Topical Therapy for Infectious and Allergic Dermatoses

Kenneth W. Kwochka, DVM, Diplomate ACVD
Veterinary Manager, Health and Wellness, Bayer Animal Health

BASIC PRINCIPLES OF TOPICAL THERAPY

- Client education on topical therapy with written discharge instructions is critical for proper use of these products.
- The medical and financial advantages of using topical therapy should be discussed. A topical treatment and maintenance program may reduce the need for long-term continual systemic medications.
- Inform owners that medicated shampoos do not typically lather well so that they do not over apply the products. It is helpful to use a general cleansing shampoo prior to the medicated shampoo to clean the skin and hair coat and reduce the amount of the more expensive medicated product.
- If necessary for the skin disease to be adequately treated, have the hair coat cut short to facilitate application of the topical product. This is especially important for long-term management of infectious diseases in longhaired dogs.
- Contact time, contact time, contact time – at least 10 minutes for most shampoos.
- Monitor for possible irritancy or hypersensitivity reactions.
- Use tepid water for bathing and cool water for rinsing when the skin is inflamed and the patient pruritic.
- At least twice weekly application is indicated initially followed by application as needed – usually every 7-14 days.
- Use sprays, rinses, flushes, mousses or wipes between shampoos for more continual and residual activity.
- Cytology, cytology, cytology – to select the product with the correct active ingredient(s) and to change treatment if necessary at the recheck visit.

SELECTION AND USE OF TOPICAL AGENTS

The main clinical indications for topical therapy are divided into microbial infections (bacterial and fungal) and inflammatory/allergic dermatoses. Antiseborrheic shampoos containing sulfur, salicylic acid, tars and other ingredients for primary scaling disorders (primary idiopathic seborrhea) were commonly used in the past. However, it is now clear that most of these dogs did not have primary scaling disorders but scaling and crusting secondary to infections and allergies. Thus, antiseborrheic shampoos are rarely needed in favor of addressing the specific infection and/or inflammatory dermatosis.

Microbial Infections

This is the most common indication for topical therapy. Clients should be strongly encouraged to use topical products to assist in the treatment and control of recurrent infections. The key to successful long-term management of recurrent infections is to find the cause. The infections are generally associated with underlying allergies (atopic dermatitis, cutaneous adverse reactions to foods, parasitic hypersensitivities, etc.) or endocrinopathies (hypothyroidism, hyperadrenocorticism). However, even patients successfully managed for their allergies on restricted diets, allergy immunotherapy and/or pharmacologic agents such as glucocorticoids, modified cyclosporine (Atopica®, Novartis/Elanco) or oclacitinib (Apoquel®, Zoetis) will have periodic flare-ups and develop cutaneous infections.

<u>Bacterial Pyoderma</u>

The most common organism isolated from pyoderma lesions in dogs is *Staphylococcus pseudintermedius*.

Staphylococcus schleiferi and *S. aureus* are other important pathogens.[1] *Pseudomonas aeruginosa* is rarely isolated from the skin.

The prevalence of staphylococcal resistance has increased worldwide in recent years with some dermatology referral clinics reporting anecdotally that up to 70% of pyoderma referral cases are associated with methicillin- or multi-drug-resistant staphylococci. Although not as common, staphylococcal resistance is also of concern in general practice due to the apparent potential for rapid development of antimicrobial resistance. In a Canadian study, 60 dogs with pyoderma associated with methicillin-sensitive *S. pseudintermedius* (MSSP) were treated with a course of systemic antibiotics.[2] After one course of treatment, follow-up cultures from the skin now revealed carriage of methicillin-resistant *S. pseudintermedius* (MRSP) in 28.3% of the dogs.

Methicillin-resistant *S. pseudintermedius* carriers may be at increased risk of development of infections in certain situations.[1] Risk factors may include antimicrobial administration, hospitalization or surgery within 30 days prior to the onset of infection.[3]

On a positive note, it has been demonstrated that topical therapy may reduce the duration of systemic antibiotic use[4] and that topical therapy alone may resolve superficial bacterial infections.[5] Additionally, in a randomized, blinded study a 4% chlorhexidine digluconate shampoo and solution were as effective as amoxicillin–clavulanic acid in the treatment of canine superficial pyoderma.[6]

In their 2014 guidelines for the diagnosis and antimicrobial therapy of canine superficial pyoderma, the Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases stated that…

"Topical therapy alone (without co-administration of systemic antimicrobial drugs) is encouraged as a desirable and recommended approach to the treatment of superficial bacterial folliculitis (SBF) unless precluded by owner and/or patient factors. This is particularly true in the following circumstances: (i) localized lesions of SBF; (ii) early stages of generalized SBF when lesions are mild; and (iii) to help prevent recurrence of SBF while diagnostic procedures for primary underlying skin disease are pursued."[7]

Chlorhexidine

Chlorhexidine is an antiseptic agent with activity against the common bacteria causing cutaneous infections. It is bactericidal by acting on the cytoplasmic membrane. Stability, bioavailability, adherence characteristics and antimicrobial activity can be significantly affected by the formulation into which chlorhexidine is incorporated.[8,9,10,11]

Dermatologists typically use 3% or 4% chlorhexidine shampoos (ChlorhexiDerm® 4%, Bayer; Hexadine®, Virbac; TrizChlor™ 4, Dechra) in their bacterial pyoderma cases. Ideally, a shampoo should be used at least twice a week initially and then as needed to control recurrence thereafter. *In vitro* antimicrobial data and *in vivo* clinical efficacy data are lacking for most commercial veterinary formulations available in the US. ChlorhexiDerm® 4% Shampoo demonstrated *in vitro* the ability to eliminate 10^{5-7} colony forming units of *S. (pseud)intermedius* with $\leq$1 minute of contact time even when diluted 1/25 with saline.[9] An *in vitro* pilot study further confirmed the anti-staphylococcal efficacy of specific formulations of chlorhexidine and chlorhexidine/miconazole using minimal bactericidal concentrations.[11] This study also determined that neither a chloroxylenol nor an acetic/boric acid shampoo was effective against MSSP or MRSP.

