

VETERINARY DERMATOLOGY

Being Proactive: A Multimodal Approach for Success

Skin and ear diseases are two of the main reasons companion animals are presented to veterinarians.^{1,2} In fact, atopy and otitis were the top two canine claims for at least two major pet insurance companies in 2017 and were within the top ten feline claims. Pyoderma was also among the top ten canine claims. This seems to correlate with many veterinarians' clinical experience of the high proportion of cases seen each week involving skin and ear problems. Clearly, skin and ear health are important aspects of companion animal veterinary medicine.

The American College of Veterinary Dermatology (ACVD) task force estimated in 2001 that 8 - 10 million dogs (15% of the population) suffer from skin disease.³ Pet allergies typically manifest as itchy, inflamed skin causing pets to scratch, lick, and chew. This in turn allows pathogen colonization. These skin disorders can be controlled, but are likely to require lifelong management.

BENEFITS TO TREATING DERM CASES

1. Prevents the condition from worsening.
2. Improves quality of life for both patient and owner.
3. Maintains the client relationship.
4. Is a continual source of revenue to the vet hospital.

DERMATOLOGY DIAGNOSTICS

Atopic dermatitis (AD) is only one of many causes of pruritus in dogs and cats. Animals with AD often also have secondary problems exacerbating their itch. It is therefore imperative to properly diagnose and treat all underlying causes of itch in order to have a successful outcome.⁴ Consequently, each pruritic animal that presents to your clinic should receive a

thorough workup for the itch to identify primary and secondary causes in an effort to develop a multimodal treatment plan and provide a long-term solution. Common etiologies for pruritus include: atopic dermatitis, adverse reactions to foods, insect hypersensitivity, ectoparasites, and bacterial and fungal infections.

The basic diagnostic workup for every pruritic patient starts with a thorough history and physical exam.⁵ Ask questions about chronicity, recurrence, previous treatments (especially history of antibiotic use), and seasonality. A minimum database for pruritic patients includes flea comb, skin scrape, and skin cytology. Bacterial culture and DTM cultures should be performed when indicated. Flea combing is not only a diagnostic aid, but helps prove to clients that fleas are present. Superficial skin scrape should be performed over a wide area to find scabies mites, and deep scrape a small area until it bleeds to find *Demodex* spp. Perform skin and ear cytology to determine if yeast or bacteria are present and to evaluate inflammatory infiltrates like neutrophils and eosinophils. Cytology can also aid in monitoring clinical progress and may be necessary at all subsequent visits.⁶

Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) is increasingly prevalent, and veterinarians must be on the lookout for resistant infections and culture every time resistance is suspected. Clinical indications for culture include deep pyoderma lesions (e.g. nodules and draining tracts), surgical site infections, non-healing wounds, mixed infections of rods and cocci, recurrent infections, and lack of response to empirical antibiotic treatment.⁷ Whenever MRSP is suspected, treatment should be based on culture and sensitivity results rather than simply choosing "big gun" antibiotics. While

awaiting results, topical therapies can and should be used.

Diagnosis of atopic dermatitis is only truly achieved after other causes of pruritus, including food allergy when the itch is non-seasonal, have been ruled out. It is based on signalment, clinical signs, and disease history.⁴ Atopic dermatitis is not diagnosed based on allergy testing as normal animals can test positive on skin and serum tests. Therefore, those tests should be utilized after the diagnosis of atopy is made to determine the specific trigger allergens for that patient and as a therapeutic tool in initiating allergen specific immunotherapy.

PATHOPHYSIOLOGY OF CANINE ATOPIC DERMATITIS

Canine atopic dermatitis (CAD) is a multifaceted disease that usually manifests between six months and three years of age.⁴ Contributing factors include both genetics and environmental conditions. These affect the immunological response and skin barrier function.⁸ In 2006, the International Task Force on Canine Atopic Dermatitis defined CAD as "a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features associated with IgE antibodies most commonly directed against environmental allergens".⁹

