisturizers might alleviate any skin dryness that would occur after the baths.

DIETARY SUPPLEMENTATION WITH EFA

In normal dogs, dietary supplementation with EFA, or the feeding of EFA-rich diets (especially those rich in the omega-6 EFA linoleic acid) usually results in improvement in coat quality and gloss. Two diets have had this improvement documented in good quality clinical trials: Specific Skin & Joint Support (Dechra Veterinary Products) or the Hill's Prescription Diet Canine d/d Salmon & Rice. Not all EFA-rich diets appear to have such coat improvement effect. 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 any, might not be seen before two months of supplementation.

TOPICAL LIPID FORMULATIONS
At this time, there is insufficient evidence supporting the use of topical formulations containing EFA, essential oils, or complex lipid mixtures for improvement of coat quality, barrier function or any other clinically relevant benefit in dogs with AD.

OTHER DIETARY SUPPLEMENTS:
Several nutritional supplements (e.g. pantothenate, choline, nicotinamide, histidine and inositol) have been shown to increase the production of skin lipids *in vitro* and to decrease transepidermal water loss *in vivo* in healthy dogs. Additional studies are needed to confirm the clinical benefit of diets containing these supplements in dogs with AD.

REDUCTION OF PRURITUS AND SKIN LESIONS WITH PHARMACOLOGICAL AGENTS

TREATMENT WITH TOPICAL GLUCOCORTICOIDS OR TACROLIMUS
As discussed above, 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). The most common and important adverse events following the prolonged application of a potent topical glucocorticoid on the same area are thinning of the skin (cutaneous atrophy), black heads (comedones) and superficial hair follicle cysts (milia). The risk is lower with intermittent application of topical glucocorticoids.

As an alternative to topical glucocorticoids, 0.1% tacrolimus ointment (Protopic, Astellas) 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. The application of tacrolimus might be followed by signs suggesting mild irritation.

TREATMENT WITH ORAL GLUCOCORTICOIDS OR CICLOSPORIN
There is strong evidence of the efficacy of oral glucocorticoids and ciclosporin for 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 arises earlier with glucocorticoids than with ciclosporin.

As discussed above, oral glucocorticoids (e.g. prednisone, prednisolone, methylprednisolone) should be started at approximately 0.5 mg/kg once to twice daily, and then reduced, as signs decrease, to the lowest dose and frequency (e.g. twice daily to once daily to every other day) needed to maintain good quality of life, control of signs and minimal side effects. Side effects of oral glucocorticoids (e.g. increased appetite, drinking and urination, predisposition to urinary tract infections) are common and normally proportional to dosage and duration of administration. At this time, because of the risk for adverse effects, the use of long-acting injectable glucocorticoids is not recommended unless there is an inability to treat the patient orally.

In an attempt to reduce the dose of oral glucocorticoids needed to control clinical signs of AD, veterinarians are encouraged to investigate medications or supplements proven to have a steroid-sparing effect, for example, the glucocorticoid-antihistamine combination Temaril-P (Pfizer), the EFA-combination Viacutan Plus (Boehringer Ingelheim) and the Chinese herbal supplement Phytopica (Intervet-Schering).

Modified ciclosporin (Atopica, Novartis) should be started at a dosage of 5 mg/kg once daily and continued at this dosage until a halving or a satisfactory decrease of severity of signs is achieved. After this improvement is reached, the dose should be reduced by either increasing dosage intervals (e.g. going from every day to every other day) or by decreasing the daily dose by half. After a further reduction of signs exceeding approximately 75%, the administration could be reduced to twice weekly or a 75% reduction of the original daily dose. After beginning ciclosporin administration, the onset of satisfactory clinical benefit normally cannot be expected before four to six weeks. To increase the speed of clinical sign improvement, the administration of a short course of oral glucocorticoids – as described above – during the first two weeks of ciclosporin administration might be beneficial. Minor adverse events (e.g. vomiting, diarrhoea) are common after initiating ciclosporin therapy; most improve spontaneously upon further administration of this drug.

TREATMENT WITH SUBCUTANEOUS INTERFERONS

There are studies providing evidence of the efficacy of injections of recombinant canine gamma-interferon (Interdog, Toray) to treat dogs with AD in Japan. Suggested effective dosages are 5,000 to 10,000 units/kg, subcutaneously, three times weekly for four weeks then once weekly. Side effects are minimal. Similarly, recombinant feline omega interferon (Virbagen Omega, Virbac) also appears effective to treat dogs with AD in Europe. Suggested doses of one to five million units three times weekly for four weeks and then every month are well tolerated.

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 preventatives, that is every single day at the recommended dosage, to keep blocking histamine receptors before histamine is released. The main side effect of most antihistamines is sedation.

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. As discussed above, 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.

Finally, there is some evidence of very low, or complete lack of efficacy of leukotriene inhibitors, dextromethorphan or capsaicin to treat dogs with AD. Consequently, these drugs should not be used to treat dogs with this disease.

IMPLEMENT STRATEGIES TO PREVENT RECURRENCE OF SIGNS

AVOIDANCE OF FLARE FACTORS

Avoidance of known flare factors is the strategy most optimal 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, wherever and whenever possible.

IMPLEMENTATION OF PROACTIVE (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 at this time, 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 whom intradermal test or IgE serology 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 dismissing it as ineffective.