

## **Defective Skin Barrier in Canine Atopic Dermatitis What's Wrong and Can We Fix It?**

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Allergic pruritic skin disease of dogs had been equated with allergic upper respiratory disease since the mid-1960's.<sup>1</sup> Whether cutaneous signs and respiratory signs occurred together or separately, the disease erroneously became referred to as allergic inhalant dermatitis (AID). It was thought that dogs would become sensitized to environmental allergens through the respiratory tract, allergen-specific IgE antibodies would be produced in genetically predisposed individuals and these antibodies would bind mast cells and basophils in the dermis. Upon re-exposure to the offending allergen, mast cells and basophils would degranulate resulting in the release of inflammatory cytokines leading to erythema and pruritus.

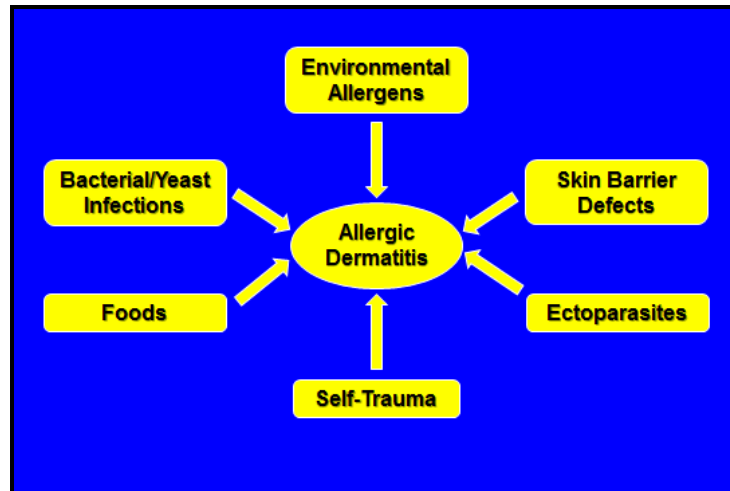
In fact, respiratory disease is rarely seen with canine allergic skin disease. Thus, the term AID has been replaced with canine atopic dermatitis (AD) now defined as a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features associated with IgE antibodies most commonly directed against environmental allergens.<sup>2</sup> Since this definition was adopted by the International Task Force on Canine Atopic Dermatitis in 2006,<sup>2</sup> new research suggests that canine AD is a multifaceted disease determined by a combination of genetic and environmental factors affecting both the immunologic response as well as primary or secondary skin barrier dysfunction.<sup>3</sup> Instead of through the respiratory tract, sensitization to environmental allergens appears to occur directly in the skin after cutaneous penetration<sup>4</sup> and skin barrier dysfunction may increase the risk of allergic sensitization.<sup>5</sup> This is the reason why clinical signs of AD are seen in areas of the skin with contact exposure to environmental allergens.

### **Canine Atopic Dermatitis with Secondary *Malassezia* Infection**



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In addition to genetic and environmental factors and skin barrier abnormalities, concurrent allergic diseases and triggering factors may contribute to the severity of allergic skin disease in general.

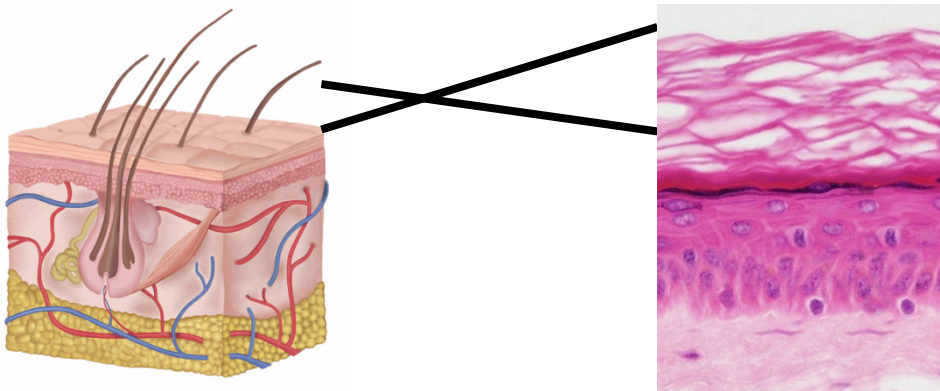


Secondary bacterial colonization and infection is of special concern because 1) bacterial pyoderma is commonly seen in clinical practice, 2) 60% of recurrent pyoderma may be associated with canine AD<sup>6</sup> and secondary infections aggravate clinical signs,<sup>7</sup> 3) staphylococcal colonization is increased in atopic skin,<sup>8</sup> 4) staphylococcal antimicrobial resistance is increasing in veterinary practice,<sup>9</sup> and 5) staphylococcal colonization has been demonstrated to disrupt human skin barrier function and further contribute to inflammation.<sup>10</sup>

