Atopy, pyoderma and the skin: Barrier function and beyond.....

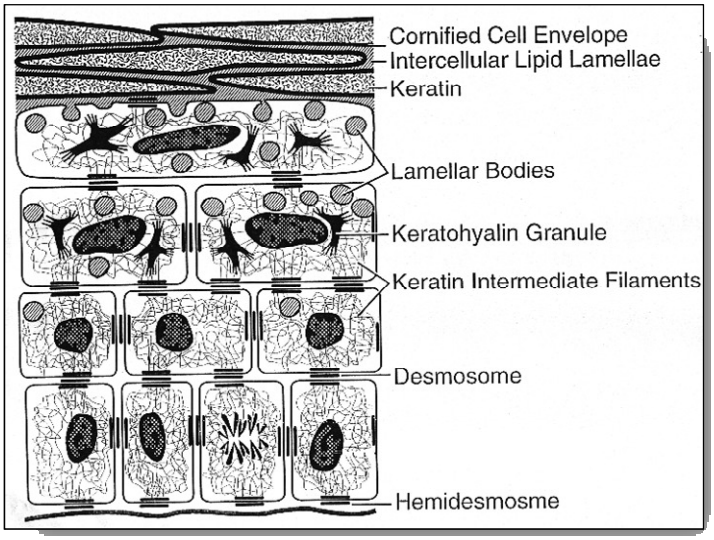
Rusty Muse DVM, ACVD
Animal Dermatology Clinic, Tustin, CA

Introduction

What is an epidermal barrier?

The anatomical/physical barrier of the skin consists of two parts. Some of this barrier function resides within the **stratum corneum**, but once this barrier has been breached the tight junctions found at the level of the **stratum granulosum** between the keratinocytes are the next level of defense.

The first epidermal barrier is created by **epidermal cornification**, the end point of epidermal **differentiation.** An effective epidermal barrier requires intricate organization and formation of the keratin intermediate filaments and the intercellular lipids together with tight regulation of desquamation. The **stratum corneum** (SC) consists of a sheet of **corneocytes** embedded in an **intercellular lipid matrix** and is the primary barrier against pathogen entry . It is also largely responsible for the **regulation of water loss** from the body (transepidermal water loss (TEWL) and is also able to withstand physical forces.



.

Lipids are very important in barrier function, stratum corneum water holding, cohesion and desquamation of corneocytes and control of epidermal proliferation and differentiation. **Ceramides** are the most important lipid component for the lamellar arrangement of the stratum corneum. Ceramides are composed of **polyunsaturated fatty acids** (such as the omega-6 linoleic acid contained in sunflower oil) and sphingosines.

An effective epidermal barrier requires intricate organization and formation of the keratin intermediate filaments**. Filaggrin** (FLG) is a keratin filament-associated protein necessary for organization of the keratin intermediate filaments. It comes from **profilaggrin** in the keratohyalin bodies of the granular layer. FLG and keratin both undergo proteolysis during cornification and form acidic substrates that are hygroscopic (trap water) and also affect pH dependent enzymes involved with desquamation. Lower or defective FLG reduces the ability of the epidermis to trap water, and increases rate of

breakdown of the cornified layer by causing premature breakdown of the corneodesmosomes that hold the corneocytes together. Together these epidermal components form an effective flexible **epidermal barrier** against the penetration of environmental irritants, allergens and infections and transepidermal water loss and dessication.

So what goes wrong?

There is significant evidence for both **innate and acquired defects of the epidermal barrier** in atopic humans and dogs. It is thought that in humans and most probably in dogs that inherited innate barrier function defects are a significant primary risk factor for atopic dermatitis. Whereas the traditional dogma stressed the importance of IgE-mediated early and late-phase hypersensitivity reactions to airborne allergens, the current theory suggests that in the acute phase of the disease, **epidermal barrier defects** facilitate **contact of environmental (and possibly microbial) allergens** with **epidermal immune cells**.

