Topical Therapy for Infectious and Allergic Dermatoses

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BASIC PRINCIPLES OF TOPICAL THERAPY

- Client education on the use of topicals with written discharge information is mandatory.
- 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 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 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 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.

Microbial Infections

This is the most common indication for topical therapy. I recommend pushing owners aggressively on the need to be vigilant with the use of topical products to successfully treat and control recurrent infections. We do find the cause of recurrent bacterial and yeast infections in most of our patients and they are generally associated with underlying allergies (atopic dermatitis, cutaneous adverse reactions to foods, parasitic hypersensitivities, etc.) or
endocrinopathies (hypothyroidism, hyperadrenocorticism). However, even our patients successfully managed for their allergies on restricted diets, allergy immunotherapy and/or pharmacologic agents such as glucocorticoids, modified cyclosporine (Atopica, Novartis) or oclacitinib (Apoquel, Zoetis) will have periodic flare-ups and develop cutaneous infections.

**Bacterial Pyoderma**

The most common organism isolated from pyoderma lesions in dogs is *Staphylococcus pseudintermedius*. *Staphylococcus schleiferi* and *S. aureus* are other important pathogens. *Pseudomonas aeruginosa* is rarely isolated from the skin.

**Chlorhexidine**

Chlorhexidine is an antiseptic with activity against most of the common bacteria causing cutaneous infections. It is bactericidal by acting on the cytoplasmic membrane. Stability, bioavailability and adherence characteristics can be significantly affected by the formulation into which it is incorporated. Chlorhexidine has some degree of residual activity by adherence to the skin surface and hair coat.

A recent 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. 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, 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, Vetoquinol) demonstrated no inhibition at any time point.

Dermatologists typically use 3% or 4% chlorhexidine shampoos (ChlorhexiDerm 4% Shampoo, Bayer; Hexadine, Virbac; TrizChlor 4, Dechra) in their bacterial pyoderma cases. A shampoo should be used at least twice a week initially and then as needed to control recurrence thereafter. For more residual 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. It 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 recent studies, a 2.5% benzoyl peroxide shampoo
was compared to a 3% chlorhexidine shampoo as sole treatment for canine bacterial overgrowth\(^2\) and canine superficial pyoderma\(^3\) 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. Repeated use of benzoyl peroxide shampoos on dogs with atopic skin disease may cause further disruption of epidermal barrier function and increased percutaneous penetration of potential allergens. Moisturizing agents and fatty acids have been added to some benzoyl peroxide shampoos 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.\(^4\)

**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.\(^5\) However, neither immediate nor residual anti-staphylococcal activity of hairs was demonstrated in a recent antibacterial shampoo study.\(^1\) Ethyl lactate is usually not as clinically effective as chlorhexidine\(^6\) and is reserved for those patients with sensitive, inflamed, and pruritic skin that cannot tolerate more potent 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 over 30 years. Nisin is a 34 amino acid, lanthionine-containing, water-soluble polypeptide which is effective in rapidly killing gram-positive bacteria at low (µg) concentrations. 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.\(^7\) *In vitro* data demonstrates low MIC90s for nisin against methicillin-resistant strains of *S. pseudintermedius*, *S. aureus* and *S. schleiferi*.\(^8\) Clinical efficacy for staphylococcal overgrowth and superficial pyoderma in dogs has been demonstrated in an open trial.\(^9\) Nisin is marketed in 6” x 8” towelettes (Preva Wipes, Bayer) for antibacterial and cleansing activity.

**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. 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. 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 MIC90 range of 2-4 µg/mL with the majority at 2 µg/mL. 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, safe, 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. 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 most commonly used as a shampoo at 2% in combination with 2% chlorhexidine (Malaseb, Bayer) and as a flush (Malaseb Flush, Bayer). *In vitro* synergistic antifungal and antibacterial activity have been demonstrated with chlorhexidine and miconazole at equal concentrations in aqueous formulations.

**Methicillin-Resistant Staphylococcal Pyoderma**

Methicillin-resistant staphylococcal skin infections are increasing in general and specialty practice. Many MRS isolates are now multi-drug resistant such that the only systemic options are human oral and parenteral antibiotics that are prohibitively expensive, may require hospitalization, have potentially serious side effects, and lead to ethical questions concerning their use in animals. Aggressive topical therapy is required to successfully treat and control these infections. Diligent owners and their veterinarians are successfully treating and preventing these resistant infections by managing the underlying primary dermatosis, following normal hygienic practices, keeping the patient’s hair coat short, using antimicrobial shampoos with at least a 10 minute contact time every 1-3 days initially, and applying antimicrobial rinses, sprays, flushes, wipes, or ointments on focally affected areas 1-2 times a day on the non-shampoo days.

The most commonly utilized product options available at this time are:

- 3-4% chlorhexidine shampoo
• 2% chlorhexidine - 2% miconazole shampoo
• 3-4% chlorhexidine sprays and wipes
• 25 µg/mL nisin wipes
• 0.2% chlorhexidine – 0.2% miconazole flush
• 2% mupirocin ointment
• sprays or soakings with sodium hypochlorite diluted at various concentrations
• lactoferrin, lysozyme, lactoperoxidase shampoo and rinse (Zymox, Pet King Brands)
• 1% amikacin sprays (compounded) reserved for otherwise unresponsive patients.

