Canine Atopic Dermatitis – A practical approach

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Definition
Canine Atopic Dermatitis (CAD) is defined as an inflammatory and allergic skin disorder, affecting genetically predisposed dogs, with characteristic clinical features. It is generally associated with IgE antibodies most commonly directed against environmental allergies (Type 1 hypersensitivity). The patient becomes sensitised to environmental antigens that cause no reaction in non-atopic dogs. In addition, is now also recognised that CAD is a complex and multifactorial disease involving immune dysregulation, allergic sensitisation, skin barrier defects, microbial colonisation and environmental factors. CAD affects 3 to 15% of the canine population. In some studies up to 50% of dermatology cases are CAD cases.

Pathophysiology
CAD is mainly caused by aeroallergens that gain access to the body via the percutaneous route. Outbreaks of atopy have also been linked to allergens presented via other routes e.g. the digestive tract. Numerous allergens have been identified in the pathogenesis of CAD. These include house dust and storage mite allergens, pollens from grasses, trees and weeds, mould spores, epidermal allergens, insect allergens and miscellaneous allergens such as kapok. The majority of cases result from hypersensitivity to house dust and storage mite allergens, leading to a non-seasonal dermatitis. Pollens usually lead to a seasonal dermatitis.

Atopic dogs are predisposed to penetration of the allergens because they have an inherited dysfunction of the immune system as well as a defective cutaneous epidermal barrier function.

From a practical perspective this means that all of the potential components that contribute to the pathogenesis (immune dysfunction, infection, and epidermal barrier defects) need to be identified and considered in the diagnosis and eventual treatment plan for successful control.

The following steps are important in the pathogenesis:
1. Allergens access the body via the percutaneous route. Alteration of the epidermal barrier function facilitates penetration via this route.
2. Once the allergen enters the epidermis it binds to the epidermal Langerhans cells where it undergoes internal processing and is presented to naïve T cells in the draining lymph nodes.
3. In allergic individuals this leads to Th2 differentiation/polarisation and these Th2 lymphocytes release cytokines including IL-4, IL-5, IL-13 that stimulate IgE production by B cells that bind to cutaneous mast cells.
4. Re-exposure to allergens causes mast cell degranulation, cytokine release along with homing of T cells to the epidermis. This leads to cutaneous inflammation, erythema and pruritus.
5. A variety of inflammatory mediators are involved including histamine, leukotrienes and proteases from mast cells and interleukins from keratinocytes.
6. Atopic dogs have impaired cell-mediated immunity predisposing them to secondary bacterial and yeast infections.
7. It has become clear that in addition to the complex immune response, both epidermal barrier dysfunction and infection play an important and interrelated role in the pathogenesis and severity of disease.

Epidemiology
The peak age of onset is between one and three years of age, with a range of 6 months to 6 years. It is relatively uncommon but not impossible to see the disease first appear in middle aged or older dogs.
It can affect any breed, but there is a greater incidence in pure bred dogs such as Terriers, Golden and Labrador Retrievers, German Shepherd dogs, Dalmations, English Bull dogs and Shar Pei dogs. There are significant variations between breeds affected between different countries. This confirms that although there a genetic component, environmental factors play a more important role.

Clinical signs may initially be seasonal or non-seasonal, depending on the allergens involved. Around 80% of all atopic dogs eventually have non seasonal clinical signs. Approximately 80% of atopic dogs initially manifest clinical signs from spring to autumn, and 20% begin in winter.

**Clinical signs**
The main clinical feature of CAD is pruritus. It ranges from mild to severe, but most cases are moderately to severely pruritic.

Lesion distribution initially is very typical. The face (rubbing), ears, paws and distal extremities (chewing) and ventral aspects (scratching) are predominantly affected. As the disease progresses and becomes chronic, the entire body may become affected in about 40% of cases.

Primary lesions seen are erythematous macules and papules. These are very soon changed into secondary lesions due to self-trauma, secondary bacterial and Malassezia dermatitis and chronic inflammation. Chronic cases are often characterised by seborrheic skin changes, salivary staining, marked scaling and varying alopecia. Marked seborrhoea is seen in 12% of atopic dogs. 60% of affected cases suffer from secondary pyoderma, usually a folliculitis, and/or Malassezia infections.