The significance of a defective epidermal barrier is that it **loses water** through the skin resulting in itchy dry skin with loss of skin flexibility, increased penetration of irritants and potential allergens, especially house dust mites and a lowered ability to prevent microbial colonisation. Dust mite proteases have also been reported to directly trigger inflammation in the epidermis potentially leading to interference with barrier homeostasis, and to cleave tight junctions. With increased allergen penetration, there is increased exposure of the immune system (via Langerhans cells), thereby increasing the likelihood of development and IgE-mediated exacerbation of cutaneous inflammation.

Barrier repair is fundamental in the management of atopic dermatitis in humans, and is becoming increasingly important in the management of atopic dogs.

How does this apply to the management of atopic dogs?

✓ What is the best shampoo type for allergic skin?

Rationale for 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. Because frequent shampooing might further dry and irritate the skin, especially with anti seborrheic or antimicrobial products, owners should be reminded to report any exacerbation following bathing so that a different shampoo might be prescribed. In some cases, moisturisers might alleviate any skin dryness that would occur after the baths

Shampoo therapy must be gentle in order to remove surface allergens **with minimal disruption to the epidermal lipid barrier**. Shampoos, rinses or sprays can offer soothing, anti-pruritic benefit. Gentle technique, with 5 to 15-minute shampoo contact time, followed by 5 to 10 minute thorough rinsing is ideal used once to twice a week initially and then tapered to once to twice a month. There is limited residual effect from shampoos which may be potentially extended for products containing spherulites.

It is important to be careful when shampoo is applied to inflamed skin. The shampoo vehicle may act as an irritant. Ensure owners do not observe increased itching, redness, scaling or greasiness affecting the trunk within 48 hours of bathing as these may be consistent with shampoo triggered irritation. It is often best to dilute the shampoo before applying to help prevent shampoo irritation. In

dogs that cannot tolerate these products we will use either dilute baby shampoo or QV wash. **Conditioners** should follow shampoos, or be used between shampoos, with moisturising role or increased residual effect; some require rinsing

✓ What is the best shampoo type for allergic AND infected skin?

In both human and veterinary AD, and at particularly high prevalence in dogs, there is a tendency to colonization and infection with *Staphylococcal* bacteria which exacerbates clinical disease. In dogs and potentially cats with AD there is a similar propensity for colonization and infection with *Malassezia* yeasts. Antimicrobial shampoos are only beneficial for use in dogs that develop recurrent surface bacterial overgrowth or bacterial and/or *Malassezia* infection. **Treatment of infection is determined by results of cytology and clinical diagnosis of microbial overgrowth or true superficial infection** e.g. bacterial folliculitis. The latter will require systemic antimicrobial therapy.

Long term management of human and canine AD patients with recurrent infections, antiseptics rather than antibiotics are recommended to prevent infection or reduce bacterial counts. The main advantages of antiseptics over antibiotics are their much lower potential to induce resistance in *Staphylococcal* strains with repeated use, the availability of a range of formulations, and their low risk for inducing contact allergy. Whole body (often twice weekly baths) or critical regions treatment can be considered. Correct concentrations should be carefully checked, because most antiseptics are toxic or at least irritating in higher concentrations. Although efficacy is proposed, there are no data from controlled trials to prove effect.

Shampoo and conditioner products: antimicrobial

Chlorhexidine gluconate: broad-spectrum antibacterial and antifungal activity (mechanism of action not clearly evaluated); lasts longer than povidone iodine, and at 0.5% solution is more effective than povidone iodine; shampoo formulation it is more effective than either benzoyl peroxide or povidone iodine shampoos; 1% concentration is necessary for good anti-*Malassezia* effect

Well tolerated, with low irritancy, toxicity and potential to cause contact sensitisation >0.1% is not recommended for open wounds due to delayed healing effects; corneal irritation and ulceration can occur; several cases of severe immediate-type allergic reactions to chlorhexidine have been reported, and specific IgE antibodies were detectable in most patients affected.