For decades it was theorized that dogs were exposed to allergens through inhalation, but now recent research suggests that allergen entry is through the skin.¹⁰ In this percutaneous route of exposure, loss of normal barrier function plays an important role. Allergens enter through barrier defects and contact immune cells. The main antigen-presenting cells in the epidermis are the Langerhans cells, which present processed antigen to T-lymphocytes. This then initiates the immune response.¹¹ When the immune response is triggered, there is a release of inflammatory mediators, which promotes inflammation and pruritus. *Staphylococcus* spp. colonize the damaged skin and cause more inflammation and pruritus,

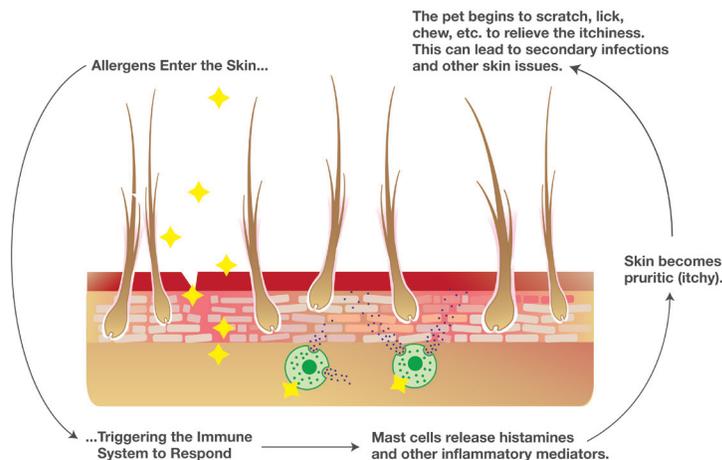


Figure 1: The faulty epidermal barrier and the self-perpetuating cycle of itch and inflammation. Note that the broken epidermal barrier allows allergens, bacteria, and yeast to penetrate into the skin. After these pathogens trigger the immune response, mast cell degranulation results in erythema and pruritus.

OTITIS EXTERNA

Otitis externa is the most common clinical sign seen in dogs with atopic dermatitis. It is thought to occur in 50-80% of atopic dogs and may be the only clinical sign in some of these cases.²⁷ Causes of otitis externa can be classified into four main categories: primary causes (e.g. allergy, foreign bodies, parasites), secondary causes (e.g. fungal, bacterial, over cleaning), predisposing factors (e.g. poor conformation, excessive moisture, polyps), and perpetuating factors (e.g. changes in microflora, damaged epidermal barrier).²⁸

creating a self-perpetuating cycle.⁸

CAD lesion distribution supports the percutaneous exposure theory, as lesions are often found in ventral hairless areas like axillae, inguinal region, abdomen, and limbs as well as perioral, periocular, and pinnae.¹¹ Primary lesions include erythematous patches and papules, but most dogs also have secondary lesions of excoriations, alopecia, lichenification, and hyperpigmentation, which are due to self trauma. Secondary infections are also common.⁴

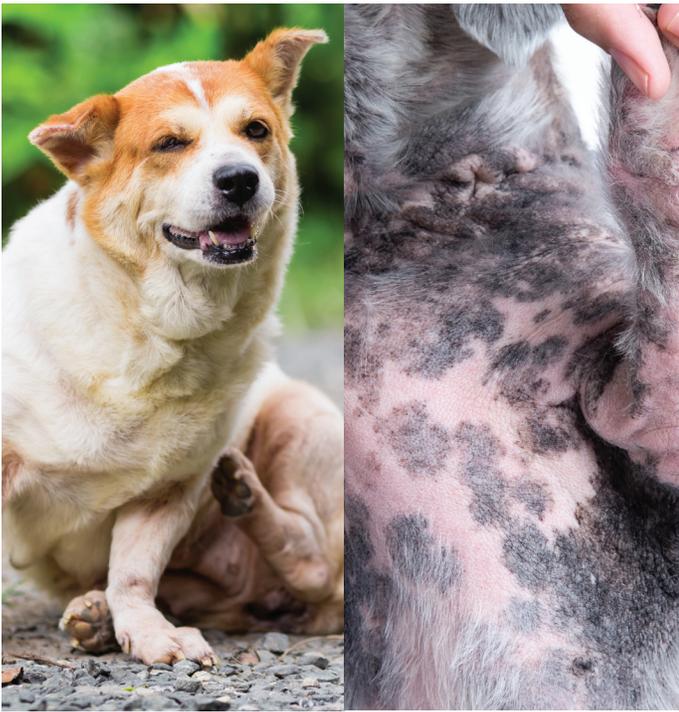


Figure 2: Atopic dogs with classic CAD distribution lesions.