80% of cases are accompanied by otitis externa. In some cases this may be the only presenting sign. Initially the inside of the pinna and the vertical canal are affected, but in chronic cases the horizontal ear canal may also become affected. Seborrhoeic skin disease and secondary bacterial and Malassezia infections may all contribute to the objectionable odour of atopic dogs.

Non cutaneous clinical signs reported to occur occasionally in atopic dogs include rhinitis, asthma, urinary and gastrointestinal disorders and cataracts.

**Diagnostic approach**
Any itchy dog may potentially have CAD, but there are also many other causes of pruritus. A diagnosis of CAD can only be made once all other causes of pruritus have been eliminated. This is done by following a step by step approach to a pruritic dog. It is very important to make a diagnosis as some of the causes of pruritus, e.g. flea bite dermatitis/allergy, mites and cutaneous adverse food reactions (CAFR) are treatable. It is very important to explain to the owner of the pruritic dog that you are going to work according to a plan to find out why their pet is pruritic. It is very easy to just give a “magic” corticosteroid injection to take the itch away, but obviously the pruritus will return again and again until a diagnosis is made and treatment options can be given. They should understand that it is in the best interest of their pet that a diagnosis is made from the onset and treated or managed according to the cause. This process usually takes time and the owners and clinician should not expect a cure in one visit for a problem that has been going on for months/years. The relationship should be cooperative and in the long run they will save money and their pet will benefit.

It is important to take time with the initial dermatological examination, to sit down with the owner and take a detailed history. Thereafter it helps to hospitalise the patient for a few hours and do the clinical examination and in house diagnostic tests when there is more time. The owners return later and the diagnostic and therapeutic plan is discussed in detail. Follow up examinations can be done in normal 15 minute consultation slots.

1. **Historical features** – age of onset, breed, chief complaint, where did the pruritus start at first, describe the lesions seen, diet, previous response to treatment (drugs used, dosages, duration of treatments given), lesions present in in-contact animals or owners. It helps to have a form
with all the relevant questions which the owners can fill in prior to the first consultation. This helps to get all the necessary information.

2. **Clinical examination** – lesion distribution, types of lesions present, presence of secondary bacterial and yeast infections (pustules, crusts, epidermal collarettes, greasy seborrhoea, offensive odour). Never underestimate the role that fleas can play in any pruritic patient. The presence of fleas or flea dirt is very significant and should be shown to the owners.

3. **Skin scrapings** – Skin scrapings should always be done to rule out Sarcoptes and other mites. Sarcoptes mites are not easy to find on scrapings. Crusted papules on elbows, hocks and ear pinnae give the best results. A single mite or egg is diagnostic. Although Demodex is not usually pruritic, it should be ruled out because it may cause a secondary pyoderma that may often be pruritic. Many pruritic dogs have been on chronic corticosteroid treatment which leads to immunosuppression and demodicosis. Cheyletiella is often found on cello tape impression smears of dandruff present on the skin. If a mite is suspected, a therapeutic trial should be performed (see later).

4. **Skin and ear canal cytology** – Cytology is very important, easy, quick and inexpensive and can be performed in-house. Samples are taken from all affected areas as the infections are often regional. Ear buds are effective for taking samples from the external ear canal and cello tape impression smears are very effective to determine the presence of secondary bacterial and Malassezia infections on the skin. It is a good habit to grade these infections at the various sites from 0 to 4+. This helps to determine response to treatment. The presence of the numbers of eosinophils, neutrophils, monocytes, etc. should also be recorded and graded.

5. **Therapeutic trial** - At this stage all secondary infections present should be treated for a minimum of three weeks. This is necessary in order to determine what contribution the infections are making towards the pruritus. Often the lesions will resolve with this treatment, but not necessarily the pruritus. Cephalexin at 20 mg/kg BID or amoxicillin-clavulanic acid at 20 mg/kg BID is effective in most cases. Severe cases of Malassezia are treated with systemic ketoconazole at 5-10 mg/kg once daily. In less severe cases topical ketoconazole or chlorhexidine shampoos are often effective. If fleas are present or Sarcoptes or other mites are diagnosed or suspected, these should be treated at this stage. Remember the principle of “treat what you see and see what is left”. The owners are asked to score the pruritus before initiating any treatment out of ten. Most owners will score 9/10 or 10/10. If at all possible no drugs to suppress the pruritus symptomatically should be given. This will obviously give a false impression that the other treatments are effective. If the pruritus is severe, a short course of prednisolone, 0.5 - 1 mg/kg OID, for 3 to 5 days may be given. This will bring relief to the dog and also help to win the confidence of the owner.