Povidine iodine: stable chemical complex of iodine; minimal use due to greater potential for local irritation; excellent bactericidal, fungicidal, virucidal, and sporicidal effects, however only short duration of effect (4-8 hours)

Significant potential for local (drying, irritation, discolouration) and systemic (thyroid function) side-effects limit use in human and veterinary AD.

Benzoyl peroxide 2.5-5% products have persistent antibacterial effects for 48hrs, even in the face of optimal conditions for bacterial growth; superior to chlorhexidine, povidone iodine, and triclosan. Drying and irritation are common problems in veterinary patients, especially with products >2.5%, and moisturising is often important.

Sodium hypochlorite: **bleach** (diluted to 0.005% solution; full strength typically 3-6%, diluting ~1 in 300) for twice weekly full-body bath; shown to be effective for maintenance treatment after *S. aureus*

eradication in human AD, with only submerged body parts improved (not head and neck); unsure if antibacterial or astringent effects.

Textiles with antiseptic properties (silver-coated textiles or alkoxysilane quarternary ammonium [AEGIS]-coated silk) might present a useful alternative for these patients. Silver-coated textiles have been shown to decrease the staphylococcal colonization and improve eczematous skin lesions in humans.

Potassium permanganate ($KMnO_4$; 1/10 concentration) antibacterial activity significantly lower than 0.1% chlorhexidine.

✓ What about other topical products?

With skin barrier defects known to play a role in the pathogenesis of human AD and now suspected in canine AD, the potential value for topical products improving barrier function for AD patients is evident. In addition, regular use of topical glucocorticoids in humans has experimentally resulted in further disruption of epidermal barrier function by inhibiting epidermal synthesis of fatty acids, and further increasing the need for barrier repair treatment.

A range of barrier repair treatments focusing on skin hydration and restoration of skin lipids are well established in the care of human AD, however are only recently becoming more of a focus in veterinary AD. Options include:

Moisturizers: contain variable combinations of naturally occurring skin lipids and sterols as well as artificial or natural oils, humectants, emollients, and lubricants. There are a number of major components to moisturisers:

Humectants: keep water in by attracting water from deep within the skin towards the surface e.g. carboxylic acid, lactic acid, urea, sodium lactate - non-oily; may cause irritation and prevent water loss via transpiration e.g. propylene glycol, glycerol, polyvinylpyrrolidone, sorbolene

Emollients: fill spaces between skin cells with oil; include a variety of oils (almond, corn, coconut, olive, peanut, safflower, sesame); animal fats (lanolin), and hydrocarbons (mineral oil, paraffin oil, petrolatum)

Emulsifiers: help distribute oils in a water solution (e.g. acetyl alcohol, laureth-5, lecithin, steric acid, stearyl alcohol)

✉ A tip for severely itchy dogs

Severely inflamed skin can benefit from occlusion where a more rapid response is required as this will significantly increase absorption of the medication. Immerse dog in the laundry tub or bath for 5 to 10 minutes with dilute QV oil in bath water, pat dry gently, apply moderate potency topical corticosteroid, for instance topical 1% mometasone (Elocon cream); immerse a small T-shirt or bodysuit in hot water, wring out so not dripping but still damp and place warm wet T shirt on the dog and leave for 20 to 30 minutes. Occlusion and hydrotherapy hydrate the skin and increases penetration of the steroid and gives rapid relief.

✓ Can we use topical lipids to improve itchy skin?

Recent evidence indicates that some humans with AD have decreased cutaneous barrier function as a factor in the pathogenesis of their disease. Human patients with AD commonly exhibit xerosis, a term describing abnormal skin dryness. In these patients it is hypothesised there are changes in the chemical composition of the epidermal lipid barrier and increased transepidermal water loss. Similar to humans, atopic dogs probably have defective epidermal lipid barriers. This implies that in the future, we may be able to evaluate skin barrier function in atopic dogs and to restore its function via either topical or dietary means.

