Topical therapy in veterinary dermatology

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Abstract

Topical therapy is extremely important in the management of allergic, infectious, and seborrheic disorders. Numerous commercial formulations are available for veterinarians and may include diverse active ingredients. Canine skin is often more sensitive than is human skin due to anatomical and physiological differences, including differences in the thickness of the *stratum corneum*, skin pH and hair follicle density which can facilitate cutaneous penetration of active ingredients. Therefore, it is highly recommended to use topical formulations registered only for applications in dogs. The application of topical formulations for treatment of canine superficial pyoderma, keratoseborrhoeic disorders and atopic dermatitis will be emphasized in this report.

Key words: *topical therapy; canine superficial pyoderma; keratoseborrhoeic disorders; atopic dermatitis*

How do I treat canine superficial pyoderma topically?

Superficial pyoderma is a common diagnosis in dogs with a prevalence of up to 10-20% of all dogs presented in private practices; the condition is often recurrent and causes varying degrees of pain and pruritus depending on the extent of lesions (Hillier et al., 2014). Superficial bacterial folliculitis, bullous impetigo and exfoliative pyoderma associated-epidermal collarets are the three main manifestations of superficial pyoderma in dogs (Banovic et al., 2017a). These conditions are frequently recurrent and difficult to treat due to the worldwide emergence of methicillin-resistant strains; *Staphylococcus* (S.) *pseudintermedius* is the principal pathogen and *S. schleiferi* strains recently has been recognized as another causative agent (Hillier et al., 2014).

Patients with canine atopic dermatitis exhibit frequent, sometimes recurrent, staphylococcal and yeast skin infections, which can exacerbate pruritus and dermatitis; therefore, patients predisposed to secondary staphylococcal pyoderma should be considered and screened for canine atopic dermatitis (Olivry et al., 2010; Hillier et al., 2014).

With the emergence of multi-drug resistant bacteria-including *Staphylococcus* species-that are important to human beings and companion animals, topical antimicrobials have gained popularity as an alternative to systemic antibiotics (Olivry et al., 2010; Mueller et al., 2012). Topical treatment is

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an effective primary option for focal and generalized superficial pyoderma; topical therapy decreases bacterial counts and reduces surface colonization of bacteria, thus helping to prevent or reduce the incidence of recurrences. Furthermore, topical therapy is safer and achieves higher antimicrobial concentrations compared with systemic antibiotics (Olivry et al., 2010).

What is an effective active antiseptic ingredient?

Multiple products from numerous manufacturers are available for use in veterinary medicine with many companies relying on *in vitro* data to support the active ingredient choices (Olivry et al., 2010; Mueller et al., 2012). However, there is a lack of *in vivo* efficacy and comparative studies for most of these products. Thus, it is recommended that products should be selected based on evidence based medicine and randomized blinded clinical studies.

In 2012, a review of topical therapies concluded that the best evidence of efficacy in cases of canine pyoderma exists with antiseptic products containing either chlorhexidine or benzoyl peroxide (Banovic et al., 2017a). Furthermore, a recent published study comparing the efficacy of topical chlorhexidine (combined shampoo and spray formulations both at 4%) with systemic amoxicillin-clavulanic acid for the treatment of canine superficial pyoderma has shown that topical therapy with chlorhexidine digluconate products alone may be as effective as systemic therapy with amoxicillin-clavulanic acid (Mueller et al., 2012). Chlorhexidine, a bisbiguanide antiseptic, is most commonly used in veterinary dermatology at various concentrations (0.5%-4%) of the water soluble gluconate form, however, some *in vitro* studies have also indicated that a higher concentration of the active ingredient is not always more effective (Olivry et al., 2010; Mueller et al., 2012; Jeffers, 2013).

Synthetic cationic polymers are becoming widely used in people as antimicrobials due to their broad-spectrum bactericidal activities and high therapeutic index. Polihexanide (polyhexamethylene biguanide, PHMB) has a broad antimicrobial spectrum, including Gram-positive and Gram-negative bacteria, biofilm-building bacteria, and fungi including *Candida* spp. (Hübner and Kramer, 2010). Similarly to chlorhexidine, polihexanide interacts with acidic, negatively charged phospholipids in the bacterial membrane, leading to increased fluidity, permeability and loss of integrity, followed by the death of the organism (Ikeda et al., 1984; Gilbert and Moore, 2005). The advantage of polihexanide is that it does not contain the toxic terminal chlorobenzene substituents like chlorhexidine (Hubner et al., 2010). The results of a recent study indicate that polihexanide has comparable *in vitro* antimicrobial efficacy with chlorhexidine against common canine pathogenic microorganisms (*S. pseudintermedius, Pseudomonas aeruginosa*) affecting the skin and presents a potential alternative agent to chlorhexidine for skin and wound antisepsis in veterinary medicine (Banovic et al., 2013). Thus, further antimicrobial efficacy should be confirmed by in vivo studies on local tolerability and clinical efficacy in dogs.