The most important differential diagnoses for CAD are:

a) Cutaneous allergy dermatitis (FAD) – may co-exist in the same patient, typical distribution involves lower back and posterior and inner thighs.

b) Cutaneous Adverse food reactions (CAFR) – difficult to distinguish, similar clinical features. May also co-exist in the same patient. Differences – CAFR can occur at any age, a primary papular eruption is often present, often corticosteroid resistant pruritus.

c) Parasitic dermatoses – rule out Sarcoptes (affects elbows, hocks, ears), Cheyletiella (dandruff), Otodectes (usually in ear canals too), Fleas (flea dirt, fleas present, affects lower back region).

d) Allergic contact dermatitis (ACD) – very rare in dogs, lesions are restricted to contact areas where hair is absent or thin.

After 3 weeks the patient should be re-evaluated. The owner should score the dog again. The dog should be checked thoroughly to see how the pruritus and the lesions have responded to the treatment. Follow up cytology has to be performed to grade infections that may have remained. It is important to evaluate the pruritus score as well as the appearance of the lesions – lesion resolution
Treatment principles

- It is very important to remember that CAD cannot be cured. It can only be managed as well as possible, with the aim to give the patient a better quality of life, as in most cases the dog cannot be protected against allergen exposure.
• It is important to remember that every allergic dog has an allergic threshold. The allergic load can often be tolerated by an allergic dog without disease manifestations. A small increase in the load may push the patient over the threshold and cause or initiate clinical signs which are called “flare ups”.
• The allergic threshold is not fixed and can be raised or lowered by various trigger factors, such as food, infections (staphylococci and/or Malassezia), external parasites and environmental allergens.
• The threshold may therefore be controlled by treatment of the secondary infections, control of ectoparasites and treatment of any associated cutaneous adverse food reactions.
• Each case is different and treatment must be tailored according to each patient and treatment usually involves a combination of treatments.
• Barrier repair is becoming increasingly important in the management of CAD in dogs. This can be facilitated by bathing regularly with appropriate shampoos and dietary and topical fatty acid supplementation.
• Successful long-term management also requires substantial and ongoing owner commitment. The owners need to understand the concept of the allergic threshold so that they can help to determine and avoid triggering factors and adjust long term management accordingly.
• The management and treatment plan may change over time as the disease changes.

1. Avoidance of allergen:
• In theory this would be the best possible treatment, but usually this is not possible or practical.
• In most cases the aim is to decrease exposure.
• In cases where house dust mites are the cause, keeping pets more outdoors or away from bedrooms and off fabric furniture (where the highest concentrations of mites are) may help. Other suggestions to decrease the numbers of house dust mites include washing bedding in hot water (> 70°C), avoiding stuffed toys, keeping the dog overnight or during the day in a non-carpeted room and running the air conditioner during hot and humid weather. There are products available that are miticidal. A recent study by Christophe Rême and colleagues has shown that good in-house control of house dust mites with acaricidal products can significantly alleviate clinical signs in atopic dogs. Pyriproxifen has been shown to be effective in reducing mite proliferation.
• Suggestions where moulds are the allergens responsible for the allergy are to avoid dusty food, avoid having large numbers of house plants, and to clean the environment and bedding with chlorine bleach solutions.
• For pollens the best ways to avoid the allergens include keeping the dog out of fields, keeping the grass cut short, rinsing the dog off after periods in high grass or weeds, keeping the dog inside at dusk and early morning in heavy pollen season, using air conditioners, and keeping the dog away from the lawn when it is mowed.