In another study, dogs were bathed with a non-medicated shampoo vehicle or a 3% chlorhexidine/phytosphingosine shampoo (Douxo® Chlorhexidine PS Shampoo, Ceva) weekly for four treatments with assessment of bacterial counts pre-treatment and out to day 26.[10] There were no significant differences in bacterial numbers between placebo and treatment sites prior to therapy and on nearly all subsequent time points,

groups and areas of the skin. Additionally, there was no or only a very small difference in bacterial adherence between areas shampooed with the antimicrobial agents and with placebo at the same time points.

The residual clinical anti-staphylococcal activity of chlorhexidine when formulated with miconazole will be discussed later in this review.

For potentially more sustained activity, a chlorhexidine spray (TrizChlor™ 4, Dechra) or wipe (Douxo® Chlorhexidine 3% PS, Sogeval; TrizChlor™ 4, Dechra), a 0.2% chlorhexidine and 0.2% miconazole flush (Malaseb® Flush, Bayer) or 25 µg/mL nisin impregnated wipes (Preva™ Wipes, Bayer) can be used between shampoos.

Benzoyl Peroxide

Benzoyl peroxide is metabolized in the skin to benzoic acid, which alters pH and acts as an oxidizing agent to damage bacterial cell walls. *In vitro* benzoyl peroxide had inferior anti-staphylococcal activity in comparison to chlorhexidine and chlorhexidine/miconazole based on comparative minimal bactericidal concentrations.[11]

Benzoyl peroxide is clinically effective in staphylococcal pyoderma and is used in shampoos (Benzoyl Plus™, Vétoquinol; DermaBenSs™, Dechra; Pyoben®, Virbac) and a gel (Pyoben®, Virbac). In two separate studies, a 2.5% benzoyl peroxide shampoo was compared to a 3% chlorhexidine shampoo as sole treatment for canine bacterial overgrowth[12] and canine superficial pyoderma[5] with comparable results in the first study while chlorhexidine was more effective in the second study.

Because of its comedolytic, keratolytic and degreasing activity, benzoyl peroxide has most commonly been used in greasy dogs with pyoderma, deep pyoderma and pyoderma associated with demodicosis. These should be its only uses since repeated use of benzoyl peroxide shampoos on dogs with atopic skin disease may cause further disruption of an already defective epidermal barrier and increased percutaneous penetration of potential environmental allergens and microbial pathogens. Moisturizing agents and fatty acids have been added to some benzoyl peroxide shampoos in an attempt to offset epidermal lipid loss and excessive drying, but this approach has not been documented to be effective. It is an irritant in 10% of dogs and may bleach hair and clothing.[13]

Ethyl Lactate

Ethyl lactate (Etiderm®, Virbac) is hydrolyzed in the skin to ethanol and lactic acid, thus lowering the skin pH and acting similarly to benzoyl peroxide. The active metabolites have been shown to penetrate hair follicles and sebaceous glands. One study demonstrated comparable clinical efficacy to benzoyl peroxide in dogs with surface and superficial pyoderma.[14] However, neither immediate nor residual anti-staphylococcal activity of hairs was demonstrated in a recent antibacterial shampoo study.[8] Ethyl lactate was not as clinically effective as chlorhexidine for canine superficial pyoderma[15] and is usually reserved for those patients with sensitive, inflamed and pruritic skin that cannot tolerate other antimicrobial formulations.

Nisin

Nisin is a naturally-derived antimicrobial from *Lactococcus lactis*. It is found in cow's milk and cheese and has been used as a natural food preservative in human foods for decades. Nisin is a 34 amino acid, lanthionine-containing, water-soluble polypeptide which is effective in rapidly killing gram-positive bacteria at low (µg) concentrations.[16] The positive charge of nisin binds the molecule in a perpendicular orientation to the bacterial cell wall followed by rapid formation of pores, leakage of cell contents and bacterial cell death.[17] *In vitro* data demonstrate low MIC_{90s} for nisin against methicillin-resistant strains of *S. pseudintermedius*, *S. aureus* and *S. schleiferi*.[16] Clinical efficacy for staphylococcal overgrowth and superficial pyoderma in dogs has been demonstrated in an open trial.[18] Nisin is marketed in 6" x 8" towelettes (Preva™ Wipes, Bayer) for antibacterial

and cleansing activity. The towelettes have also been used to cleanse contact areas of dogs with environmental allergies in an attempt to help remove pollens from the skin surface after outdoor exposure.