Clearly application of various topical therapies, namely moisturisers and emollients, sphingosine therapies, fatty acids and barrier creams to humans with AD improves objective measurements of barrier function, and can improve clinical signs as well.

In the veterinary literature, however, there is limited evidence at this stage to suggest these products may assist in the management of the atopic patient. Currently there are two published studies documenting the effect of topical products on barrier function in dogs.

Tretter,S ,Mueller, RS. The influence of topical unsaturated fatty acids and essential oils on normal and atopic dogs- a pilot study. Vet Derm 2010, 21 311-328

Seven dogs with atopic dermatitis and five normal dogs were treated with a spot-on containing essential oils and unsaturated fatty acids once weekly for 8 weeks. In all dogs, transepidermal water loss (TEWL) was measured before and after treatment. In atopic dogs, lesions and pruritus were assessed before and after treatment. The mean CADESI and pruritus scores and TEWL in atopic dogs decreased.

Piekutowska A, and Pin D, et al., 2008. Effects of a topically applied preparation of epidermal lipids on the Stratum corneum barrier of atopic dogs. Journal of Comparative Pathology 138 (4): 197-203.

This study, based on the examination of biopsy samples, was designed to evaluate by electron microscopy and ruthenium tetroxide post-fixation, the effect of a new topical skin lipid complex (SLC) containing ceramides, free fatty acids, and cholesterol (Allerderm Spot On) on the structural deficit in the skin of five dogs with AD. After repeated applications of SLC to the non-lesional skin of dogs with AD, there was an increase in epidermal lamellar lipids. It is suggested that the treatment with SLC stimulated the production and secretion of endogenous SC lipids, contributing to the formation of an improved epidermal barrier.

Topical lipid products

Product	Ingredients	Formulations
Dermoscent Essential 6 ®	Linoleic acid	Spot on
*Duoxo®	Phytosphingosines	Shampoo Spray Spot on
*Allerderm Spot on ®	Ceramides, fatty acids	Spot on

Three new non-steroidal barrier creams have entered the human market, designed specifically to further enhance barrier repair, and are approved in the US for structural rather than chemical actions, requiring less efficacy data for approval.

Atopiclair® contains hyaluronic acid (moisturising agent), glycyrrhetinic acid (proposed anti-inflammatory effects); and other factors thought to have anti-oxidant properties and to restore the barrier function of the skin. Multicentre, randomized, vehicle-controlled clinical studies confirmed that safe and effective in mild to moderate AD in both children and adults

MimyX® contains lipids, including triglycerides, squalene, phospholipids and phytosterol (moisturising, and replicating stratum corneum framework to maintain skin barrier), and N-palmitoylthanolamine (proposed anti-inflammatory). Reported comparable efficacy with low-potency steroids in AD, measured by pruritus reduction and barrier repair.

Epiceram® designed with a ratio of ceramides, cholesterol, and free fatty acids thought to optimize restoration of skin barrier function. Pilot study suggesting efficacy requires confirmation.

✓ What role do oral fatty acid supplements play?

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 with an associated reduction of transepidermal water loss.

Dietary components also affect the composition of the stratum corneum and it may be helpful to attempt to restore epidermal ceramides by feeding a diet rich in linoleic acid. Sources of **gamma linoleic acid** include **evening primrose oil** which can be supplemented at a dose rate of **1g/5kg bwt**

Cold pressed safflower oil can be used at a dose rate of 1ml/kg daily. (1 tablespoon is 15ml, 1 teaspoon is 5ml)

Supplementing dogs with safflower oil for barrier repair

Size	Amount
5kg	7ml
10kg	12ml
20kg	20ml
40kg	35ml

✓ What about other dietary supplements?

Several nutritional supplements (e.g. pantothenate, choline, nicotinamide, histidine and inositol) have been shown to increase the production of ceramide 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.