### **The Skin Barrier in Canine Atopic Dermatitis**

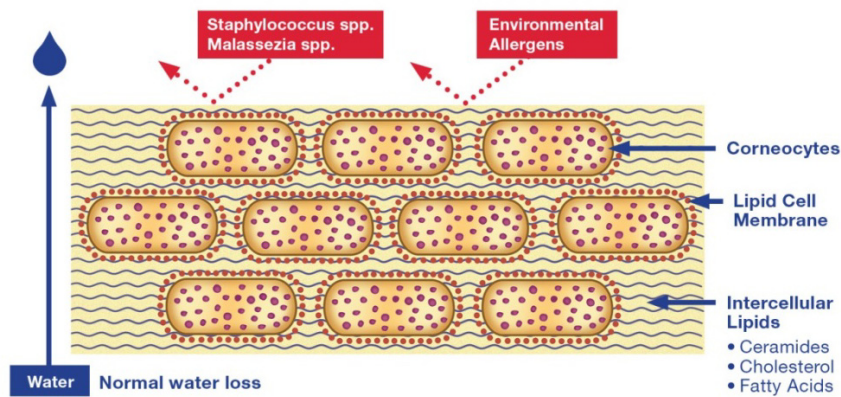
The stratum corneum is the primary protective layer of the skin responsible for control of water loss, referred to as transepidermal water loss (TEWL), and protection from penetration of environmental allergens and microbial pathogens.

#### **Canine Stratum Corneum**



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## Healthy Skin Barrier

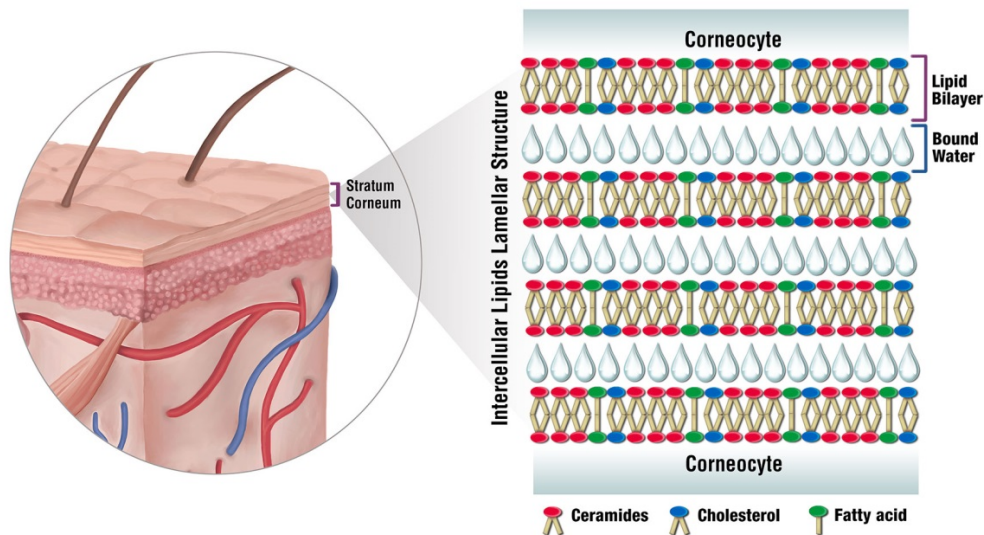


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The evidence to support stratum corneum dysfunction in canine AD has been critically reviewed,<sup>3,11</sup> and primary or secondary functional, biochemical and ultrastructural abnormalities have been documented:

- 1) In spite of technical limitations associated with measuring water loss through the skin of dogs, increased TEWL as a measure of potential barrier dysfunction has been documented in dogs with spontaneous<sup>12</sup> and experimental<sup>13</sup> AD. Lesional skin and AD predilection sites show greater water loss than visibly normal skin.
- 2) Intercellular stratum corneum lipids are important for normal barrier function. The lipids are comprised of ceramides, cholesterol and free fatty acids and highly-organized into multilayered lipid lamellae.