Mupirocin

Mupirocin (Muricin®, Dechra) is an antibiotic isolated from *Pseudomonas fluorescens* with greater than 90% of the formulation comprised of pseudomonic acid A. It is an excellent ointment formulation for localized staphylococcal skin infections with the following beneficial characteristics: bactericidal, enhanced activity at an acid pH, no cross-resistance with other classes of antibiotics and virtually no systemic penetration but excellent local penetration in a relatively short period of time after application.[19] Historically, mupirocin has been used twice daily for focal skin infections such as impetigo, focal superficial and deep pyoderma, callus and pressure point pyoderma, infected chin acne, fold pyoderma, mucocutaneous pyoderma and interdigital abscesses.

Mupirocin is the most commonly utilized topical antibiotic for treatment of humans with methicillin-resistant staphylococcal (MRS) infections. Unfortunately, the prevalence of resistance has risen to over 60% in several published studies.[19] Therefore, it is medically and ethically prudent to reserve use of mupirocin in veterinary patients to those with MRS skin infections documented by culture and susceptibility and not responsive to more conventional topical antiseptics and antibiotics. The use of mupirocin in severe focal deep non-MRS infections such as interdigital abscesses is also justified given the usually slow and incomplete response of these infections to systemic antibiotics and other forms of topical therapy.

Miconazole

Miconazole is a topical imidazole antifungal agent that works by inhibiting the synthesis of ergosterol, a critical component of fungal cell membranes. Although its primary use has been for dermatophyte and yeast infections, it also has activity against some gram-positive bacteria including methicillin-sensitive and methicillin-resistant staphylococci. Results of a study of 112 methicillin-resistant *S. pseudintermedius* isolates from dogs showed an MIC_{90} range of 2-4 µg/mL with the majority at 2 µg/mL.[20] These MICs are well below miconazole concentrations available with topical therapy at 0.2-2% (2,000-20,000 µg/mL). Additionally, miconazole is narrow spectrum, readily available and of low priority for use in human MRS patients.

Anti-staphylococcal activity appears to be somewhat miconazole-specific since ketoconazole does not result in bacterial cell membrane damage or bactericidal activity.[21] Miconazole is minimally absorbed after topical application, rarely sensitizing and nonirritating, even to mucus membranes. Miconazole is available in 1-2% creams and sprays but is also used as a shampoo at 2% in combination with 2% chlorhexidine (Malaseb® Shampoo, Bayer) and as a flush (Malaseb® Flush, Bayer). *In vitro* synergistic antifungal[22] and antibacterial activity[23] have been demonstrated with chlorhexidine and miconazole at equal concentrations in aqueous formulations. In a more recent *in vitro* study, a 1:1 ratio of miconazole and chlorhexidine demonstrated antibacterial synergistic effect for 49/50 isolates of methicillin-resistant *S. aureus* (MRSA), 31/50 isolates of methicillin-sensitive *S. aureus* (MSSA), 12/49 isolates of MRSP and 23/49 isolates of MSSP.[24]

If properly formulated, chlorhexidine may have residual activity by adherence to the skin surface and hair coat. A European study assessed residual *in vitro* anti-staphylococcal activity of hairs plucked from 42 dogs up to 7 days after receiving the last of four antibacterial shampoo applications over 10 days.[8] Six different shampoos were studied. When compared to a non-medicated placebo shampoo base, a 3% chlorhexidine shampoo (Pyohex®, Dermcare Vet) and a 2% chlorhexidine and 2% miconazole shampoo (Malaseb®, Dermcare Vet in Germany, Bayer in the US) demonstrated significant residual activity out to 7 days after the last shampoo. A 0.8% chlorhexidine shampoo (Dermazyme® Losham with ActiBac, Ceva) and a 4% chlorhexidine shampoo (Hexocare®, Alfavet) had variable and inconsistent residual activity. The authors suggested that the disappointing results with the 4% chlorhexidine shampoo were probably related to formulation issues. A 10% ethyl lactate shampoo (Etiderm®, Virbac) showed bacterial inhibition in only 2 hair samples from 2 dogs and a 2.5% benzoyl

peroxide shampoo (Peroxyderm®, Vétoquinol) demonstrated no inhibition at any time point.

Additional Antimicrobial Agents

Sodium hypochlorite (bleach) and its active ingredient, hypochlorous acid, have bactericidal and fungicidal activity. Dilute bleach baths and rinses have been used in humans for atopic eczema infected with *S. aureus* including MRSA.[25] Concentrations have varied but have generally been in the range of 0.005% twice weekly for 5-10 minutes. Anecdotally, success has been reported with dilute bleach baths, rinses and sprays in dogs with staphylococcal skin infections but there are no published data documenting clinical efficacy.[13,26] Results of an *in vitro* study suggested that concentrations of 0.05-0.1% with a 15 minute contact time are required to effectively kill MRSP strains isolated from canine skin.[27] Another *in vitro* study demonstrated antimicrobial effectiveness of sodium hypochlorite diluted to 0.00156% for *Staphylococcus pseudintermedius*, *Pseudomonas aeruginosa* and *Malassezia pachydermatis* after 3 and 5 minutes of contact time.[28] Other factors to consider in deciding to use dilute bleach include: commercial bleach comes in various concentrations which must be taken into account when diluting; no safety data have been published on the use of dilute bleach in dogs; activity is affected by organic matter; solutions should be made up fresh before each use; bleaching of the hair coat and materials in the household may occur; surfactants are added to some commercial bleach solutions which may result in cutaneous irritancy; bleach is regulated by the EPA so it is a violation of Federal Law to use in a manner inconsistent with its labeling.