2. Control of secondary infections:
• Control of secondary infections is vital in the management of a CAD case because infections often contribute significantly to the pruritus induced by allergy. In some cases good infection control may be sufficient to keep the patient below the allergic threshold.
• Pulse or weekend treatment is often instituted after the initial 3 weeks and has been shown to be very effective. Cephalosporins or amoxicillin-clavulanic acid are the most commonly used antimicrobials for this purpose. A study by Didier Carlotti has shown that there is no increase in the development of resistance against cephalosporins when using them for pulse or weekend treatment.
• Chronic Malassezia overgrowth often exists concurrently with the bacterial overgrowth. Pulse therapy with systemic ketoconazole has been shown to be very effective.
• The use of weekly topical antimicrobial shampoo, e.g. chlorhexidine may in some cases be sufficient to control the overgrowth without necessitating systemic medications.
3. **Allergen specific immunotherapy (ASIT):**
   - The cornerstone of therapy of CAD is Immunotherapy (hypo sensitisation or desensitisation). This is the practice of administering gradually increasing quantities of an allergen extract to an allergic patient to ameliorate the symptoms associated with subsequent exposure to the causative allergen.
   - It “down regulates” the allergic response and may raise the allergic threshold. It alters the balance between TH1 and TH2 cells, which moderates the sensitivity and tolerance to allergens.
   - ASIT should be considered for young patients; patients where concurrent treatment with topical shampoos, systemic antibacterial and systemic anti-yeast medications is not able to control pruritus sufficiently; cases where corticosteroids have to be used at high dosages for control of pruritus or where side effects are unacceptable.
   - There is now a choice between injectable and oral immunotherapy.
   - Response to ASIT may take 3 to 10 months.
   - The success rate is 65 – 75%.
   - It is important to note that only a minority of cases will be totally controlled by ASIT alone. The majority of cases will benefit from ASIT but may require symptomatic treatment, including corticosteroids for some parts of the year.
   - It is very important to explain to clients that the target of ASIT is to reduce the amount of immunosuppressive treatment needed. If owners understand what to expect rather than believing that total control is the target, client compliance and satisfaction will be much better.
   - Most cases require lifelong control with immunotherapy, supplemented from time to time with other medical therapy.

4. **Suppression of inflammation:**
   4.1 **Antihistamines:**
   - H1 antihistamines may sometimes give partial relief to the pruritic patient.
   - They are usually used in conjunction with prednisolone to help lower the dose of prednisolone required to control the pruritus and inflammation.
   - A selected antihistamine should be administered for 10 to 15 days before evaluating its effectiveness. If the patient does not respond to one type, it may be worthwhile to try another.
   - In a recent study by Ewert and co-workers, a combination of hydroxyzine (25 – 100 mg/dog/day) and chlorpheniramine (1 – 4 mg/kg/day) resulted in an improvement of more than 50% in lesion scores in 18% of dogs and of the pruritus score in 30% of the dogs. The investigators judged the treatment satisfactory in 24% of dogs.
   - H2 antihistamines have no action on pruritus.
   - Antihistamines commonly used, together with dosages, are given in the table below.

<table>
<thead>
<tr>
<th>ANTIHISTAMINES</th>
<th>DOSAGE</th>
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<tbody>
<tr>
<td>Chlorpheniramine</td>
<td>0,4 mg/kg q8h</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>2,2 mg/kg q8h</td>
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<tr>
<td>Hydroxyzine</td>
<td>2,2 mg/kg q8h</td>
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<tr>
<td>Loratidine</td>
<td>0,25-1 mg/kg q24h</td>
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<tr>
<td>Clemastine</td>
<td>0,1-0,25 mg/kg q12h</td>
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<tr>
<td>Cetirizine</td>
<td>2,5-20 mg q24h</td>
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   4.2 **Corticosteroids:**
   - These drugs are highly effective in relieving pruritus, except when fleas or other ectoparasites and/or severe bacterial and/or Malassezia infections are present concurrently.
   - Corticosteroids have various anti-inflammatory properties. They are strong inhibitors of the synthesis of pro-inflammatory cytokines with keratinocytes and Langerhans cells their principal targets.
   - They are used in many CAD cases and have been one of the most commonly prescribed drugs over the past thirty years for the treatment of CAD.
• Once the secondary infections and other complications have been treated and the patient is still pruritic, it is one of the treatment options for patients where immunotherapy is not a treatment option.