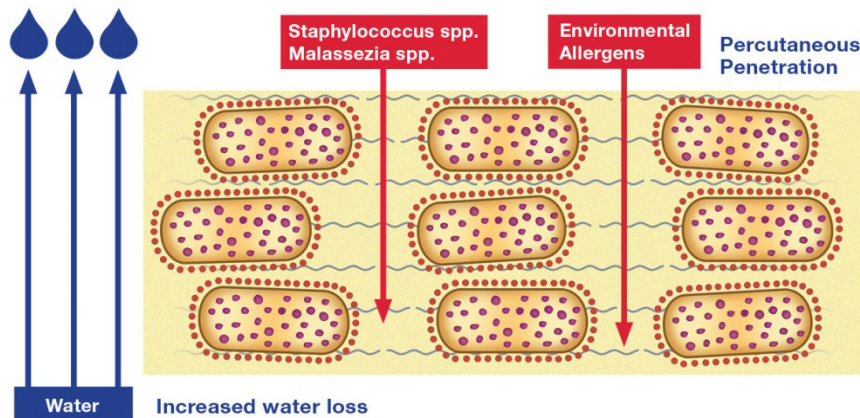
### Stratum Corneum Intercellular Lipid Lamellae



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In the non-lesional skin of dogs with AD, there is a decrease in the amount of lipid present and disorganization of the normal lamellar pattern and corneocytes.<sup>14,15</sup> These abnormalities are worsened with allergen challenge in dogs with experimental AD.<sup>16</sup>

## Abnormal Skin Barrier



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- 3) Ceramides are waxy lipids important in cell membranes and stratum corneum lipid bilayers to maintain barrier integrity. Total ceramides<sup>12</sup> and some ceramide subclasses<sup>17</sup> are reduced in the non-lesional stratum corneum of dogs with AD. This ceramide reduction has been associated with increased TEWL.<sup>12</sup>
- 4) Filaggrin is an epidermal protein that is incorporated into the corneocyte lipid envelope, which is partly responsible for the skin barrier function. Expression of this protein is decreased with atopic inflammation in some dogs but genetic mutations in filaggrin have yet to be documented.<sup>18,19</sup>
- 5) Removal of stratum corneum layers by tape stripping results in increased TEWL<sup>20</sup> and stronger cutaneous allergen sensitization<sup>5</sup> in dogs, thus documenting the importance of an intact stratum corneum for barrier function.

### Clinical Relevance of the Abnormal Skin Barrier to General Practice

The evidence summarized above supports primary and/or secondary defects in stratum corneum barrier function in the pathogenesis and clinical abnormalities in dogs with AD. Whether a primary genetic abnormality or a secondary abnormality precipitated by gross or subclinical cutaneous inflammation, this is a clinically relevant problem that is likely to contribute to the dog's disease throughout its life. As such, the defective skin barrier and factors (e.g. inflammation and infection) that contribute to its dysfunction should be treated using appropriate systemic (e.g. antibiotics, glucocorticoids, cyclosporine, oclacitinib, omega-3 fatty acids, allergen-specific immunotherapy, antihistamines) and topical therapy for acute flare-ups of AD and prophylactically in an attempt to decrease frequency and severity of these flare-ups.

<b>Goals of Topical Therapy in Canine Atopic Dermatitis</b>
<b>Gently remove environmental allergens and clean the skin surface</b>
<b>Treat and control recurrent bacterial and yeast skin infections</b>
<b>Treat and control inflammation and pruritus</b>
<b>Hydrate the epidermis</b>
<b>Restore the defective stratum corneum barrier</b>