Treatment is continued until full clinical resolution and negative cytology. For patients with recurrent infections, long-term maintenance may be indicated with topicals as frequently as needed to prevent flare-ups. Transient or long-term MRS colonization of the nares, anus, rectum, ear canals, and other body sites may occur after clinical resolution of pyoderma.\textsuperscript{14}

\textit{Malassezia} Dermatitis

This cutaneous infection is similar to bacterial pyoderma in that it tends to be recurrent and due to the same list of underlying causes. Generalized infection warrants both systemic and topical treatment whereas topicals alone may be effective for yeast otitis, yeast pododermatitis, and for prevention of recurrent infections.

\textit{Chlorhexidine, Miconazole, Ketoconazole, and Climbazole}

Chlorhexidine used alone as a 3-4% shampoo may be effective in yeast dermatitis but in the one published clinical study it required application three times per week versus twice a week for a 2% chlorhexidine and 2% miconazole combination.\textsuperscript{15}

In a published evidence-based review of treatments for \textit{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.\textsuperscript{16} 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 \textit{Malassezia} dermatitis.\textsuperscript{17} 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, Sogeval). Similar combinations are also found in other formulations including leave-on lotions/conditioners and pledgets/wipes.

\textit{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. Two-percent acetic acid and 2% boric acid formulations (MalAcetic, Dechra) have most commonly been utilized.
Summary of Topicals for Microbial Infections of the Skin

A recent 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. 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 2-3% chlorhexidine against bacteria (> 1 D-B, P-C, R studies)
- Good evidence to recommend 2% chlorhexidine - 2% miconazole against bacteria and Malassezia (> 1 D-B, P-C, R studies)
- 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 Skin Diseases

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 is a multifaceted disease resulting from a complex interaction between environmental and genetic factors. 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, 2) abnormal morphology (quantity and organization) of lamellar lipids in the stratum corneum, 3) decreased free and protein-bound ceramides in the epidermis, and 4) abnormalities in filaggrin expression. 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.

Various treatment regimens have been utilized with some success in an attempt to correct the above-mentioned abnormalities. What remains less clear based on the current data is how well improvement in the barrier actually contributes to improvement in the clinical signs and pruritus associated with the disease. The goal of topical therapy in atopic dermatitis is to: 1) gently remove environmental allergens from the skin surface, 2) help control recurrent infections associated with and further contributing to pruritus, 3) control the inflammation and pruritus, 4) hydrate the epidermis, and 5) replenish the defective epidermal barrier.

Moisturizing and Hydrating Agents

Water itself has hydrating and cooling effects, especially when used along with effective emollients and humectants. It is also important that immediately after a shampoo when the skin is still wet that a leave-on rinse or spray be applied to increase residual activity. Rinses and
sprays can also be utilized between shampoos but are more effectively applied when the skin and hair are wet.

Moisturizing products with various combinations of emollients, emulsifiers, humectants, fatty acids, and ceramides are indicated to address multiple aspects of the defective epidermal barrier. Some of the commonly utilized shampoos in this category include Allermyl (Virbac), AvenaLyt (Bayer), DermAllay (Dechra), Dermal-Soothe (Vetoquinol), Douxo Calm (Sogeval), HyLyt EFA (Bayer), and Relief (Bayer). After bath rinse and/or spray options include DermAllay (Dechra), Douxo Calm (Sogeval), Humilac (Virbac), HyLyt EFA (Bayer), and Relief (Bayer).

**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.\(^{21,22}\) 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.\(^{23}\) A double-blinded, randomized, controlled study of 32 dogs with atopic dermatitis assessed this product applied three times weekly for 4 weeks.\(^{24}\) 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.

Essential 6 Spot-On (Dermoscent, LDCA, France) contains hemp and neem seed oils, other natural plant-derived oils, and fatty acids designed to replenish the hydro-lipidic film, hydrate the skin, and deodorize. This product was evaluated in a multicenter, randomized, double-blinded, placebo-controlled field study on 48 dogs with atopic dermatitis.\(^{25}\) It was applied as directed once per week for 8 weeks to the dorsal neck. Significant improvement was noted for pruritus and for CADESI scores in the treated but not the placebo group. Improvement was seen in both severely and mildly-moderately affected dogs. No adverse effects were seen during the study. Additionally, results of an open study in dogs with atopic dermatitis 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.\(^{26}\)

Another family of topical products (Douxo Shampoos, Sprays, Mousses, and Spot-on; Sogeval) contains phytosphingosine, a pro-ceramide. Preliminary results of one study suggested that in dogs with allergic dermatoses the shampoo and/or spray work as well as an antipruritic shampoo.\(^{27}\) 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 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 in an attempt to reduce the frequency and severity of allergic flare-ups.
In addition to atopic dermatitis, these products are being used for a number of applications with variable success including recurrent pyoderma, sebaceous adenitis, color dilution alopecia, ceruminous and allergic otitis, feline chin acne, vitamin A-responsive dermatosis, nasal and footpad hyperkeratosis, ear margin seborrhea, and idiopathic scaling in dogs and cats.

References