Royal Canin® SS 21 Skin Support diet contains inositol and pantothenic acid and may be useful in atopic dogs that do not have any adverse reactions to chicken. It is important to remember that this study was conducted in normal dogs and this outcome remains unproven in atopic dogs.

Watson AL, Fray TR, Bailey J et al. Dietary constituents are able to play a beneficial role in canine epidermal barrier function. Experimental Dermatology 2006; 15: 74–81

Science Diet Adult Sensitive Skin. While this diet is commonly available over the counter and is used often by clients erroneously as a "food trial diet for allergies", it does have increased omega 3 and 6 levels which could be beneficial as well in individual cases. No studies to support this particular product have been done and published.

✓ How do we put this all together?

Managing atopic dogs requires a multi-therapeutic approach. A veterinarian has to incorporate the short-term management of acute pruritus in the atopic dog as well as longer term strategies to try and prolong the interval between these flares. **Long term prevention plans** are crucial for chronic AD, with a combination of treatment interventions being ideal. All attempts should be made to avoid or reduce the trigger factors, which in dogs may include food, flea and environmental allergens, *Staphylococcal* bacteria and *Malassezia* yeast. Skin and coat hygiene and care should be optimized by bathing regularly with suitable non-irritating shampoos/conditioners. Dietary or topical fatty acid supplementation should now be considered as a viable adjunctive therapy for AD.

The severity of pruritus and skin lesions can be reduced with a combination of medications as needed, including topical and oral glucocorticoids, topical and oral calcineurin inhibitors, and barrier repair products. The dosages and types of medications required should be tapered as the pruritus reduces with the aim to extend safer treatment options while reducing those with more potential adverse effects. Allergen-specific immunotherapy is recommended in veterinary AD whenever feasible, in an attempt to prevent recurrence of clinical signs upon further exposure to environmental allergens.

Checklist for Managing the Chronic Canine AD

- ✓ **Check for flare factors**
  - Check for **fleas**: flea therapeutic trial: Capstar or Comfortis
  - Check for a new **adverse food reaction**: elimination diet
  - Check for **infection:** cytology; topical or systemic antimicrobial treatment
- ✓ **Improve skin and coat care:**
  - **Bath with a non irritating shampoo**
  - **Use topical humectants and moisturizers after bathing**
  - **Use topical lipids for barrier function**
  - **Begin dietary supplementation with essential fatty acids**
  - **Consider dietary supplementation with other nutrients**
- ✓ **Reduce pruritus and skin lesions:**
  - Topical corticosteroids or tacrolimus (local lesions)
  - Oral corticosteroids or cyclosporine (widespread lesions)
  - Use corticosteroid sparing agents: antihistamines, omega 3 FA
- ✓ **Long term prevention**
  - Immunotherapy