TREATMENT: A MULTIMODAL APPROACH

After performing diagnostics, the next step is development of an appropriate therapeutic plan. The main goals are to bring the patient fast relief, treat and prevent infections and infestations, and prevent or minimize future flares. It is important to partner with your client and set reasonable expectations at this stage, as frustration and ongoing expense are common. Excellent client communication is essential and may require discussion with all parties in a household with multiple dog owners.

Dogs with CAD rarely only have CAD, especially at the beginning of treatment. Concurrent allergies and secondary infections frequently complicate the clinical picture and contribute to the pruritus. These have to be addressed along with the underlying atopic disease. Atopic dogs are at increased risk of developing flea allergy and food allergy when compared to non-atopic individuals, and it is not uncommon to observe multiple allergies in the same patient.⁵ Dermatologists believe there is a pruritus threshold, and multiple flare factors

are responsible for pushing an animal over the threshold, making them pruritic.¹² In those cases, elimination or control of one allergy may cause the other allergy to become subclinical. For this reason, an important part of managing these animals includes control of all the concurrent allergies of an individual patient.

An effective treatment plan for pruritic patients is multimodal, attacking the problem on several fronts. Therapies to be considered include: allergen-specific immunotherapy (ASIT), immunomodulators including glucocorticoids, infection and infestation control, supplements, diet therapy, and topicals.

CAD is almost always a life-long condition, but five percent of dogs receiving ASIT have resolution of signs without needing further treatment.^{4,13} ASIT can also decrease or eliminate other systemic drug use. It has anywhere between a 50-80% success rate. Commercially-available serum tests have variable results, and intradermal skin testing is still considered the gold standard. Advantages of ASIT include collaboration with an ACVD specialist who can manage the case and the appropriate response and make adjustments to the immunotherapy. Disadvantages include

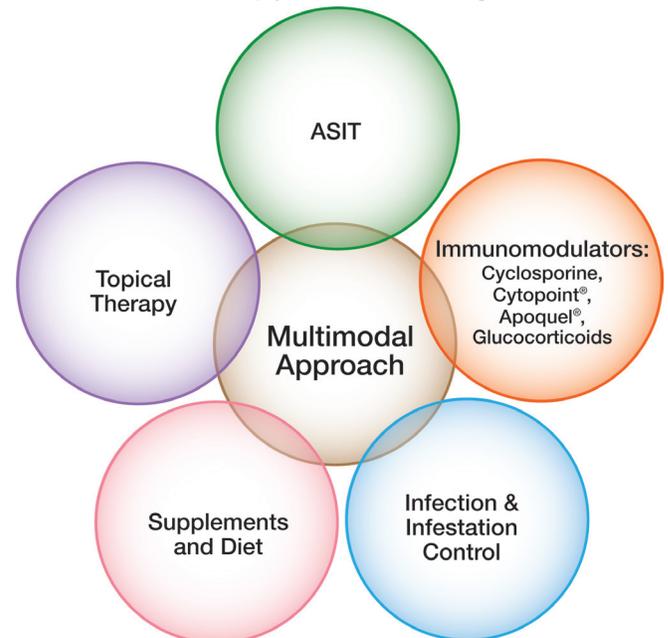


Figure 3: Multimodal approach to managing skin disease. Often several modalities must be used to treat primary and secondary causes of skin disease simultaneously.

cost (testing and treatment) and response time, as it may take 6-12 months for full immune response.

Immunomodulators, including glucocorticoids, are a powerful weapon in the arsenal to fight pruritus. These have variable onset and duration of action, cost, and safety profiles.

