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Managing Canine and Feline Atopic Dermatitis

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Atopic dermatitis (AD) is a chronic multifactorial inflammatory skin disease[1]. The pathogenesis of AD remains unclear, but the disease results from dysfunctions of skin barrier and immune response, where both genetic and environmental factors play a key role. Recent studies demonstrate the substantial evidence that shows a strong genetic association with AD[1].

Immune system plays a key role in the pathogenesis of AD[1]. It is a heritable disease in which affected dogs develop immunoglobulin E (IgE) antibodies to environmental allergens[1].

Aeroallergens enter the body via the percutaneous route. Once in the epidermis these bind with Langerhans cells which present it to naïve T cells in the draining lymph nodes[1].

In human medicine, the relationship between the immune-dysregulation observed in AD and the development of mycosis fungoides (MF) has triggered considerable interest due to the increasing number of patients with MF who have a previous history of AD[2].

A study suggests an association between AD and MF in dogs[2]. Improved understanding of the pathogenesis of atopic dermatitis in dogs has led to more effective treatment plans, including skin barrier repair and new targeted treatments for management of allergy-associated itch and inflammation[3].

The house dust mites (HDM) *Dermatophagoides farinae* and *D. pteronyssinus* are important environmental allergens implicated in the pathogenesis of human and canine atopic dermatitis[3].

The intent of this review article is to provide an update on the etiologic rationale behind current recommendations that emphasise a multimodal approach for the management of atopic dermatitis in dogs. Increasing knowledge of this complex disease process will help direct future treatment options[2].

Favrot listed eight criteria for making the diagnosis of atopy in the canine[4].

- Onset of clinical signs in an animal less than 3 years of age
- Dog living mainly indoors
- Pruritus responds to glucocorticoids
- Pruritus occurs at onset in the absence of skin alteration
- Front feet affected
- Ear pinnae affected
- Ear margins not affected
- Lumbosacral area not affected

CLINICAL SIGNS

Pruritus is the chief clinical presentation and the most common symptoms include erythema (Figure 1), itching, excessive scratching, rubbing on the carpet, hair loss, greasy or flaky skin with a foul odour.

Atopy in the canine is usually most noticeable by the pet licking at and excoriating the paws (Figures 1 – 3).

The groin (Figure 4) and axillae are usually a common area of the indication of allergic dermatitis. Acute moist dermatitis (Figure 5) is also a common indication of atopy.

The peak age of onset of canine atopic dermatitis (CAD) is between one and three years. However, atopy can develop in middle-aged and older dogs.

Figure 1

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Figure 2

Figure 3

Figure 4

Figure 5

Successful management of canine atopic dermatitis depends on recognition of certain factors. The skin barrier may be defective, predisposing the pet to percutaneous penetration of allergens and the secondary bacterial infections. The skin may be more readily colonised by *Staphylococcus*. The pet may also develop antibodies to *Malassezia* and *Staphylococcus*.

Furthermore, the diagnosis of canine atopy is a diagnosis of exclusion. This includes 1) avoidance and 2) control of secondary bacteria and yeast infections. Evaluation for cutaneous adverse food reactions (CAFR) is an important aspect of managing atopy. A home-cooked exclusion diet or a commercial diet can be fed for at least 8 weeks. Commercial diets such as Hills Prescription Diet ZD ULTRA Allergen-Free Canine, Hills prescription Diet d/d Canine, or Royal Canin Hypoallergenic Canine and for cats, Royal Canin Hypoallergenic Feline can be used once the diagnosis is confirmed.

Avoidance is illusive in the case of pollens. However, it is possible to eliminate environmental feathers and fabrics. Mould can be treated with antiseptic or antifungal sprays.

Anti-mould paint can be applied to walls. House dust mites can be reduced with frequent vacuuming, air purification devices, and acaricide sprays and foggers (some of which contain an Insect Growth Regulator), the use of cushions and covers that can be washed at high temperatures as well as beds for dogs. Protective covers produced for asthmatics can be used (Teflon – expensive). Cat avoidance could assist the proven cat allergen sensitive atopic dog.