There is a stable, non-toxic, pH neutral, non-bleaching formulation of hypochlorous acid (Vetericyn® VF, Innovacyn) which is commercially available. It has been advocated as a treatment for pyotraumatic dermatitis and to control bacterial overgrowth and secondary infections, including some associated with MRS.[13] However, results of a pilot study showed no difference in clinical or cytologic improvement in dogs with superficial pyoderma when sprayed with this formulation or saline twice a day for 28 days.[29]

<u>*Malassezia* Dermatitis</u>

Malassezia pachydermatis is classified as a lipophilic, non-lipid-dependent, non-mycelial, saprophytic yeast that is commonly found on the skin, in the ear canals and on mucosal surfaces of normal dogs and cats.[30] Skin disease occurs when a hypersensitivity reaction develops and/or with cutaneous overgrowth of the yeast. Cutaneous overgrowth is similar to bacterial pyoderma in that it tends to be recurrent and due to the same list of underlying causes, especially cutaneous allergies. Generalized infection generally warrants both systemic and topical treatment to achieve rapid remission of clinical signs.

Chlorhexidine, Miconazole, Ketoconazole and Climbazole

Chlorhexidine used alone as a 3-4% shampoo may be effective in yeast dermatitis. In the one published clinical study a 3% formulation (Microbex® Shampoo, Virbac) required application three times per week initially versus twice a week for a 2% chlorhexidine and 2% miconazole combination (Malaseb® Shampoo) to achieve comparable clinical and cytologic improvement over the 6 weeks of the study.[31]

In a published evidence-based review of treatments for *Malassezia* dermatitis in dogs, only the combination of 2% chlorhexidine and 2% miconazole shampoo could be recommended with good evidence for efficacy used twice per week.[32] Subsequent to this review, a blinded randomized trial compared a 2% chlorhexidine and 2% miconazole shampoo (Malaseb®) twice weekly, oral ketoconazole daily at 10 mg/kg and the topical and systemic combination in dogs with *Malassezia* dermatitis.[33] Topical therapy alone was as effective as systemic therapy in reduction of yeast numbers and clinical improvement while the combination was superior to systemic treatment alone.

Chlorhexidine has also been combined with 1% ketoconazole (KetoChlor®, Virbac; Mal-A-Ket™, Dechra) and

0.5% climbazole (Douxo® Chlorhexidine PS+Climbazole Shampoo, Ceva). Similar combinations are also found in other formulations including leave-on lotions/conditioners and pledgets/wipes. In European studies, a shampoo with 2% climbazole (product undisclosed)[34] and a wipe with 0.5% climbazole, trisEDTA and 0.3% chlorhexidine (CLX® Wipes, ICF)[35] have been shown to reduce yeast populations on canine skin but with no concurrent assessment of clinical improvement. Neither of these products is available in the United States.

Acetic Acid, Selenium Sulfide and Sulfurated Lime

These ingredients provide alternatives to chlorhexidine and the azole antifungals but are not supported by the same degree of evidence.[36]

Summary of Topicals for Microbial Infections of the Skin

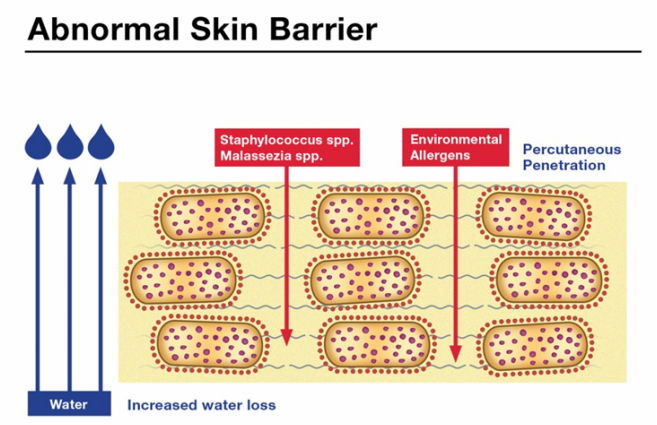
A literature review was published in which the authors evaluated the 9 *in vitro* and 21 *in vivo* studies on topical antimicrobial treatment of skin infections.[36] Recommendations were made based on quality assessment of the studies and categories of evidence for efficacy. Known reported adverse events were also considered when formulating the final recommendations. The authors concluded that there is:

- Good evidence to recommend ≥2% chlorhexidine against bacteria (≥ 1 Double-Blinded, Placebo-Controlled, Randomized study)
- Good evidence to recommend 2% chlorhexidine - 2% miconazole against bacteria and *Malassezia* (≥ 1 D-B, P-C, R study)
- Lesser evidence to recommend 2-3% benzoyl peroxide against bacteria (open trials) and yeast (*in vitro* studies)
- Conflicting evidence on the efficacy of ethyl lactate
- Insufficient evidence to recommend any other topical therapy for cutaneous infections

Allergic Dermatoses

Canine atopic dermatitis is the allergic skin disease for which there has been the most new research directly impacting topical product development and use. Research findings suggest that canine atopic dermatitis (CAD) is a multifaceted disease resulting from a complex interaction between environmental and genetic factors.[37] CAD has been 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.[38] Since this definition was originally adopted by the International Task Force on Canine Atopic Dermatitis,[37] 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.[39] Instead of primarily through the respiratory tract, sensitization to environmental allergens appears to occur more directly in the skin after cutaneous penetration[40] and skin barrier dysfunction may increase the risk of allergic sensitization.[41] This is the likely reason why clinical signs of AD are seen in areas of the skin with contact exposure to environmental allergens.