Glucocorticoids are economical and highly effective at stopping pruritus, but have many side effects and are not recommended for long-term use. Cyclosporine has been used successfully for many years and is available as a generic to decrease costs. Newer immunomodulators include Apoquel® and Cytopoint® from Zoetis. Not enough research has been done to evaluate using steroids and other immunomodulators concomitantly long term, but theoretically, this could lead to a higher risk of immunosuppression.¹³

To eliminate the possibility of parasites contributing to a pruritic flare, all patients should be prescribed an effective, regionally-appropriate parasite control. For most locations, this requires year-round prevention. Since another cause of pruritus is infection, appropriate antimicrobial therapy should be initiated when necessary. Choices should be based on compatible clinical signs and cytology, using culture and sensitivity when appropriate.

Dermatology patients should be on supplemental support and a high-quality diet, even if they are not food allergic. Essential fatty acids improve coat quality and reduce transepidermal water loss.⁴ The free form lacks a glycerol backbone so metabolism is not required. This provides greater bioavailability of EPA and DHA.¹⁴ Palmitoylethanolamide is another supplement providing skin support, and is discussed below.

An important component of any multimodal dermatology approach is topical therapy. Topicals aid in removal of allergens and infectious agents, help control pruritus, and repair the skin barrier. Use of topical therapy is important for successful outcomes.



TOPICAL THERAPY & EPIDERMAL BARRIER

Topical therapies like shampoos, mousses, sprays, and wipes are underused in veterinary dermatology, but provide numerous benefits to these cases. When used as maintenance therapy, they can even reduce the frequency and severity of recurrent pyoderma.¹⁵

Use of topical therapies has many advantages,¹⁶ and these can be seen in the blue box on page six. These advantages are sometimes dismissed because topical therapy can be time consuming and labor intensive. However, most owners are willing to partner with their veterinarian by adding topicals to the multimodal treatment plan when properly educated on why the prescribed therapy is important and when appropriate selections fit into their lifestyle.

Several newer technologies have been developed that provide distinct benefits for patients with skin problems including atopic dermatitis. One of the most important of these is ceramides. Ceramide deficiency is an important part of skin disease, especially in atopic patients. It causes increased transepidermal water loss and decreased barrier function. Topical application of ceramide lipid complexes replenish depleted ceramides and ameliorate clinical signs.^{8,19}

A BRIEF REVIEW OF SKIN ANATOMY

Familiarity with basic dermal anatomy aids in understanding how to best treat conditions involving this important organ. The skin is divided into three distinct layers: the hypodermis (subcutis), the dermis, and the epidermis.

The hypodermis is the insulation layer and is composed mostly of fat, vasculature, and glands. The dermis is comprised of hair follicles and sebaceous glands. It is an integral part of the connective tissue system and provides tensile strength and elasticity for the skin. Cell growth, proliferation, adhesion, migration, and wound healing all begin in the dermis.

The epidermis is the outermost layer. It is composed of multiple layers of cells which are defined by their position and morphology. Eighty-five percent of the cells in this layer are keratinocytes (corneocytes). The epidermis is in contact with the environment and consists of four distinct layers: the stratum basale (innermost), stratum spinosum, stratum granulosum, and the stratum corneum (outermost).⁵

The stratum corneum is the most important layer for barrier function. Structurally, it is a layer of cornified keratinocytes (corneocytes) bound together by an extracellular lipid matrix composed of free fatty acids, cholesterol, and ceramides. The keratinocytes and extracellular matrix form a “brick-and-mortar” system which maintains the skin barrier, preventing invasion of allergens and infectious agents.^{5,17} Ceramides in particular play a crucial role in this barrier, representing 50% of the lipids in the stratum corneum. They are composed of a fatty acid and sphingoid base. One type of sphingoid base is phytosphingosine.⁸ When the stratum corneum is compromised, skin inflammation and irritation occur as allergens, bacteria, and fungi penetrate the broken barrier.

Two electron microscopy studies report similar findings of defective epidermal lipid barrier in atopic dogs.^{18,19} In atopic dogs, the deposition of lipid is more heterogeneous in the stratum corneum as compared to healthy controls. Many areas in the inter-corneocyte spaces lack lipids or often exhibit an abnormal lipid structure. In the healthy canine stratum corneum, lipids are well arranged in compact sheets and fill in the space between cell layers.