BOG and MOG are acronyms for bacterial and *Malassezia* overgrowth. Microbial overgrowth may be defined as a clinical disease due to the colonisation of the skin by microbes. In the dog, this includes *Malassezia* overgrowth (MOG) due *to Malassezia pachydermatis* and bacterial overgrowth (BOG) due to *Staphylococcus pseudintermedius*. The lipophilic but not lipo-dependent yeast *Malassezia pachydermatis* is part of the normal cutaneous flora of the dog.

Alteration of the cutaneous microclimate or host defence mechanisms (ectoparasitic, allergic, endocrine and keratinisation disorders, treatment with glucocorticoids or antibiotics) allow *Malassezia pachydermatis* to multiply and to become pathogenic. In addition, it has been shown that *Malassezia pachydermatis* could play an allergenic role in regard to a type 1 (immediate) hypersensitivity. Skin testing with a *Malassezia* extract may show immediate hypersensitivity reactions. Pruritus is always present and severe, and pets may exude a strong odour of rancid fat. There may also be localised or diffuse erythema, erythematous papules and macules.

Systemic therapy is often necessary, particularly when clinical signs are severe, and the lesions are extensive. Ketoconazole is the most commonly used drug. The dose is 5 to10 mg/kg /day (up to 200 mg/day). It is recommended to give the drug with food. Biochemistry panels are necessary if the drug is given over an extended period. Itraconazole may also be used (5 to 20 mg kg daily or other day). Shampoos containing 2 % miconazole, chlorhexidine (at least 3%), a combination of both (2% each) and ketoconazole (2%) are the most appropriate. Leave-on rinses include enilconazole (10 % diluted 50 times) and lime sulphur. Topical treatments should be administered at least once a week.

An important aspect in BOG is that when a certain density level of *Staphylococci* is exceeded, they express particular characteristics and switch their metabolism from cell proliferation to toxin production. Glucocorticoid therapy could also be a perpetuating cause in BOG. Erythema, lichenification and hyperpigmentation, seborrhoea oleosa, excoriations and self-induced alopecia are sometimes noted, as well as otitis externa.

Topical therapy is beneficial in canine BOG. Clipping may be useful, at least in the most severely affected areas. The chief useful topical products are chlorhexidine, povidone-iodine, benzoyl peroxide shampoo and ethyl lactate shampoo. For the control of bacterial infections, an antibiotic effective against *Staphylococcus pseudintermedius* is necessary.

Empirical antibiotic selection includes cephalexin, clavamox, trimethroprim-sulfa, fluoroquinolones, and clindamycin. Antibiotics for the management of pyoderma are listed in Table 1. Bear in mind that although antibiotics are essential to protect human health and animal health as well as animal welfare, excessive or inappropriate use can lead to the appearance of bacteria which are resistant to antibiotic treatment.

Antibiotic resistance puts disease control throughout the world at grave risk. A National Strategy Framework has been formulated for antimicrobial resistance in South Africa for the years 2014 to 2024 Details can be obtained on the website: http://www.savc.org.za/pdf_docs/3.A5%20Antimicrobial%20Resistance%20National%20Strategy%20Framework%202014-2024_final.pdf

Table 1. Antibiotics for the management of canine pyoderma

ANTIBIOTIC	DOSE	INTERVAL
Clavulanate-amoxicillin	12.5–25 mg/kg	BD
Cephalexin	22-30mg/kg	BD
Cefadroxil	22–30 mg/kg	BD
Lincomycin	22 mg/kg	BD
Clindamycin	11 mg/kg	OD/BD
Enrofloxacin	5–20 mg/kg	OD
Marbofloxacin	2.5–5 mg/kg	OD
Orbifloxacin	2.5–7.5 mg/kg	OD
Pradofloxacin	3 mg/kg	OD

TREATMENT OPTIONS[5]

Improved understanding of the pathogenesis of atopic dermatitis in dogs has led to more effective treatment plans, including skin barrier repair and new targeted treatments for management of allergy-associated itch and inflammation. Current recommendations emphasise a multimodal approach for the management of atopic dermatitis in dogs. Increasing knowledge of this complex disease process will help direct future treatment options.

