DITCHING THE ITCH WITH A HAPPY SKIN BARRIER

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LEARNING OBJECTIVES: Learn how the epidermal barrier dysfunction and abnormal immune system response play roles in the pathogenesis of canine atopic dermatitis. Review various therapeutic modalities intended to help improve epidermal barrier dysfunction (as well as the abnormal immune system response), so as to help reduce pruritus and other clinical signs in dogs with atopic patients.

KEY SKIN PATHOPHYSIOLOGIC POINTS

- The skin is the largest organ of the body and covers most of the body
- Some skin functions
    - Anatomic and physiological barrier between animal and environment
    - Immunoregulation
    - Preventing water loss
- Major skin layers
    - Epidermis
        - Stratum basale
        - Stratum spinosum
        - Stratum granulosum
        - Stratum corneum (main layer we will focus on)
            - Major role in barrier function
            - Composed of corneocytes and intercellular lipid layers
    - Dermis
    - Subcutis
- Skin contains: blood and lymph vessels, nerves, fibroblasts, immune cells, other
- Keratinization
    - Normal maturation process of the epidermis where epidermal cells from the stratum basale morph and mature into corneocytes which then are eventually shed into the environment
    - Keratinization typically takes about three weeks in dogs, thus give therapies aimed at improving the epidermal barrier time to work (2-3 months)

ATOPIC DERMATITIS: PATHOGENESIS AND GOALS OF THERAPIES

- Oral, inhaled and percutaneous routes of allergen exposure are all important and are additive
- Percutaneous absorption of allergen is the most important route of exposure
- Route of exposure does not determine the distribution of the lesions
- Epidermal barrier is structurally abnormal or dysfunctional in atopic individuals
- Th2 >Th1 imbalance tends to allow for the production of cytokines such as IL-4, IL-5, IL-10, IL-13 and IL-31
- The epidermal barrier dysfunction and abnormal inflammatory cascade in atopic dermatitis, along with other factors (e.g. genetics, microbiome, environment, etc.), can create a vicious cycle where Th2 immunity and inflammation lead to barrier damage,

and epidermal barrier damage leads to a shift to more Th2 immunity and inflammation which leads to more epidermal barrier damage and so on
- Therapeutic modalities are aimed toward reducing inflammation as well as improving epidermal barrier dysfunction

CANINE ATOPIC DERMATITIS – DIAGNOSIS AND CLINICAL SIGNS

- Diagnosis is based on compatible history and clinical signs as well as ruling out other causes of pruritus, especially ectoparasites
- Typically starts between 6 months and 3 years of age
- Seasonal, non-seasonal or non-seasonal with seasonal flares
- Clinical signs: pruritus (main sign), erythematous macules, patches and small papules as well as excoriations, alopecia, lichenification and hyperpigmentation
- Most commonly affected areas: face, concave pinnae, ventral neck, axillae, inguinal area, abdomen, perineum, ventral tail base, paws, flexural and medial limbs, periocular and perinasal areas
- Secondary skin and ear infections are not uncommon
- Favrot's criteria can be helpful in determining if the canine patient has atopic dermatitis
    - Two versions exist where when five of the seven or eight criteria are met, there is a high likelihood that the dog has atopic dermatitis (with approximately 80-85% sensitivity and specificity)

Version 1	Version 2
- Age of onset < 3 years	- Age of onset < 3 years
- Mostly indoor lifestyle	- Mostly indoor lifestyle
- Pruritus with no lesions at onset	- Front feet affected
- Front feet affected	- Pinnae affected
- Pinnae affected	- Pinnal margins NOT affected
- Pinnal margins NOT affected	- Dorsolumbar area NOT affected
- Dorsolumbar area NOT affected	- Pruritus responsive to corticosteroids
	- Recurrent or chronic yeast infections

THERAPEUTICS AND THEIR ROLE IN IMPROVING THE EPIDERMAL BARRIER DYSFUNCTION AND REDUCING THE ABNORMAL IMMUNE RESPONSE

Avoidance of the allergen(s) causing atopic dermatitis is most ideal, but typically difficult and impractical. Aiming therapeutic modalities toward both the epidermal barrier dysfunction and the aberrant immune response potentially allows for maximal therapeutic success. While some patients will respond to one therapeutic modality, others will do best with a multimodal therapeutic approach. Setting realistic goals with clients is often helpful.