References

1. Olivry T, and DeBoer D, 2010. Treatment of canine atopic dermatitis: 2010 clinical practice guidelines from the International Task Force on Canine Atopic Dermatitis. Veterinary Dermatology 21 (3): 233-248.
2. Olivry T, and Sousa C, 2001. The ACVD task force on canine atopic dermatitis (XIX): general principles of therapy. Veterinary Immunology and Immunopathology 81: 311-316.
3. Wollenberg A, and Schnopp C, 2010. Evolution of conventional therapy in atopic dermatitis. Immunology and Allergy Clinics of North America 30 (3): 351-68.
4. Plotz S, and Ring J, 2010. What's new in atopic eczema? Expert Opinion on Emerging Drugs 15 (2): 249-67.
5. Simpson E, 2010. Atopic dermatitis: a review of topical treatment options. Current Medical Research and Opinion 26 (3): 633-640.
6. Olivry T, and Sousa C, 2001.The ACVD task force on canine atopic dermatitis (XX): glucocorticoid pharmacotherapy. Veterinary Immunology and Immunopathology 81: 317-322.
7. DeBoer D, and Marsella R, 2001. The ACVD task force on canine atopic dermatitis (XII): the relationship of cutaneous infections to the pathogenesis and clinical course of canine atopic dermatitis. 81: 239-249.
8. Darsow U, Wollenberg A, et al., 2010. ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. Journal of the European Academy of Dermatology and Venereology 24(3):317–28.
9. Guaguere E, 1996. Topical treatment of canine and feline pyoderma. Veterinary Dermatology 7 (3): 145-151.
10. Fraser J et al, 2004. An in vitro study of the anti-microbial efficacy of a 1% silver sulphadiazine and 0.2% chlorhexidine digluconate cream, 1% silver sulphadiazine cream and a silver coated dressing. Burns 30: 35–41.
11. Silver S 2003. Bacterial silver resistance: molecular biology and uses and misuses of silver compounds. FEMS Microbiology Reviews 27: 341-353.
12. Nuttal T et al., 2009. Efficacy of a 0.0584% hydrocortisone aceponate spray in the management of canine atopic dermatitis: a randomized, double blinde, placebo-controlled trial. Veterinary Dermatology 20 (3): 191-198.
13. Olivry T, Foster A, et al., 2010. Interventions for atopic dermatitis in dogs: a systematic review of randomized controlled trials. Veterinary Dermatology 21 (1): 4-22.
14. Ahlstrom L et al., 2010. Barazone decreases skin lesions and pruritus and increases quality of life in dogs with atopic dermatitis: a randomize, blinded, placebo-controlled trial. Journal of Veterinary Pharmacology and Therapeutics 33 (6): 573-582.
15. Marsella R et al., 2004. Investigation on the clinical efficacy and safety of 0.1% tacrolimus ointment (Protopic) in canine atopic dermatitis: a randomized, double-blinded, placebo-controlled, cross-over study. Veterinary Dermatology 15 (5): 294-303.
16. Bensignor E and Olivry T, 2005. Treatment of localised lesions of canine atopic dermatitis with tacrolimus ointment: a blinded randomized controlled trial. Veterinary Dermatology 16 (1): 52-60.
17. Gooding S, Canter P, et al., 2010. Systematic review of topical capsaicin in the treatment of Pruritus. International Journal of Dermatology 49: 858–865.
18. Marsella R, Nicklin C, et al., 2002. The effects of capsaicin topical therapy in dogs with atopic dermatitis: a randomized, double-blinded, placebo-controlled, cross-over clinical trial. Veterinary Dermatology 13 (3): 131-139.
19. Marsella R and Samuelson D. 2009 Unraveling the skin barrier: a new paradigm for atopic dermatitis and house dust mites. Veterinary Dermatology 20: 533–40.
20. Loflath A, von Voigts-Rhetzet A, et al., 2007. The efficacy of a commercial shampoo and whirlpooling in the treatment of canine pruritus – a double-blinded, randomized, placebo-controlled study. Veterinary Dermatology 18 (6): 427-431.

21. Abramovits W and Boguniewicz M. 2006 A multicenter, randomized, vehicle-controlled clinical study to examine the efficacy and safety of MAS063DP (Atopiclair) in the management of mild to moderate atopic dermatitis in adults. Journal of Drugs in Dermatology 5:236-44.
22. Abramovits W, and Perlmutter A. 2006 MimyX cream. Skinmed 5:29-30.
23. Simpson E et al. 2008 EpiCeram for the treatment of mild-to-moderate Atopic Dermatitis – A Pilot Study. International Investigative Dermatology Meeting, Kyoto, Japan.
24. Fluhr J et al, 2008. Glycerol and the skin: holistic approach to its origin and Functions. British Journal of Dermatology 159: 23–34.
25. Piekutowska A, and Pin D, et al., 2008. Effects of a topically applied preparation of epidermal lipids on the *Stratum corneum* barrier of atopic dogs. Journal of Comparative Pathology 138 (4): 197-203.