Essential fatty acids (EFA)

Drugs that restore barrier function may be helpful. EFAs have anti-inflammatory and immune-modulating effects and contribute to the correction of epidermal lipid defects. Both omega-3 and omega-6 fatty acids can have immune-modulatory effects, although oral supplementation for up to 3 months may be necessary before these are apparent. A cornerstone of the management of atopy is the restoration of the epidermal barrier to reduce percutaneous allergen penetration. Fatty acids (oral and spot-on formulations) and dermatology-specific diets can enhance the lipid layer of the skin.

Dietary control

Several companies market diets specifically to help in cases of itchy dogs. Most of these are based around the addition of EFAs. Some have combinations of vitamins or minerals which may help the skin.

Few independent studies have been done on the effectiveness of these diets. Hill's Prescription Diet 'Derm Defense with Histaguard Complex' is a blend of bioactives and phytonutrients. Derm Defense contains a proprietary blend of whole egg, antioxidants (Vitamin E, C), Omega 3 fatty acids and sources of polyphenols, which together is Hill's HistaGuard Complex. Royal Canin Skin Support diet adds a blend of curcumin, aloe vera, Vitamin C, taurine, as well as a patented blend of B vitamins and amino acids and Omega 3 fatty acids.

Table 2. Antihistamine dose rates for pruritic skin disease in dogs and cats

DRUG	DOSE RATE DOG	DOSE RATE CAT	COMMENTS
Amitriptyline	1-2mg/kg BD	0.5-1.0mg/kg OD/BD	Used if psychogenic component.
Cetirizine	1 mg/kg OD/BD	1mg/kg OD/BD	Once daily dosage is an advantage.
Chlorpheniramine	0.5mg/kg BD/TD	2-4 mg per cat	Sedation which may reduce with time.
Clemastine	0.05-1.5mg/kg BD	0.34-0.68mg per cat BD	Sedation. May cause diarrhoea in cats.
Cyproheptadine	0.5-2.0mg/kg BD/TD	2-4mg per cat OD/BD	Sedation. Appetite stimulant.
Hydroxazine	2.0mg/kg BD	8 mg per cat BD	Sedation. Useful in urticaria.
Promethazine	1mg/kg BD	0.8-1.6mg per cat BD/TD	Sedation. Antemetic.

Antihistamines

Treatment of the atopic patient includes antihistamines. Antihistamines used in the dog and cat include amitriptyline hydrochloride, cetirizine hydrochloride, chlorpheniramine maleate, clemastine fumarate, cyproheptadine hydrochloride, hydroxazine hydrochloride and promethazine hydrochloride (Table 2).

Ciclosporin

Ciclosporin has been licenced for use in both dogs and cats. Its mode of action is inhibition of the T-cell receptor-activated signal transduction pathway and is widely accepted as an excellent drug for use in atopic dermatitis. In the dog, it is initially dosed at 5 mg/kg once daily orally for 4-6 weeks to induce remission and then reduced by either halving the daily dose or decreasing the frequency to an alternate day regime. Dosing 2 hours before and after a meal is recommended.

Ciclosporin is a selective immunomodulator used for the treatment of atopic dermatitis[5]. A new 100 mg/ml oral solution formulation (Cyclavance®, Virbac) has been developed as a pharmaceutical equivalent to the marketed capsule formulations[6]. Although there is less data on its use in cats, cyclosporin can be administered to this species at 7 mg/kg once daily *per os*. Ciclosporin appears to be well tolerated in most species but can produce gastro-intestinal effects.

Glucocorticoids

Topical hydrocortisone aceponate spray (Cortavance, Virbac) is useful for symptomatic treatment of inflammatory and pruritic dermatoses in dogs and has been shown to be comparable to systemic cyclosporin therapy in efficacy. Glucocorticoids have been the most commonly prescribed drugs for atopic dermatitis. Studies provide high-quality evidence in support of oral low-dose alternate day administration of glucocorticoids (Figure 5).