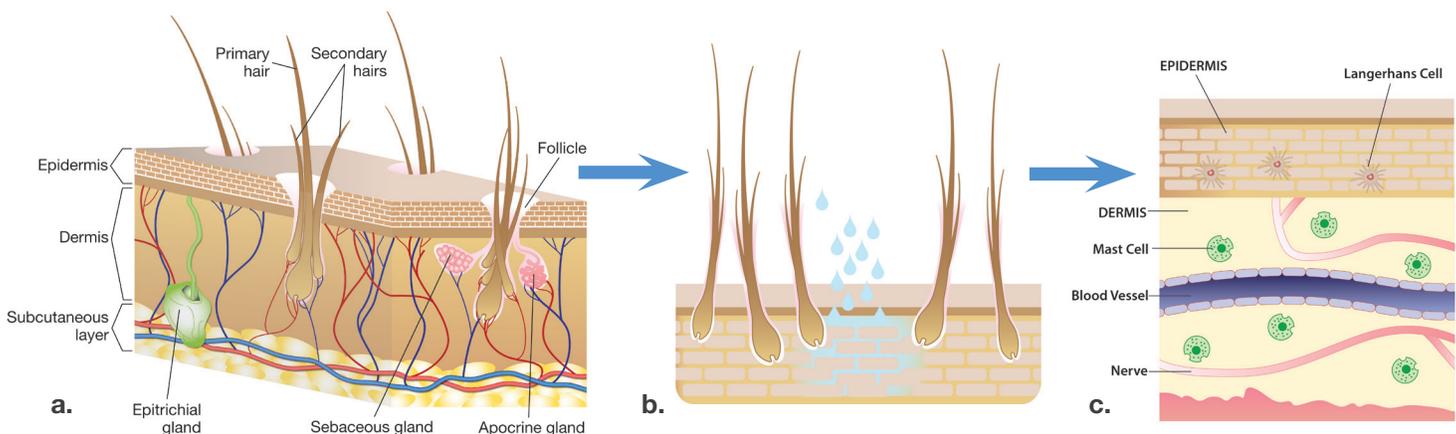


Figure 4: **a.** The normal haired skin of the dog. Note there are three distinct layers: the dermis, epidermis, and subcutaneous layers. There are three types of secretory glands: epitrichial, sebaceous, and apocrine. Dogs also have multiple hairs per follicle. **b.** The normal epidermal barrier of a dog. The diagram shows the corneocytes and lipid working together to form a "brick-and-mortar" barrier. **c.** Depiction of the epidermis and dermis showing two of the major cells involved in dermatitis: Langerhans cells and mast cells.

Another technology is Tris-ethylene diamine tetra-acetic acid (tris-EDTA). By itself, tris-EDTA is bacteriostatic, but when used in combination with an antibiotic, it becomes bacteriocidal, decreasing the MIC of even multi-drug resistant antibiotics. It works by damaging the outer wall of bacteria, making the organisms more permeable, and has a synergistic effect with antibiotics and other agents like chlorhexidine.^{21,22} Tris-EDTA is also an antibiofilm agent and may help overcome resistance induced by upregulation of *Pseudomonas* spp. efflux pumps.^{33,21}

Other technologies include colloidal silver/silver sulfadiazine, which has some antimicrobial effects; novasomes, which are microvesicles providing long-lasting moisturizing effects; and spherulites, which break down slowly over time, releasing specific ingredients.^{23,34}