In cases where corticosteroids have to be used, the following rules should be followed:
1. Only short acting, oral products, e.g. prednisolone, prednisone and methyl prednisolone should be used. Prednisolone and prednisone are equally effective in dogs.
2. Ideally an alternate-day regime should be used, often together with antihistamines and oral essential fatty acids, which make it possible to reduce the dose of corticosteroid required.
3. The starting dose is 1 mg/kg once a day and the dose is halved every 4 to 5 days. A maintenance dose of ½ mg/kg every other day or less is considered “safe”. Increasing the interval between prednisolone dosing decreases the risk of side effects and pituitary suppression. 1 mg/kg every other day equals 0.33 mg/kg daily.
4. Prednisolone has a half-life of 12 hours, but its biological effect lasts for 4 to 7 days after the last dose. This is the reason why cortisone responsive atopic dogs relapse approximately 5 to 7 days after the last dose of cortisone.
5. The use of injectable forms, especially the “long acting” corticosteroids, is not advised due to the high risk of side effects.
6. A patient on chronic corticosteroid therapy should be examined every three months to monitor weight, inspect the skin for infectious complications and check the urine for urinary tract infections which are very common in these patients.
7. A poor or no response to corticosteroids may indicate that the diagnosis of CAD is not correct, the CAD is complicated by secondary infections or other causes of pruritus e.g. CAFR may be concurrently present.

4.3 Oral Essential fatty acids (EFAs):
• Omega-6 and Omega-3 fatty acids have three main functions in the skin: structural components of cells membranes, maintenance of the epidermal water barrier and precursors for the production of pro- and anti-inflammatory eicosanoids.
• Both Omega-6 and Omega-3 fatty acids can have immuno-modulatory effects. The main Omega-6 fatty acid in cell membranes is arachidonic acid (AA), which is the precursor for the production of prostaglandin E2 (PGE2), leukotriene B4 (LTB4) and 12-hydroxyeicosatetraenoic acid (12-HETE), which are all potent inflammatory mediators. When Omega-3 fatty acids are given orally or a diet is supplemented with Omega-3 fatty acids, part of the AA in cell membranes can be replaced by eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA may then be used instead of AA for the production of eicosanoids, resulting in a different and less inflammatory set of compounds (e.g., PGE3, LTB5 and 15-HETE instead of PGE2, LTB4 and 12-HETE). The substitution of Omega-3 for part of the Omega-6 fatty acids may therefore lead to reduced inflammation which is beneficial in inflammatory conditions.
• Many dermatologists consider an omega-6: omega-3 ratio of between 5: 1 and 10: 1 optimal for treating patients with skin disease. This 5-10: 1 ratio may be more applicable to dogs with a normal skin and coat without any underlying pathology. Lower ratios, which are created by adding more omega-3’s, may be more beneficial for dogs with underlying pathology.
• In their practical guidelines paper, the Canine Atopic Dermatitis Task Force conclude that oral EFAs have a role to play in the management of chronic CAD, but there is still no consensus regarding particular combination, dosage, ratio and formulation.
• EFAs require up to 2 months of supplementation before any benefit might be seen.
• They are not suitable for monotherapy of CAD, but rather as part of the management programme.
• EFAs are considered corticosteroid reducing agents, because when used in combination with antihistamines, antimicrobial agents, topical medications and medicated shampoos, they have been shown to reduce the dosage corticosteroid required.

• Many CAD patients benefit from specially formulated diets for skin disorders that typically have increased EFA levels. Several publications have reported that veterinary diets with a novel protein and carbohydrate combination with omega-6 and a high level of omega-3 fatty acids (providing a ratio of 2.7:1 omega-6:3) can result in a significant improvement of pruritus and lesion scores in CAD, as well as a significant improvement of skin and coat condition. The incorporation of high levels of omega-3 fatty acids that help to reduce the inflammation, and highly digestible ingredients, such as high quality protein and fats needed for repair of the epidermal barrier, are all possible reasons for why such diets are beneficial in CAD.