Studies have demonstrated primary and/or secondary functional, chemical and ultrastructural abnormalities in the epidermis of dogs with atopic dermatitis including: 1) increases in transepidermal water loss (TEWL) as a measure of decreased barrier function,[42,43] 2) abnormal morphology (quantity and organization) of lamellar lipids in the stratum corneum,[44] 3) decreased free and protein-bound ceramides in the epidermis[42,45] and 4) abnormalities in filaggrin expression.[46,47] These abnormalities may be associated with increased environmental allergen and microbial pathogen penetration of the skin barrier leading to cutaneous inflammation and secondary infections associated with atopic dermatitis.



The evidence summarized above supports primary and/or secondary defects in stratum corneum barrier function in the pathogenesis and clinical abnormalities in CAD. 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.

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

Cleansing, Moisturizing and Hydrating Agents

Various treatment regimens have been utilized with some success in an attempt to correct the above-mentioned abnormalities.[48] 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. There is at least some indirect evidence that removal of allergens from the skin surface by shampooing may be effective. Hair clippings and dander samples from 25 dogs were collected before and immediately after washing for analysis of Can f 1 antigen levels. Air sampling for Can f 1 antigen was conducted in some of the homes. Washing twice weekly with a proprietary shampoo maintained reduction in recoverable Can f 1 from the hair (84% reduction; $p<0.0001$), dander (86% reduction; $p<0.0001$) and air samples (61% reduction; $p=0.014$).[49]

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 CAD predilection sites between shampoos. Cool water rinses, cool water wipes, commercial moisturizing wipes and antibacterial wipes 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), Cortisoothe® (Virbac), DermAllay™ (Dechra), Dermal-Soothe™ (Vétoquinol), Douxo® Calm (Ceva), Epi-Soothe® (Virbac), HyLyt® (Bayer), and Relief® (Bayer). Rinse and spray options include Cortavance® (Virbac)(currently not approved in the US), DermAllay™ (Dechra), Dermal-Soothe™ (Vétoquinol), Douxo® Calm (Ceva), 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.

Ceramides and Fatty Acids

Because skin barrier impairment has been linked, in part, to ceramide, cholesterol and fatty acid abnormalities, there has been interest in topical application of these molecules. Ceramide is sphingosine bound to a fatty acid and important in cell membranes and stratum corneum lipid bilayers to maintain barrier integrity. At this time there is evidence that the chemical and structural integrity of the stratum corneum can be improved with a topical ceramide-containing emulsion (Allerderm Spot-On®, Virbac) administered twice weekly.[50,51] 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.[52] A double-blinded, randomized, placebo-controlled study of 32 dogs with atopic dermatitis assessed this product applied three times weekly for 4 weeks.[53] The Canine Atopic Dermatitis Extent and Severity Index (CADESI) in the treated but not the placebo group improved 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.

Another family of topical products (Douxo® Shampoos, Sprays, Mousses, and Spot-on; Ceva) contains phytosphingosine, a pro-ceramide. An open, non-controlled study using weekly shampoos (Douxo® Calm Shampoo) and twice-weekly mousse (Douxo® Calm Mousse) application was conducted on five atopic dogs over 21 days.[54] Values for skin hydration, total cholesterol, total ceramides and stratum corneum thickness were increased at day 21 but were not statistically different from pre-treatment levels. Neither clinical atopic dermatitis scores nor pruritus was monitored. Results of two non-placebo-controlled studies suggest that in dogs with allergic dermatoses the shampoo (Douxo® Calm Shampoo) and spray (Douxo® Calm Spray)[55] or shampoo and mousse (Douxo® Calm Mousse)[56] work as well as another antipruritic shampoo (Allermyl®) to control clinical signs and pruritus. At the time of this review, there have been no placebo-controlled reports on clinical efficacy of any phytosphingosine-containing veterinary formulations for allergic or inflammatory dermatoses.

A topical spot-on formulation containing plant-derived essential oils and high in polyunsaturated fatty acids (Dermoscent® Essential 6 Spot-on for Dogs, Bayer) was developed to restore the skin barrier and hydrate and deodorize the skin.[57] When added to a canine *in vitro* skin equivalent model, the resultant epidermis was thicker with an increased number of viable cell layers and a more continuous basal membrane. The stratum corneum was more dense and compact and the ceramide percentage in the stratum corneum lipids was significantly increased.[57] This formulation was evaluated in a multicenter, randomized, double-blinded, placebo-controlled field study on 48 dogs with environmentally-induced pruritus and clinical signs consisting of erythema, excoriations, lichenification and alopecia.[58] It was applied as directed once per week for 8 weeks to the dorsal neck. There was significant improvement in mean pruritus score (25% decrease, p=0.036) and clinical score (39% decrease,

p=0.011) in the treated group versus the placebo group. Improvement was seen in both severely and mild-moderately affected dogs. No adverse effects were seen during the study. In an open study in dogs this spot-on (7 dogs applied weekly) and a spray consisting of plant-derived essential oils (Atop 7®, Bayer)(7 dogs applied daily) for 8 weeks demonstrated significant improvement in clinical scores and pruritus in both groups, with no difference between groups.[59]

In a multicenter, open, non-controlled trial with final evaluation of 168 dogs (Dermoscent® Essential 6 Spot-on for Dogs) and 73 cats (Dermoscent® Essential 6 Spot-on for Cats, Bayer) with bad smell, flaking and/or greasy skin, the product was applied once a week on the skin between the shoulders for 4 weeks. In dogs, significant improvement was seen at 28 days in hair shine, odor and skin balance (oiliness) while in cats both hair shine and skin balanced significantly improved. Odor was not evaluated in the cats since no owners reported a bad smell at the start of the trial. *P* values for all parameters were < 0.0001.