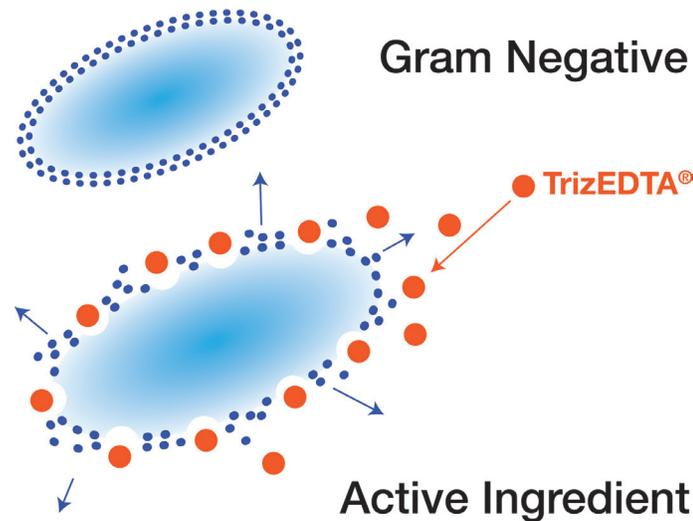


Figure 6: Graphic illustration of Dechra TrizEDTA® technology. TrizEDTA helps to perforate the cell wall. This action on the pathogen potentiates antimicrobial killing power.^{21,22}

ADVANTAGES OF TOPICAL THERAPY¹⁶

- Remove allergens from coat/skin
- Repair barrier function
- Minimal side effects
- Easy access to skin
- Provide immediate relief
- Aid in reducing the need for systemic treatment
- Moisturize
- Remove debris
- Remove inflammatory mediators and pathogens
- Reduce recurrence of disease when used as maintenance therapy

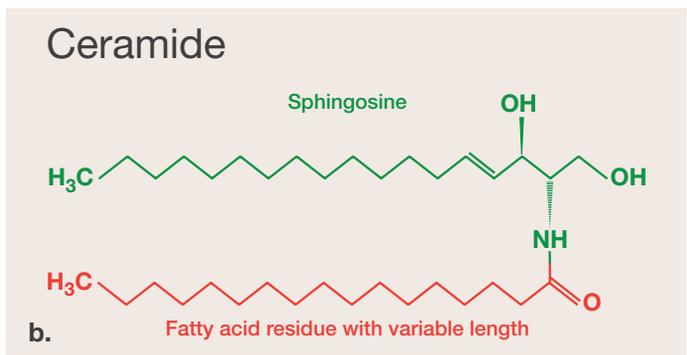
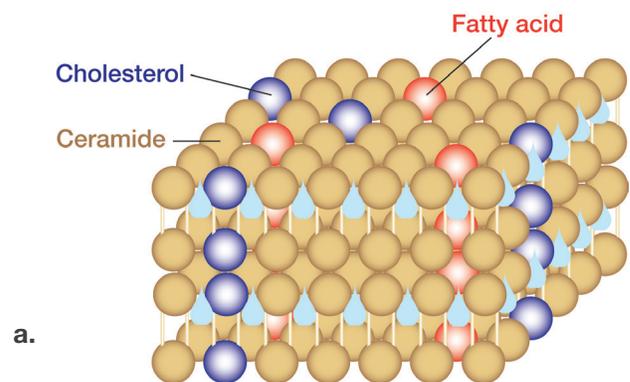


Figure 5: a. The lipid portion of the epidermal barrier. This lipid portion is comprised of ceramides (50%), cholesterol (25%), and fatty acids (25%).^{8,17} Topical application of ceramides in patients with atopy may help repair the defective epidermal barrier.¹⁹
b. Chemical structure of a ceramide shows the fatty acid chain and the secondary sphingosine chain.

CHOOSING THE RIGHT TOPICAL FOR EACH PATIENT

When selecting topical therapy, consideration should be given to the agents used and their efficacy for the particular clinical signs exhibited. Shampoos can be categorized as antimicrobial (antifungal and antibacterial), anti-seborrheic, anti-pruritic, moisturizing, and general cleansing. The chart below shows common active ingredients and their indications.

With the increasing prevalence of MRSP and other resistant infections, antimicrobial shampoos are a vital component of dermatology treatment plans. Antibacterial agents include chlorhexidine, benzoyl peroxide, and acetic and boric acids. Chlorhexidine especially has broad spectrum activity, working against both gram-negative and gram-positive bacteria as well as *Malassezia* yeast.²³ It also has been shown to have residual activity for at least 10 days after application. In a study examining activity in spray form against *Staphylococcus pseudintermedius*, the zone of inhibition around a combination of 2% miconazole, 2% chlorhexidine, and tris-EDTA was larger than the more concentrated chlorhexidine formulations, showing a synergistic effect with miconazole.^{24,25} Antifungal agents include miconazole (which is also synergistic with chlorhexidine against *Malassezia*²³), ketoconazole, climbazole, chlorhexidine, and lime sulfur.