• One of the studies that evaluated such diets was a multi-centered, double-blinded, randomised study that evaluated the clinical response to an 8 week period of feeding one of three veterinary diets marketed for dogs with atopic dermatitis and one supermarket diet. Fifty dogs were included and the three veterinary diets evaluated were a selected protein diet based on salmon & rice (diet A), a select protein diet based on fish & potato (diet B, Eukanuba Veterinary Diet Dermatosis FP) and a hydrolysed soy diet (diet C). The supermarket control diet was diet D. The results showed that after 8 weeks on the veterinary diets, both the Canine Atopic Dermatitis Extent and Severity Index (CADESI-03) and pruritus scores of dogs assigned to the fish & potato diet were significantly decreased and it was the only diet to significantly improve both scores, whereas dogs assigned to the selected salmon & rice diet (diet A) only showed significantly less pruritus. No significant changes were detected with the hydrolysed diet C for the CADESI or pruritus scores. The authors summarised “Based on the results of this study, changing the diet of dogs with atopic dermatitis may be a useful adjunctive therapeutic measure in addition to conventional therapies.” The clinical benefit of the Dermatosis Fish & Potato diet was thought to be linked to being an omega-3 fatty acid enriched diet with an omega-6:3 ratio of 2.7:1.

4.4 Cyclosporine:
• Oral cyclosporine is a thoroughly evaluated drug for the treatment of CAD. It is a calcineurin inhibitor.
• Cyclosporine acts mainly on T helper lymphocytes. It also acts on mast cells, eosinophils and Langerhans cells, reducing their antigen presentation functions and inhibits the synthesis of keratinocyte associated cytokines and prevents delayed hypersensitivity reactions.

5. Stress control:
• Stress and anxiety can be triggers that can cause a flare up in an allergic patient’s condition.
• Examples include boarding, family going on holiday, loss of a family member, a new baby or pet or moving to a new home.
• Some of the anti-histamines (e.g. hydroxyzine, cetirizine, clemastine) or serotonin reuptake inhibitors (e.g. fluoxetine, clomipramine) may be helpful in treating CAD because of these anti-anxiety effects.

6. Topical treatment:
Topical treatment is a very important component in effective management of CAD and includes shampoos, topical lipids, sprays, creams and ointments.

6.1 Shampoos
• Shampoos rehydrate the skin and result in the patient looking, smelling and feeling better.
• They help to remove allergens from the skin surface, help to restore the epidermal barrier and help to control inflammation and secondary skin infections.
• There are a variety of shampoos available that may be helpful in the management of an allergic skin disease:
6.1.1 Cleansing, non-irritating, barrier restoring shampoos
These shampoos are used to improve or restore the epidermal barrier, e.g. EFA treatment shampoos, hypoallergenic shampoos, shampoos containing ceramides.

6.1.2 Soothing shampoos
- Colloidal oatmeal is a safe and effective soothing antipruritic agent, commonly used in shampoos. The exact mechanism of this effect is poorly understood. This agent is safe, only provides short term relief (24-48 hours) of mild pruritus and has no antimicrobial properties.
- EFA treatment shampoos have soothing effects because they are rich in essential fatty acids and essential oils, with a natural soothing agent from pumpkin seeds. These shampoos also hydrate the skin and reinforce skin barrier function.

6.1.3 Antimicrobial shampoos
Antimicrobial shampoos may be used to control secondary bacterial and/or yeast infections and should be used every 7 to 14 days, depending on the current situation. Antimicrobial agents include:
- **Chlorhexidine digluconate**: An antiseptic effective against most bacteria, fungi and Malassezia pachydermatis. It is bactericidal by action on the cytoplasmic membrane, which causes leaking of intracellular components, is characterised by a rapid kill, has a 36-hour residual activity and is non-toxic and non-irritant. In a study by Jasmin et al a 3% chlorhexidine shampoo was highly effective in the treatment of Malassezia dermatitis and concurrent bacterial pyoderma when present.
- **Povidone-iodine**: An iodophore which slowly releases iodine to tissue. It is an effective broad-spectrum antimicrobial and is useful for local lesions. It has a prophylactic effect because of its persistence on the skin, but should not be used repeatedly for generalized skin problems due to its irritant and staining properties.
- **Benzoyl peroxide**: It is metabolised in the skin to benzoic acid. Much of its microbicidal activity derives from the lowered skin pH which disrupts microbial cell membranes. It is also an oxidizing agent, which releases nascent oxygen into the skin and produces a series of chemical reactions resulting in permeability changes and rupture of bacterial membranes. It has an excellent prophylactic effect and its follicular flushing, keratolytic degreasing and comedolytic activity are additional benefits. It is generally used in concentrations of 2 to 3%, which are well tolerated, but irritation can occur at higher concentrations (erythema, pruritus and pain).
- **Quaternary ammonium compounds**: They are surface acting agents. They have less effect and are only useful for limited bacterial involvement. They have no residual effect and have to be applied often for good effect.