"Big Gun" and "Little Gun" Treatment Modalities

- "Big Gun" treatments: glucocorticoids, oclacitinib (Apoquel), ilunocitinib (Zenrelia) and lokivetmab (Cytopoint), cyclosporine-modified (Atopica, Cyclavance, Sporimune, Modulis), allergen-specific immunotherapy, other
- Many "Big Gun" therapies aim primarily at reducing the aberrant immune response which in turn should reduce pruritus and improve the skin barrier dysfunction
- Marsella et al evaluated house dust mite sensitized research atopic beagles who received oral prednisone (0.5 mg/kg q12h x 2 weeks, then q24h x 1 week, then every

other day), Apoquel (0.5 mg/kg q12h x 2 weeks, then q24h x 2 weeks), Cytopoint (2 mg/kg SQ once), Atopica (5 mg/kg q24h) or no treatment (control) for 28 days while being challenged twice weekly with house dust mite allergen
    - During the first 2 weeks of the study, dogs that received twice daily prednisone and Apoquel showed good clinical improvement
    - Cytopoint was beneficial in preventing allergic flares
    - Apoquel and Cytopoint were shown to have positive effects on improving skin barrier parameters
    - Atopica treated dogs improved, but not to the degree noted in dogs treated with Cytopoint or during the first two weeks of Apoquel or prednisone therapy
        - Note: Atopica can take up to six weeks to show good effect
- Allergen-specific immunotherapy (ASIT) is considered the only disease modifying treatment and is considered safe long-term.
- Many of these aforementioned therapies are well tolerated with good efficacy, however alone do not help all dogs with atopic dermatitis
- Multimodal therapy for better control canine atopic dermatitis
    - Consider multiple “Big Gun” therapies and/or adding in “Little Gun” therapies
- “Little Gun” therapies
    - Tend to be well tolerated with minimal side effects
    - May help to reduce the number or amount of other medications needed
    - May help to reduce the overall cost of treatment
    - May be the only therapy required in dogs with mild atopic dermatitis
    - Examples: topicals that contain ceramides, phytosphingosines, ophytrium, fatty acids, essential oils and/or steroids or some oral supplements such as oral fatty acids, Dermaquin, Redonyl Ultra.
    - Ceramides/ Phytosphingosines
        - Major components of the stratum corneum
        - Several (not all) studies did showed improvement of the skin barrier ultrastructurally as well as clinically
    - Ophytrium™
        - Works on skin barrier, cutaneous microbiome, inflammation
        - Douxo S3 products
        - Improvement in clinical and pruritus scores
    - Topical essential oils and fatty acids (Dermoscent Atop7)
        - Atop7 + Cytopoint versus Cytopoint alone: dogs receiving both did better and interval between Cytopoint injections was increased
            - Conclusion: There is a benefit to combination therapy
    - Topical steroids
        - After the atopic dermatitis was controlled, topical steroids applied twice weekly as maintenance were found to reduce future atopic flares in both humans and dogs
        - Adverse effects may be seen with overuse of topical steroids
    - Oral fatty acid supplementation
        - Shift inflammatory mediators towards less inflammatory mediators
        - Important in ceramide synthesis
        - Fatty acid supplementation helps ~30% of dogs with atopic dermatitis

        - Popa et al showed a significant increase in epidermal ceramides and fatty acids after treatment with a fatty acid supplement that also contained vitamins and zinc
    - Palmitoylethanolamide
        - A significant decrease in itch and skin scores was noted in an 8-week multicenter open label clinical trial where atopic dogs with moderate, non-seasonal pruritus were treated with palmitoylethanolamide ultramicronized
        - Redonyl Ultra (dogs)
        - Dermaquin (dogs and cats)
    - Hardy kiwi
        - Hardy kiwi preps were evaluated in atopic mouse model mice where the controls were dexamethasone and distilled water. Mice receiving the hardy kiwi preps showed a reduced severity of dermatitis, pruritus and a decrease in inflammatory mediators
        - Placebo-controlled clinical trial noted that hardy kiwi was a beneficial adjunctive in dogs with mild to moderate atopic dermatitis after prolonged use (2 months of treatment)
        - Dermaquin
    - Beta glucans
        - Dogs fed a diet containing beta glucans compared dogs fed the same diet without beta glucans for 90 days noted that atopic dermatitis signs improved by 63% in dogs fed the diet containing beta glucans
        - Dermaquin

SUMMARY AND TAKE-HOME POINTS

1. The skin is the largest organ of the body with functions that include a physiological barrier, immunoregulation and preventing water and electrolyte loss
2. The most important route of allergen absorption is the percutaneous route
3. Favrot's criteria may be helpful in determining if the dog has atopic dermatitis
4. Aim therapeutic modalities towards reducing inflammation and improving epidermal barrier dysfunction by using "Big Gun" therapies as well as "Little Gun" therapies
5. "Little Gun" therapies may help reduce the amount of "Big Gun" therapy needed.
6. Treating continually and early can help reduce flares and improve the overall management of atopic dermatitis in dogs.
7. Thank you for reading this. You are going to help make many itchy, atopic dogs feel better. Smile and have a great day ☺

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