What method of application will best reach the site of infection?

There are many different topical antimicrobial vehicles: shampoos, sprays, soaks, leave-on conditioners, rinses, sprays, lotions, gels, creams, wipes and ointments (Mueller et al., 2012; Jeffers, 2013). The most appropriate topical product is based on the location and extent of the infection. Shampoos are the most practical, commonly used in the authors' practice and effective in cases

of generalized pyoderma involving the patient's trunk and proximal extremities (Mueller et al., 2012; Jeffers, 2013; Borio et al., 2015). In dogs with long or thick coats, clipping may be required to improve contact at the infection site. Spot treatments (ointments, gels, creams) work best for focal/multifocal lesions and hairless areas; wipes are ideal for intertriginous areas (facial folds, lip folds, interdigital areas, perivulvar region); and sprays are beneficial for focal lesions or sparsely haired areas (abdomen, ventral thorax, axillary area) (Mueller et al., 2012; Jeffers, 2013).

How much contact time is required and how frequent should the therapy be applied?

For most active ingredients, a minimal contact time of 10 minutes is preferred (Mueller et al., 2012; Jeffers, 2013; Hillier et al., 2014; Borio et al., 2015). The duration of contact time is based on *in vitro* data showing stronger kill against the most common skin pathogens, like *S. pseudintermedius*, with longer antiseptic time exposures. Client compliance can be an issue in topical therapy; when a medicated shampoo is used, it is imperative that the owner understands the importance of contact time before rinsing. Bathing should be performed 2 to 3 times a week when used as a monotherapy (Mueller et al., 2012; Jeffers, 2013; Hillier et al., 2014; Borio et al., 2015), frequent bathing should be continued for 7 days past resolution of clinical signs associated with the infection.

Other therapies (sprays, wipes, gels, lotions) should ideally be applied twice a day until clinical resolution; these may be used immediately in case of pyoderma recurrences (Mueller et al., 2012; Jeffers, 2013; Borio et al., 2015). It has been suggested that crusts associated with pyoderma be removed before application of these products. To prevent potential removal by the patient (licking the areas), the products may be applied at times when the patient can be distracted via feeding or before walks.

In cases of canine atopic dermatitis and after the superficial pyoderma resolution, once weekly bathing should be continued using non-antiseptic moisturizing oatmeal based shampoos. Topical antiseptics can disrupt cutaneous homeostasis by nonspecific killing of the normal microflora. Therefore, using antiseptic shampoos as continuous indefinitely treatment on a weekly to biweekly basis may result in altered balance of the microbiota, a condition known as dysbiosis. This could predispose atopic patients to more recurrent flare ups.

Are there new developments in topical products for superficial pyoderma?

Antimicrobial peptides (AMPs) are naturally occurring and predominantly small cationic polypeptides expressed by both epithelial cells and phagocytic leukocytes, and they possess broad-spectrum antimicrobial activity against bacteria, fungi and viruses. In addition, AMPs can promote chemotaxis and wound healing (Jenssen et al., 2006). In the case of skin infection, antimicrobial peptide expression in the skin is upregulated due to increased synthesis by keratinocytes and deposition from degranulation of recruited neutrophils (Braff et al., 2005). Recently, a new shampoo (ICF Peptivet shampoo, Cremona, Italy) containing AMP2041 antimicrobial peptide was released on the market. The product shows fast and complete *in vitro* antimicrobial activity against a panel of bacterial and fungal strains involved in canine cutaneous infections (Ghibaudo et al., 2016). However, these antimicrobial assays have been performed under non-physiological conditions, using bacterial growth media rather than a culture environment that closely resembles canine skin. Further

in vivo studies are needed to evaluate if this very promising product is able to contribute to the decrease of systemic antibiotics for superficial pyoderma in clinical practice.

Diluted bleach (a.k.a. sodium hypochlorite hereafter referred to solely as "hypochlorite") represents an inexpensive and widely available topical antiseptic. Dilute bleach baths (to an approximate concentration of 0.005% hypochlorite) have been shown to remarkably reduce the severity of infected atopic dermatitis (AD) in children over 3 months duration (Huang et al., 2011).