6.1.4 Keratomodulating shampoos
These shampoos are indicated in cases with allergy induced keratoseborrhoeic changes. Keratomodulating agents include:
- **Salicylic acid** (0, 5 – 2%) is keratolytic. It causes a reduction in skin pH, which leads to increased hydration of keratin. These actions help to soften the corneal layer. It acts synergistically with sulphur and is often present in small quantities in shampoos.
- **Sulphur** (0, 5% - 2 %) is mildly keratolytic (forms hydrogen sulphide in the stratum corneum), keratoplastic (has a direct cytostatic effect) and has numerous anti-seborrhoeic effects.

6.2 Topical lipids
- Topical lipids have been used with success in improving the epidermal barrier in human atopic dermatitis.
- There are a few published studies in the veterinary literature that have documented the effects of topical fatty acids on the barrier function in dogs. In one study the topical application of either a fatty acid containing spot-on (applied weekly) or spray (applied daily) improved both the lesions and pruritus in dogs with CAD. Another study showed that the spot-on formulation applied weekly for 8 weeks was beneficial in alleviating the clinical signs of both mild and severe cases of CAD.
A study by Piekutowska and Pin demonstrated an increase in epidermal lamellar lipids. This suggested that treatment with topical lipids stimulated the production and secretion of endogenous stratum corneum lipids, contributing to the formation of an improved epidermal barrier.

Topical lipids are more effective in restoring the hydrolipidic film faster when compared to oral EFAs.

Topical lipids also moderate sebaceous gland activity and sebum production, rebalance dry or oily coat and skin, are skin barrier enhancing and reduce TEWL for optimal skin hydration.

6.3 Topical sprays:
- A steroid-free topical spray has been developed for the symptomatic treatment of CAD. It has 100% natural active ingredients which have a synergetic efficacy and does not have any side effect of steroids. The spray is soothing, reduces skin inflammation, regenerates and repairs the epidermal barrier, decreases TEWL and has antimicrobial properties.
- A corticosteroid spray that is not absorbed systemically is also available.

6.4 Other topical treatments:
- **Topical glucocorticoids** are useful in Veterinary Dermatology. They are the sole ingredient or part of combination formulations with antimicrobial and other agents and are useful for localised lesions. Tachyphylaxis, atrophy and microbial infections can occur in cases of overuse.
- **Immunomodulators**: Tacrolimus, a calcineurin inhibitor has been shown to be effective in the treatment of localized lesions of CAD.
- **Antibiotics**: formulations containing fusidic acid and mupirocin are useful for treating localized lesions of pyoderma.
- **Antifungals**: products containing azole derivatives or nystatin can be used on localized lesions of dermatophytosis, Malassezia dermatitis or candidiasis.

Conclusions
- The control of CAD requires combination therapy.
- The concept of allergic threshold and “flare ups” is very important.
- The basis of the therapeutic approach is hyposensitisation, together with concurrent medical therapy including antimicrobials, EFAs and the frequent use of topical shampoos.
- With good management the use of corticosteroids will be considerably reduced.
- Successful management depends on a thorough understanding of the pathogenesis and of the potential complications, and on a willingness to modify the therapy in the light of a changing situation.
References

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Calneurins are calcium-dependent serine-threonine phosphatases that activate the transcription of cytoplasmic T-cell nuclear factors (NFATc) by dephosphorylating them. The activated NFATc is then translocated into the nucleus, where it upregulates the expression of interleukin 2 (IL-2), a pro-inflammatory cytokine which, in turn, stimulates the growth and differentiation of T cell response. IL-2 also promotes the differentiation of T cells into effector T cells and into memory T cells when the initial T cell is also stimulated by an antigen. Calcineurin is the target of a class of drugs called calcineurin inhibitors.