Oclacitinib

Oclacitinib maleate (Apoquel, Zoetis) is a synthetic Janus kinase (JAK) inhibitor indicated for the control of pruritus associated with allergic dermatitis and control of atopic dermatitis in dogs at least 12 months of age.

Oclacitinib is not a corticosteroid, antihistamine or cyclosporin. It inhibits the function of a variety of pruritogenic and proinflammatory cytokines, as well as cytokines involved in allergy that are dependent on JAK1 or JAK3 enzyme activity. Oclacitinib has minimal effect on JAK2-dependent cytokines involved in haematopoiesis and innate immunity.

Oclacitinib should not be used in dogs less than 12 months of age or those with serious infections. It may increase the chances of developing serious infections and may cause existing parasitic skin infections or pre-existing cancers to increase in severity. It has not been tested in dogs receiving some medications including some commonly used to treat skin conditions such as corticosteroids and cyclosporins.

Do not use in breeding, pregnant, or lactating dogs.

Most common side effects are vomiting and diarrhoea. Oclacitinib has been used safely with many common medications including parasiticides, antibiotics and vaccines.

Table 3. Oral glucocorticoid doses for the control of atopy in dogs and cats. After 7 – 14 days, doses should be reduced for maintenance to the lowest effective dose and administration reduced to every 72 hours.

DRUG	DOG	CAT	COMMENTS
Prednisolone	0.5-1mg/kg OD	2.2mg/kg OD	Polyuria, polydipsia, weight gain, poor hair coat, lethargy. Side-effects minimised by low-dose alternate day therapy
Methylprednisolone	0.8-1mg/kg OD	2.2mg/kg OD	Less severe than Prednisolone
Dexamethasone	0.07-0.16mg/kg OD	0.125-1mg/kg OD	As for prednisolone

The recommended dose is 0.5 mg/kg twice a day and tapering to half dose twice a day or once a day.

Lokivetmab

Lokivetmab (Cytopoint, Zoetis) is the first monoclonal antibody approved for veterinary use in the EU.

A single injection of Cytopoint treats the clinical signs of atopic dermatitis in dogs of any age at a minimum of 1mg/kg, repeated monthly, including pruritus and inflammation for up to 5 months.

Pentoxyphylline

Pentoxyphylline increases peripheral tissue perfusion and oxygenation and has been shown to have immunomodulatory effects by decreasing cytochrome production.

There is limited evidence of efficacy available, but a dose of 10mg/kg two to three times daily can be administered orally.

Allergen-specific immunotherapy (ASIT)

This will be based on either allergen-specific serum allergy testing or intradermal allergy testing.

ASIT has many advantages with only limited disadvantages when compared to other forms of therapy since it avoids the side-effects of glucocorticoids and cyclosporin and is cost-effective for larger dogs.

ASIT has a 60-70% success rate. Although traditionally administered via subcutaneous injection, a recent development has been the sublingual immunotherapy.

Preliminary results indicate it to be as effective as the subcutaneous route.

Osurnia

Osurnia Otic Gel Tube (Elanco Animal Health, Lilly House, Priestley Road, Basingstoke,UK) comes with a soft, flexible tip and is an innovative alcohol-free gel formulation which is gentle on a dog's ears.

The Otic Gel Tube contains terbinafine, florfenicol, and betamethasone acetate. It is recommended in dogs for acute otitis externa complicated by infections of *Staphylococcus* and *Malassezia*.

SUMMARY

All atopic pets will benefit from diligent flea control and a dietary trial to assess adverse food reactions. Control of bacterial and yeast infections reduce the amount of antipruritic therapy required. Santoro D, *et al* found that the odds of having MF was 12 times (OR = 12.54; 95% CI = 1.95–80.39; $P < 0.01$) higher in dogs with AD than in dogs without AD[2].

Shampoos and essential fatty acid therapy are low risk treatments that may be of value in certain patients. Topical glucocorticoids are also helpful.