### ***Cleansing, Moisturizing and Hydrating Agents***

Water itself has cleansing, hydrating and cooling effects, especially when used along with effective emollients and humectants. Shampoos with mild surfactant cleansing systems and cool water baths are utilized 1-2 times per week to gently remove allergens, microbial pathogens and other debris from the skin surface. Immediately after a shampoo when the skin is still wet, a leave-on aqueous or crème rinse or spray should be applied to potentially increase residual moisturizing and barrier support activity. Forced air dryers should not be used in these patients to prevent further drying of the stratum corneum. Rinses and sprays can also be used on affected areas and AD predilection sites between shampoos. Cool water rinses, cool water wipes, commercial moisturizing wipes and antibacterial wipes (Preva, Bayer) can be used daily as needed on contact areas of the body with the goal to decrease exposure of the defective barrier to environmental allergens and microbial pathogens. This may be beneficial especially after dogs have been outside with allergen exposure during times of high pollen counts.

Cleansing and moisturizing products with various combinations of emollients, emulsifiers, humectants, fatty acids and ceramides are used to address multiple aspects of the defective epidermal barrier. Ingredients incorporated into such products may include various oils, lanolin, propylene glycol, glycerin, urea, lactic acid, ceramides, omega-6 fatty acids and colloidal oatmeal. Pramoxine, diphenhydramine, hydrocortisone and triamcinolone are used when anti-inflammatory and antipruritic activity is desired such as for acute atopic flare-ups. Some of the shampoos in these categories include Allermyl (Virbac), AvenaLyt (Bayer), Cortisoothe (Virbac), DermAllay (Dechra), Dermal-Soothe (Vétoquinol), Douxo Calm (Sogeval), Epi-Soothe (Virbac), HyLyt (Bayer), and Relief and Relief HC (Bayer). Rinse and spray options include DermAllay (Dechra), Dermal-Soothe (Vétoquinol), Douxo Calm (Sogeval), Epi-Soothe (Virbac), Genesis (Virbac), HyLyt (Bayer), Relief (Bayer), ResiCort (Virbac), ResiSoothe (Virbac).

As stated above, these products are indicated to gently cleanse and moisturize the skin and mechanically remove environmental allergens. It is difficult to critically assess effectiveness of individual ingredients and formulations for barrier restoration at this time since published clinical evidence is lacking. Until such studies are available, selection of specific products is based on the practitioner's experience and clinical observations.

### ***Antimicrobial Agents***

As described above, secondary bacterial colonization and infection is an important contributing factor to skin barrier disruption and aggravation of clinical signs of canine AD. Secondary *Malassezia* overgrowth, infection and hypersensitivity reactions may also play a role in patients with AD.<sup>21,22</sup> Because of increasing staphylococcal resistance to commonly used systemic antibiotics, topical antimicrobial therapy is strongly recommended to minimize the repeated use of systemic antibiotics including helping prevent recurrence of superficial bacterial folliculitis while diagnostic procedures for primary underlying skin diseases are pursued.<sup>23</sup>

A recent literature review was published which evaluated the 9 *in vitro* and 21 *in vivo* studies on topical antimicrobial treatment of skin infections.<sup>24</sup> The authors concluded that there is good evidence to recommend  $\geq$  2% chlorhexidine against bacteria, 2% chlorhexidine - 2% miconazole against bacteria and *Malassezia* and good but lesser quality evidence to recommend 2-3% benzoyl peroxide against bacteria and yeast. However, benzoyl peroxide has potent keratolytic and degreasing activity and should not be considered for initial or long-term use in dogs with AD due to the potential to further disrupt the stratum corneum barrier.



Shampoos are commonly used 2-3 times a week with a 10 minute contact time until resolution of infection and then every 7-14 days as needed to prevent recurrence.<sup>24</sup> On non-shampoo days and when owners cannot bathe their pets, sprays, mousses, rinses, lotions and wipes are recommended. Some of the products in these categories include those with chlorhexidine: ChlorhexiDerm 4% (Bayer), Douxo Chlorhexidine PS (Sogeval), Hexadene (Virbac), TrizChlor 4 (Dechra); chlorhexidine and miconazole: Malaseb (Bayer), MiconHex + Triz (Dechra); chlorhexidine and ketoconazole: KetoChlor (Virbac); and nisin: Preva Wipes (Bayer).