Cyclosporine A is such a calcineurin inhibitor. This drug is used as an alternative to corticosteroids to control pruritus. It reduces pruritus and cutaneous lesions. At a dose of 5 mg/kg/day, it was found to be equally as effective as prednisolone.

Due to its large size and lipophilic nature availability of cyclosporine is greatly improved (50%) if the micro-emulsion formulation is used. Administration of cyclosporine as micro-emulsion formulation with food decreased the bioavailability by 22% and increased the individual variability of drug absorption – thus dosing two hours before or after a meal is recommended.

Cyclosporine is mainly absorbed from the small intestine and is metabolised in the intestine and liver by the cytochrome P450 enzyme system. The drug accumulates in the skin, liver, kidneys and fat in dogs. In controlled blinded trials 5mg/kg/day – the approved atopy dose – of cyclosporine was shown to cause a similar reduction in canine atopic dermatitis extent and severity index (CADESI) compared to 0.5 or 0.75 mg/kg of prednisolone or methyl prednisolone respectively. In another controlled blinded trial cyclosporine out performed placebo in a dose dependent fashion. The tolerability and safety of oral cyclosporine and prednisolone also appeared similar. Cyclosporine treated dogs presented with a higher frequency of gastrointestinal disorders, mainly vomiting, but also diarrhoea and anorexia, but prednisolone treated dogs tended to be more susceptible to infections. A dosage reduction to alternate day or twice-weekly treatment after an initial phase of daily treatment is usually achievable. No significant correlation was found between clinical improvement and cyclosporine blood concentrations. Therefore a reduction in the dosage is based on the clinical response to therapy rather than the measurement of serum levels of cyclosporine.

A short tapering course of prednisolone therapy expedited the efficacy of cyclosporine A in resolving pruritus and associated clinical signs in the initial week or two of treatment. A lag period of about 2-3 weeks in which no response is seen, occurs after cyclosporine treatment is started. Significant reduction in pruritus is expected in 75 – 85% of cases within 1 month of treatment. After six weeks, alternate day therapy and even twice weekly treatment has been effective.

Allergen-specific immunotherapy (ASIT) offers an alternative to either glucocorticoids or cyclosporine therapy. Identification of putative allergens is required for the formulation of ASIT and cyclosporine has been shown to have no statistically significant effects on either intradermal or serum IgE allergy tests when administered at therapeutic dose rates of 5 mg/kg orally once daily for
30 days – so you can test your patient whilst they are on treatment. Its place as an alternative to, or in combination with, prednisolone therapy is considered well established.

It is safe in dogs and does not cause nephrotoxicity or arterial hypertension as in humans. Vomiting and diarrhoea are the most commonly seen adverse effects in dogs. This is seen in 14 – 42% of cases, but is mostly mild to moderate. Papillomatous eruptions and gingival hyperplasia are occasionally seen.

Cyclosporine has been used as an aid in the treatment of numerous dermatological conditions in animals in addition to atopy, including perianal fistulation, sebaceous adenitis, pododermatitis, chronic otitis externa, and pemphigus foliaceus.

Studies looking at the pharmacodynamics of cyclosporine show that ketoconazole decreased the systemic clearance of cyclosporine. Ketoconazole causes no significant changes in cyclosporine steady state volume of distribution, or plasma unbound fraction. Ketoconazole does not significantly alter the excretion of cyclosporine and various cyclosporine metabolites in the bile/urine mixture. As a result of these findings ketoconazole has been promoted as a cost saver to reduce the dose of cyclosporine. Clinicians need to understand that this is extra label use of a registered veterinary product. It also may represent false economy because the use of ketoconazole requires biochemical monitoring for a hepatic insult and the dose of cyclosporine may in any case be reduced once disease remission is established.

References


Little bubble - “Freezing the capsules prior to administration can reduce the vomiting side effect “

......REF!!!!!!