Dermoscent BIO BALM® (Bayer) is a thick soy oil-based ointment with naturally-derived plant oils which is used to help reduce superficial dryness and manage rough, calloused skin. It has been used on thickened cracked footpads, the nasal planum and calluses, such as those found at pressure points.[60,61] A randomized, double-blinded placebo-controlled clinical trial was conducted to assess control of idiopathic nasal hyperkeratosis in dogs. Thirty-nine dogs were treated with BIO BALM or a placebo (aqueous gelling agent) applied to the nasal planum daily for 60 consecutive days. Scores for lichenification, extension of area involved, softness and total score were assessed. On day 60, changes from baseline for lichenification, extension, softness and total score were -31.2%, -18.3%, -72.8% and 36.8% in the treated group and -11.9%, 2.3%, -42.1% and -14% in the placebo group, respectively. The total score revealed a 51% overall improvement between groups at 60 days which was significant at *p*=0.0016.[62]

Summary of Topicals for Allergic Dermatoses

- Stratum corneum barrier defects are present in CAD.
- 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 CAD.
- 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 or a triamcinolone spray 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.
- Some 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 and may be an effective alternative to shampoos, rinses and sprays to enhance owner compliance.

References

[1] Weese JS. Methicillin-resistant staphylococcal infections in pets. *European J Companion Anim Pract* 2011;21:101-110.

[2] Beck KM, Waisglass SE, Dick HL, et al. Prevalence of meticillin-resistant *Staphylococcus pseudintermedius* (MRSP) from skin and carriage sites of dogs after treatment of their meticillin-resistant or meticillin-sensitive staphylococcal pyoderma. *Vet Dermatol* 2012;23:369-375.
[3] Weese JS, Frank LA, Reynolds LM, et al. Retrospective study of methicillin-resistant and methicillin-susceptible *Staphylococcus pseudintermedius* infections in dogs. ASM-ESCMID Conference on Methicillin-Resistant Staphylococci in Animals 2009; London, UK.
[4] DeJaham C. Effects of an ethyl lactate shampoo in conjunction with a systemic antibiotic in the treatment of canine superficial bacterial pyoderma in an open-label, non-placebo-controlled study. *Vet Ther* 2003;4:94-100.
[5] Loeffler A, Cobb MA, Bond R. Comparison of a chlorhexidine and a benzoyl peroxide shampoo as sole treatment in canine superficial pyoderma. *Vet Rec* 2011;169:249-253.
[6] Borio S, Colombo S, La Rosa G, et al. Effectiveness of a combined (4% chlorhexidine digluconate shampoo and solution) protocol in MRS and non-MRS canine superficial pyoderma: a randomized, blinded, antibiotic-controlled study. *Vet Dermatol* 2015;26:339-344.
[7] Hillier A, Lloyd DH, Weese JS, et al. Guidelines for the diagnosis and antimicrobial therapy of canine superficial bacterial folliculitis (Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases). *Vet Dermatol* 2014;25:163-175.
[8] Kloos I, Straubinger RK, Werckenthin C, et al. Residual antibacterial activity of dog hairs after therapy with antimicrobial shampoos. *Vet Dermatol* 2013;24:250-254.
[9] Lloyd DH, Lamport AI. Activity of chlorhexidine shampoos *in vitro* against *Staphylococcus intermedius*, *Pseudomonas aeruginosa* and *Malassezia pachydermatis*. *Vet Rec* 1999;144:536-537.
[10] Stroh A, Werckenthin C, Luis CS, et al. Influence of a phytosphingosine-containing chlorhexidine shampoo on superficial bacterial counts and bacterial adherence to canine keratinocytes. *Vet Micro* 2010;141:190-193.
[11] Young R, Buckley L, McEwan N, et al. Comparative *in vitro* efficacy of antimicrobial shampoos: a pilot study. *Vet Dermatol* 2011;23:36-40.
[12] Viaud S, Maynard L, Sanquer A. Comparison of two shampoos as sole treatment for canine bacterial overgrowth syndrome. *Vet Rec* 2012;170:675-680.
[13] Miller WH, Griffin CE, Campbell KL. Dermatologic Therapy. In: Miller WH, Griffin CE, Campbell KL, eds. *Muller and Kirk's Small Animal Dermatology*. 7th Ed. St. Louis: Elsevier, 2012;108-183.
[14] Ascher F, Maynard L, Laurent J, et al. Controlled trial of ethyl lactate and benzoyl peroxide shampoos in the management of canine surface pyoderma and superficial pyoderma. In: Von Tscharner C, Halliwell REW, eds. *Advances in Veterinary Dermatology*. Vol 1. London: Bailliere Tindall, 1990;375-382.
[15] Nagata M, Murayama N, Shibata K. Efficacy of Nolvasan Surgical Scrub containing 2% chlorhexidine acetate in topical management of canine superficial pyoderma: a randomized double-blinded, controlled study. *Jap J Vet Dermatol* 2006;12:1-6.
[16] Rankin SC, O'Shea K, Rejman JJ, et al. MIC range, MIC50 and MIC90 for nisin against *Staphylococcus isolates* from companion animals. *Vet Dermatol* 2007;18:191.
[17] Brötz H, Sahl HG. New insights into the mechanism of action of lantibiotics – diverse biological effects by binding to the same molecular target. *J Antimicrobial Chemotherapy* 2000;46:1-6.
[18] Frank LA, Kirzeder EM, Davis JA, et al. Nisin-impregnated wipes for the treatment of canine pyoderma and surface bacterial colonization. *Vet Dermatol* 2009;20:219.
[19] Conly JM, Johnston BL. Mupirocin – Are we in danger of losing it? *Can J Infect Dis* 2002;13:157-159.
[20] Weese JS, Walker M, Lowe T. *In vitro* miconazole susceptibility of meticillin-resistant *Staphylococcus pseudintermedius* and *Staphylococcus aureus*. *Vet Dermatol* 2012;23:400-402.
[21] Sud IJ, Feingold DS. Action of antifungal imidazoles on *Staphylococcus aureus*. *Antimicrob Agents Chemother* 1982;22:470-474.
[22] Perrins N, Bond R. Synergistic inhibition of the growth *in vitro* of *Microsporum canis* by miconazole and chlorhexidine. *Vet Dermatol* 2003;14:99-102.
[23] Kwochka KW. *In vitro* placebo-controlled time-kill comparison of an aqueous rinse formulation containing miconazole nitrate and chlorhexidine gluconate against bacterial and fungal cutaneous pathogens. *Vet Dermatol* 2005;16:200-201.