Once a diagnosis of MRSP has been made, systemic antibiotic options are often limited, with potential for adverse effects. Therefore, topicals have become the first-line treatment. Options include 2% mupirocin, chlorhexidine, tris-EDTA, benzoyl peroxide, and dilute bleach. These come in a variety of formulations: shampoos, conditioners, sprays, mousses, wipes, and ointments.⁷

Antiseborrheic shampoos reduce basal cell division to normalize keratinocyte turnover and eliminate excess corneal layers. Several different antiseborrheic ingredients are used in veterinary topical products. Benzoyl peroxide is antibacterial in addition to being antiseborrheic. It reduces sebaceous gland activity and has a follicular flushing activity. Salicylic acid and sulfur have a synergistic effect when used in equal concentrations that is keratolytic and softens the corneal layer.¹⁶

Safflower oil and colloidal oatmeal have antipruritic effects by protecting and moisturizing the skin. These can be used regularly to maintain healthy skin. Other antipruritic agents include topical anesthetics, antihistamines, and glucocorticoids.

ACTIVE INGREDIENTS	ANTI-PRURITIC	ANTIBACTERIAL	ANTIFUNGAL	ANTISEBBORHEA	DRYING/DEGREASING	FOLLICULAR FLUSHING	SKIN BARRIER REPAIR
Acetic Acid		X	X		X		
Boric Acid		X	X		X		
Benzoyl Peroxide	X	X		X	X	X	
Ceramides	X						X
Chlorhexidine		X	X*				
Colloidal Oatmeal	X						
EFA's	X						X
Hydrocortisone	X						
Ketoconazole			X				
Miconazole		X	X				
Salicylic Acid		X		X			
Sulfur		X	X	X	X		
TrizEDTA		X					

Figure 7: Commonly used topical therapy active ingredients and their indications. *Note that Chlorhexidine efficacy against yeast organisms is at a concentration of >3%.



DECHRA DERMATOLOGY

Dechra offers a complete line of topical products that provide antimicrobial, anti-seborrheic, anti-pruritic, moisturizing, and general cleansing activity. Our topical products are available as shampoos, spray conditioners, mousses, and wipes.

MICONAHEx+Triz® Shampoo, Spray Conditioner, Wipes, and Mousse combine the synergistic effects of 2% miconazole and 2% chlorhexidine with Dechra's patented, USP-grade Triz-EDTA®. For support of healthy skin for animals with conditions responsive to miconazole and/or chlorhexidine. The shampoo lathers nicely, and all have a lemongrass and lavender scent. These products also contain the full ceramide complex.

TrizCHLOR® 4 Shampoo, Spray Conditioner, Wipes, and Mousse consist of 4% chlorhexidine and our patented Triz-EDTA® and has an apple-kiwi scent.

Mal-A-Ket® Shampoo and Wipes and Mal-A-Ket® Plus Spray Conditioner consist of 2% Acetic acid, 2% chlorhexidine and 1% Ketoconazole our patented Triz-EDTA®. For support of healthy skin for animals with conditions responsive to ketoconazole and/or chlorhexidine. 2% Acetic acid: Cleansing, acidifying, antibacterial

For general cleansing and moisturizing and to promote relief of dry, itchy, sensitive skin. **DERMALLAY™ Oatmeal Shampoo and Spray Conditioner** contain hydrolyzed oat protein for itch relief, ceramide complex, and safflower oil. It is apple scented.

ENSURING SUCCESSFUL TREATMENT OUTCOMES

Many veterinary practices fail their clients and patients through a lack of effective communication. Dermatology patients are unlikely to ever be “cured”, instead requiring lifelong management and care. Written instructions and brochures are helpful resources for client education. Expectations should be framed from the beginning, building a treatment plan that engages the client's help and empowers them to take charge of their pet's health.²⁹

For more information please contact your Dechra Veterinary Account Manager

Visit our website: www.dechra.co.nz

Call us on: 0800 479 838



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