The author of a recent review on the therapeutic approach for canine superficial pyoderma recommended the application of 0.06–0.12% diluted sodium hypochlorite solution, two to four times weekly, as an adjunctive topical therapy for this disease (Bloom, 2014). However, the recommendation for this dilution range was based solely on personal clinical experience. Given the lack of evidence for diluted bleach usage in dogs, our initial study revealed excellent *in vitro* antimicrobial effectiveness of diluted sodium hypochlorite against isolates of *S. pseudintermedius*, *P.* and *Malassezia (M.) pachydermatis* from atopic dogs (Banovic and Lemo, 2014). Furthermore, we evaluated the antiseptic efficacy and local side effects of a single 0.05% and 0.005% diluted bleach solution application on the skin of healthy dogs (Banovic et al., 2017b). The single application at both concentrations revealed excellent tolerability as well as reduction in bacterial load evaluated using contact agar plates with neutralization medium. We followed with a repeated diluted bleach baths (0.005%) study in healthy dogs; twice weekly bleach baths for 15 minutes were safe and there was no signs of skin irritation or dryness in any dog (Banovic, unpublished data).

Interestingly, there was no change staphylococcal diversity and skin microbiome evaluated through bacterial 16S rRNA gene sequencing (Banovic, unpublished data). Further research is needed to evaluate how bleach baths modulate skin barrier function and reduction in itch intensity in atopic dogs. An alternative to bleach soaks may be a 0.011% hypochlorous acid containing solution (Veterycn, VF; Innovacyn, Rialto, CA, USA) marketed for topical treatment in veterinary medicine. However, a recent pilot study evaluating this product failed to demonstrate efficacy in treating canine pyoderma when used twice a day for 3-4 weeks (Udenberg et al., 2015).

Which topical antibiotics should I use for canine pyoderma?

Topical therapy with fusidic acid is an attractive alternative to systemic therapy based on low minimum inhibitory concentrations documented in canine pathogenic staphylococci, including strains MRSP (methicillin-resistant *Staphylococcus pseudintermedius*) (Frosini et al., 2017). Recent studies suggest that topical fusidic acid products should be useful in the treatment of canine surface and superficial pyoderma (intact follicles) caused by bacteria susceptible to fusidic acid, in countries where it is available, but not deep pyoderma (where infection extends to surrounding dermis) (Frosini et al., 2017).

Mupirocin, an antibiotic developed from the fermentation of *Pseudomonas fluorescens* (Godbeer et al., 2014), Mupirocin is a bacteriostatic antibiotic that reversibly binds to isoleucyl tRNA synthetase to disrupt protein synthesis and is widely used to eliminate nasal carriage of methicillin-resistant *Staphylococcus aureus* (MRSA) in human MRSA carriers (Godbeer et al., 2014). Mupirocin has been used only on a limited basis in veterinary medicine but is approved in the United States for the treatment of bacterial skin infections and superficial pyoderma in dogs.

Silver sulfadiazine cream can be very useful in the treatment of localized pyoderma with *Pseudomonas* spp. Silver salts precipitate proteins and interfere with bacterial metabolic activities (Rosenkrantz, 2006). It has been shown to be effective *in vitro* against *Pseudomonas* at concentrations ranging from 0.1 to 1% (Rosenkrantz, 2006).

How do I treat *Malassezia* dermatitis topically?

Malassezia yeasts are normally commensal species found primarily in the skin and ears of dogs (Rosenkrantz, 2006; Olivry et al., 2010). Similar to bacterial pyoderma, *Malassezia* dermatitis is frequently a recurrent skin infection associated with an underlying disease process such as atopic dermatitis (Rosenkrantz, 2006; Olivry et al., 2010). Topical therapy is useful in eliminating infection and reducing the yeast numbers (Bond et al., 1995; Rosenkrantz, 2006; Olivry et al., 2010). For generalized infections, shampoo therapy is most useful, while localized infections may benefit from creams, lotions, wipes and sprays. There are numerous commercially available shampoo formulations for treatment of *Malassezia* dermatitis, however, there is only strong evidence based on clinical study for use of topical miconazole/chlorhexidine shampoo treatment (Malaseb, Bayer HealthCare LLC Animal Healthy Division, KS, USA; twice a week for 3 weeks) (Bond et al., 1995) and, in severe cases, systemic treatments with azole derivatives (ketoconazole, itraconazole, terbinafine). Frequent use of systematic antifungals is not recommended because it is may be associated with increased prevalence of drug resistance.