[24] Clark SM, Loeffler A, Bond R. Susceptibility *in vitro* of canine methicillin-resistant and – susceptible staphylococcal isolates to fusidic acid, chlorhexidine and miconazole: opportunities for topical therapy of canine superficial pyoderma. *J Antimicrob Chemother* 2015;70:2048-2052.
[25] Barnes TM, Greive KA. Use of bleach baths for the treatment of infected atopic eczema. *Australasian J of Dermatol* 2013;54:251-258.
[26] Jeffers JG. Topical therapy for drug-resistant pyoderma in small animals. *Vet Clin Small Anim* 2013;43:41-50.
[27] Pariser M, Gard S, Gram D, et al. An *in vitro* study to determine the minimal bactericidal concentration of sodium hypochlorite (bleach) required to inhibit meticillin-resistant *Staphylococcus pseudintermedius* strains isolated from canine skin. *Vet Dermatol* 2013;24:632-637.
[28] Banovic F, Lemo N. *In vitro* evaluation of the use of diluted sodium hypochlorite (bleach) against *Staphylococcus pseudintermedius*, *Pseudomonas aeruginosa* and *Malassezia pachydermatis*. *Vet Dermatol* 2014;25:233-234.
[29] Udenberg T, Griffin C, Rosenkrantz W, et al. Efficacy of 0.011% topical hypochlorous acid for the treatment of canine superficial pyoderma. *Vet Dermatol* 2015;26:133.
[30] Miller WH, Griffin CE, Campbell KL. Fungal and algal skin diseases. In: Miller WH, Griffin CE, Campbell KL, eds. *Muller and Kirk's Small Animal Dermatology*. 7th Ed. St. Louis: Elsevier, 2012;223-283.
[31] Maynard L, Rème CA, Viaud S. Comparison of two shampoos for the treatment of canine *Malassezia* dermatitis: a randomized controlled trial. *J Small Anim Pract* 2011;52:566-572.
[32] Negre A, Bensignor E, Guillot J. Evidence-based veterinary dermatology: a systematic review of interventions for *Malassezia* dermatitis in dogs. *Vet Dermatol* 2009;20:1-12.
[33] Bensignor E, Hahn H, Guillot J. Topical vs. systemic treatment of *Malassezia* dermatitis in dogs: a comparative, blinded, randomized trial. *Vet Dermatol* 2012;23(Suppl. 1):84.
[34] Cavana P, Petit JY, Perrot S, et al. Efficacy of a 2% climbazole shampoo for reducing *Malassezia* population sizes on the skin of naturally infected dogs. *J Med Mycol* 2015;25:268-273.
[35] Cavana P, Peano A, Petit JY, et al. A pilot study of the efficacy of wipes containing chlorhexidine 0.3%, climbazole 0.5% and Tris-EDTA to reduce *Malassezia pachydermatis* populations on canine skin. *Vet Dermatol* 2015;26:278-281.
[36] Mueller RS, Bergvall K, Bensignor E, et al. A review of topical therapy for skin infections with bacteria and yeast. *Vet Dermatol* 2012;23:330-341.
[37] Marsella R, Olivry T, Carlotti DN. Current evidence of skin barrier dysfunction in human and canine atopic dermatitis. *Vet Dermatol* 2011;22:239-248.
[38] Halliwell R. Revised nomenclature for veterinary allergy. *Vet Immunol Immunopathol* 2006;114:207-208.
[39] Marsella R, Olivry T, Carlotti DN, et al. Current evidence of skin barrier dysfunction in human and canine atopic dermatitis. *Vet Dermatol* 2011; 22:239-248.
[40] Marsella R, Nicklin C, Lopez J. Studies on the role of routes of allergen exposure in high IgE-producing Beagle dogs sensitized to house dust mites. *Vet Dermatol* 2006;17:306-312.
[41] Olivry T, Wofford J, Paps J, et al. Stratum corneum removal facilitates experimental sensitization to mite allergens. *Vet Dermatol* 2011;22:188-196.
[42] Shimada K, Ji-Seon Y, Yoshihara T, et al. Increased transepidermal water loss and decreased ceramides content in lesional and non-lesional skin of dogs with atopic dermatitis. *Vet Dermatol* 2009;20:541-546.
[43] Hightower K, Marsella R, Flynn-Lurie A. Effects of age and allergen exposure on transepidermal water loss in a house dust mite-sensitized beagle model of atopic dermatitis. *Vet Dermatol* 2010;21:89-96.
[44] Inman AO, Olivry T, Dunston SM, et al. Electron microscopic observations of the stratum corneum intercellular lipids in normal and atopic dogs. *Vet Pathol* 2001;38:720-723.
[45] Reiter LV, Torres SMF, Wertz PW. Characterization and quantification of ceramides in the non-lesional skin of canine patients with atopic dermatitis compared to controls. *Vet Dermatol* 2009;20:260-266.
[46] Chervet L, Galichet A, McLean WHI, et al. Missing C-terminal filaggrin expression, NFkappaB activation and hyperproliferation identify the dog as a putative model to study epidermal dysfunction in atopic dermatitis. *Exp Dermatol* 2010;19:e343-e346.