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FURTHER READING

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QUESTION 1
Which of the following statements regarding atopy is INCORRECT?
a. Aeroallergens enter the body via the percutaneous route
b. Aeroallergens are presented to naïve T cells
c. Canine atopy is a genetically predisposed inflammatory dermatitis
d. Claud Favrot listed nine diagnostic criteria for atopy in the dog
e. Canine atopy is associated with IgE antibodies

QUESTION 2
Which of the following statements is most likely to be INCORRECT?
a. Desquamation is unlikely to indicate atopy
b. The peak onset of atopy is in the dog's later years
c. Atopic dogs are more likely to live inside the house
d. Excessive sebum production indicates a disease other than atopy
e. No extra minerals in the diet can assist in controlling atopy in the canine

QUESTION 3
Which of the following are not associated with the pathogenesis of atopy?
a. Mycosis fungoides
b. Inheritance
c. Skin barrier function
d. Margins of the ears
e. Lymphoma

QUESTION 4
Which of the following statements regarding the clinical presentation of atopy in the dog is FALSE?
a. Post-inflammatory hyperpigmentation is uncommon in cats
b. Responsive to dexamethasone
c. The most noticeable sign of atopy in the dog is licking at the groin
d. Atopic dermatitis is a chronic disease
e. Atopy in a dog almost always indicates IgE involvement

QUESTION 5
Which of the following statement concerning treatments is INCORRECT?
a. Diets which assist in control of pruritus include EFA's
b. EFAs in the diet have a delayed effect
c. Spot-on formulation of EFAs promote the lipid barrier of the skin to aeroallergens
d. Derm Defense is a specific Hills diet which includes a blend of taurine and aloe vera
e. Zyrtec can be used to assist with pruritus in dogs

QUESTION 6
Concerning *Malassezia* which of the following is CORRECT?
a. The presence of epidermal papules is rules out *Malassezia* as a cause
b. *Malassezia* organisms on the skin confirms this yeast as the aetiology of the dermatitis
c. A shampoo containing chlorhexidine at 2 % concentration is sufficient to be effective against *Malassezia*
d. *Malasezzia pachydermatis* has both an affinity for as well as a smell of fat
e. Long-term therapy with antifungal azoles need not be biochemically monitored

QUESTION 7
Regarding therapy of atopy, which statement is INCORRECT?
a. Topical hydrocortisone aceponate spray is marketed by Virbac as Cyclavance
b. The minimum administration of Cytopoint by injection is 1 mg/kg
c. Oclacitinib inhibits the cytokines that are JAK1 and JAK3 dependent
d. BOG can be relieved with chlorhexidine, povidone-iodine and ethyl lactate
e. Vitamins E an C act as antioxidants

QUESTION 8
Which of the following statements is INCORRECT?
a. The allergic reaction to *Malassezia* on dog epidermis involves a type 1 hypersenitvity
b. Ciclosporin's mode of action is unlikely to affect colonisation by yeasts
c. To elicit the aetiology of atopy in dogs, avoidance of the following assist: mould, house dust mite, cats, pollens
d. The allergic reaction to *Malassezia* on dog epidermis involves the humeral response
e. *Malassezia pachydermatis* is lipophilic but not lipid dependant

QUESTION 9
In the treatment of atopy in the dog, which of the following is INCORRECT?
a. Histaguard is NOT an antihistamine
b. None of the penicillin family of antibiotics is likely to assist in atopy
c. Administration of an antihistamine may stimulate appetite
d. Essential fatty acids assist in the maintenance of the dermal lipid layer
e. Phenergan assists in providing relief for itch in cats

QUESTION 10
Regarding atopy which statement is most likely INCORRECT?
a. Detection of unpleasant odours can indicate atopy
b. Atopy can be a cause of otitis externa in the dog
c. Atopy is unlikely to affect the ability to develop antibodies to bacteria
d. A common finding of atopy is inflammation of the ear pinnae
e. Osurnia contains fluazuron

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