### ***Ceramides and Fatty Acids***

Skin barrier impairment, as described above, has been linked in part to lower levels of ceramides, cholesterol and free fatty acids. Therefore, there has been interest in topical application of these and other molecules which may result in normalization of the epidermal lipids and clinical improvement in canine AD. Some therapeutic studies have demonstrated improvement in barrier structure, biochemistry and function and some have demonstrated improvement in clinical condition, but direct correlation between barrier improvement and clinical signs has yet to be documented.

The lipid composition and ultrastructural integrity of the stratum corneum can be improved with a topical ceramide, cholesterol and free fatty acid-containing emulsion (Allerderm Spot-On, Virbac) administered twice weekly for 3 weeks.<sup>15,25</sup> Corresponding clinical improvement was not assessed in the studies. An open pilot study in dogs with atopic dermatitis reported variable clinical response with the same product applied twice weekly with benefit at 4-6 weeks and maximum response at 8-12 weeks.<sup>26</sup> A yet unpublished double-blinded, randomized, controlled study of 32 dogs with atopic dermatitis assessed this product applied three times weekly for 4 weeks.<sup>27</sup> The Canine Atopic Dermatitis Extent and Severity Index (CADESI) in the treated group was significantly decreased when compared to the control group at day 28 while TEWL was variable and pruritus was not assessed. At the time of this review, this product was no longer marketed in the United States.

A topical formulation containing plant-derived essential oils and polyunsaturated fatty acids (Dermoscent Essential 6, Laboratoire de Dermo-Cosmétique Animale) was developed to replenish the lipid film and hydrate and deodorize the skin. When added to a canine *in vitro* skin equivalent model, the resultant stratum corneum was more dense and compact, and the ceramide percentage in the stratum corneum lipids was significantly increased.<sup>28</sup> The spot-on formulation of this product was evaluated in a multicenter, randomized, double-blinded, placebo-controlled field study on 48 dogs with atopic dermatitis.<sup>29</sup> It was applied as directed once per week for 8 weeks to the dorsal neck. There was significantly more improvement in pruritus and CADESI scores in the treated group than in the placebo group. Improvement was seen in both severely and mild-moderately affected dogs. No adverse effects were seen during the study. Additionally, results of an open study in dogs with AD used this spot-on (7 dogs applied weekly) and the corresponding spray (7 dogs applied daily) for 8 weeks demonstrating significant improvement in CADESI scores and pruritus in both groups, with no difference between groups.<sup>30</sup>

Phytosphingosine, a sphingoid lipid base derived from yeast, is found in several formulations (Douxo Calm Shampoo, Spray, Mousse; Douxo Seborrhea Spot-on; Sogeval). Results of an unpublished blinded, randomized, non placebo-controlled study suggested that in dogs with allergic dermatoses the shampoo and/or spray work as well as an antipruritic shampoo (Allermyl, Virbac) used as a positive control.<sup>31</sup> There have been no reports on clinical efficacy of the other formulations.

For most of the ceramide, essential oil and fatty acid spray and spot-on products, the recommendation is to apply 1-2 times weekly to focal or multiple clinically affected areas of the skin for at least the first 4 weeks and then as needed for long-term management. They should be considered as adjunctive therapy initially and then utilized long-term prophylactically in an attempt to reduce the frequency and severity of allergic flare-ups.

## **Summary**

- Stratum corneum barrier defects are present in canine AD.
- Dogs with AD are sensitized to environmental allergens and clinical signs are exacerbated through the percutaneous route.
- Concurrent triggering factors, especially cutaneous infections, may contribute to further barrier disruption and worsening of clinical signs.
- More research is needed to determine to what degree support of the barrier results in clinical improvement and control of canine AD.
- Gentle cleansing and moisturizing shampoos, rinses, sprays and wipes are indicated to help remove cutaneous allergens and provide barrier support for long-term maintenance of AD.
- Shampoos, rinses and sprays with pramoxine and hydrocortisone are indicated to help relieve cutaneous inflammation and pruritus for flare-ups and long-term maintenance of AD.
- Antimicrobial shampoos, sprays and wipes are indicated to help treat and prevent recurrent infections associated with AD.
- Lipid emulsion and plant-derived essential oil spot-on and spray formulations have demonstrated *in vitro* and *in vivo* improvement in skin barrier and/or clinical signs of AD and may be an effective alternative to shampoos, rinses and sprays to enhance owner compliance.

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