[47] Santoro D, Marsella R, Bunick D, et al. Expression and distribution of canine filaggrin in the skin of healthy and atopic beagles (abstract). *Vet Dermatol* 2010;21:323.
[48] Marsella R. Skin barrier and therapy. *Proceedings of the 2013 North American Veterinary Dermatology Forum* 2013:119-122.
[49] Hodson T, Custovic A, Simpson A, et al. Washing the dog reduces dog allergen levels, but the dog needs to be washed twice a week. *J Allergy Clin Immunol* 1999;103:581-585.
[50] Piekutowska A, Pin D, Rème CA, et al. Effects of a topically applied preparation of epidermal lipids on the stratum corneum barrier of atopic dogs. *J Compar Pathol* 2008;138:197-203.
[51] Popa I, Remoue N, Osta B, et al. The lipid alterations in the stratum corneum of dogs with atopic dermatitis are alleviated by topical application of a spingolipid-containing emulsion. *Clin Exper Dermatol* 2012;37:665-671.
[52] Fujimura M. Up-to-date information about canine atopic dermatitis and clinical effects of topical product for improvement of skin barrier function. *Companion An Prac Japan* 2010;2:80-85.
[53] Marsella R, Genovese D, Gilmer L, et al. Investigations on the effects of a topical ceramide and free fatty acid solution (Allerderm Spot-On®) on clinical signs and skin barrier function in dogs with atopic dermatitis: a double-blinded, randomized, controlled study. *Vet Dermatol* 2012;23(Suppl. 1):66.
[54] Fantini O, Zemirline C, Belliard M, et al. Restructuring effect of phytosphingosine-containing shampoo and mousse on the cutaneous barrier in five atopic dogs: Preliminary results of a field study. *Vet Dermatol* 2015;26:300.
[55] Bourdeau P, Bruet V, Gremillet. Evaluation of phytosphingosine-containing shampoo and microemulsion spray in the clinical control of allergic dermatoses in dogs: preliminary results of a multicentre study. *Vet Dermatol* 2007;18:177-178.
[56] Bensignor E, Pin D, Bourdeau P. A multicentric randomised controlled single blinded study to evaluate the value of a new protocol with a shampoo and a foam to treat canine allergic dermatitis. *Pratique Médicale et Chirurgicale de l'Animal de Compagnie* 2013;48:49-55.
[57] Cerrato S, Ramió-Lluch L, Fondevila D, et al. Effects of essential oils and polyunsaturated fatty acids on canine skin equivalents: skin lipid assessment and morphologic evaluation. *J Vet Med* 2013;Article ID 231526 (http://dx.doi.org/10.1155/2013/231526):9 pages
[58] Blaskovic M, Rosenkrantz W, Neuber A, et al. The effect of a spot on formulation containing polyunsaturated fatty acids and essential oils on dogs with atopic dermatitis. *Vet Jour* 2014;199:39-43.
[59] Tretter S, Mueller RS. The influence of topical unsaturated fatty acids and essential oils on normal and atopic dogs. *J Am Anim Hosp Assoc* 2011;47:236-240.
[60] Gaillard E, Pressanti C, Bensignor E, et al. Control of non-infected calluses in dogs with a balm containing a mixture of essential oil and essential fatty acids: an open prospective study. *Proceedings of the 25th Annual Congress of the ESVD-ECVD* 2011;PO2.
[61] Bensignor E. Use of a balm to treat idiopathic nasal hyperkeratosis in dogs: prospective study of 10 cases. *Le nouveau Practicien vétérinaire* 2011;10:57-60.
[62] Catarino M, Pressanti C, Mimouni P, et al. Control of idiopathic nasal hyperkeratosis in dogs with a mixture of essential oils and essential fatty acids (Dermoscent BIO BALM®): a randomized, double-blinded, placebo-controlled clinical trial. *Vet Dermatol* 2015;26:303.