Topical therapy for seborrheic skin diseases

Antiseborrheic shampoos function by restoring and normalizing keratinocyte turnover. These agents work in two different ways:

- a cytostatic effect is exerted on basal cells, thereby reducing their rate of division (keratoplastic).
- elimination of excess corneal cells, by increasing desquamation. Most antiseborrheic shampoos also eliminate excess corneal layers, by increasing desquamation. This is thought to be a result of ballooning of corneocytes that makes the *stratum corneum* softer and reduces the intercellular cohesion of the corneocytes and results in increased desquamation. Agents that function in this way are called keratolytic (Rosenkrantz, 2006).

There are many keratoplastic and keratolytic agents that are commercially available in shampoo formulations. Salicylic acid is a keratolytic agent that reductes skin pH which leads to an increase in the amount of water that keratin is able to absorb (Rosenkrantz, 2006). Stratum corneum hydratation increases and corenal layer softens which allows desquamation. Salicylic acid acts synergistically with sulphur, and is often present in small quantities in shampoos (Rosenkrantz, 2006). Sulphur is mildly keratolytic and has numerous other, mainly antiseborrhoeic, properties. It is also keratoplastic, due to a direct cytostatic effect and possibly because it interacts with epidermal cysteine to form cystine, an important component of the corneal layer (Rosenkrantz, 2006). It exerts synergistic activity with salicylic acid. This synergism appears optimal when both substances are incorporated into the shampoo in equal concentrations (Rosenkrantz, 2006). Selenium disulphide is keratolytic and keratoplastic by reducing epidermal turnover and impairing disulphide bridge formation in keratin. It is also antiseborrhoeic but also has irritant and drying effects. Phytosphingosine is a proceramid

(ceramides are components of the extra cellular sheets of lipids in the *stratum corneum*) and a natural component of the epidermis, with anti-inflammatory and antimicrobial effects.

Benzoyl peroxide, in addition to being antibacterial, is antiseborrhoeic, by hydrolyzing sebum and reducing sebaceous gland activity (Rosenkrantz, 2006). The skin may also become dry and moisturizers are therefore always indicated after using this product.

How to use shampoos in keratoseborrhoeic disorders?

Shampoos should initially be applied several times a week (Rosenkrantz, 2006). With time, frequency of application can gradually be reduced to give the longest interval over which treatment is still effective, usually about 2 weeks. Cases should be monitored frequently. The therapeutic agent often needs to be changed following the development of side effects, rebound effects or change in clinical presentation.

The more severe the dermatitis is, the more active and potent the shampoo must be and the more frequent will be the applications. For mild and/or pityriasiform keratoseborrhoeic disorders, keratolytic agents should be selected whereas for severe and/or psoriasiform disorders, keratoregulating (keratoplastic) agents will also be used (Rosenkrantz, 2006). In all cases but particularly in greasy seborrhea, antiseborrhoeic agents may be useful.

Concept of "proactive therapy" with topical steroids in canine atopic dermatitis

Canine atopic dermatitis is a common skin disorder in small-animal practice and is defined as a hereditary predisposition to develop pruritic inflammatory skin disease associated with IgE antibodies, which typically target environmental allergens (Olivry et al., 2010). Topical steroids have an anti-inflammatory effect and represent the mainstay of therapy for bringing human atopic dermatitis under control (Wollenberg et al., 2008). Reactive treatment (only when skin lesions develop) with topical steroids following the presence or absence of visible lesions was the traditional mainstay of AD treatment in humans (Wollenberg et al., 2008). This strategy is well established with good short-term results; however, it is difficult to achieve long-term remission between flares, because the normal-looking non-lesional skin of patients with AD is not normal (Wollenberg et al., 2008). Proactive therapy is defined as the low-dose, intermittent application of anti-inflammatory therapy to previously affected skin; this approach targets invisible inflammation in the usually relapsing 'problem zones' of patients with AD (Wollenberg et al., 2008). Topical steroids are divided into VII classes of potency, from low (class VII) to high (class I) (Jacob and Steele, 2006). The clinical efficacy and the risk of local (e.g. skin thinning, comedones and alopecia) and systemic (*i.e.* hypothalamus-pituitary axis suppression due to systemic absorption) side effects correlate with potency class and duration of use and frequency of application (Rosenkrantz, 2006).

As suggested in human AD (Wollenberg et al., 2008), clearing the skin lesions with daily application of steroids for 1-2 weeks should be followed with the intermittent use of the same product (e.g. 2-3 times/week) even if visible lesions have disappeared. This "proactive treatment" approach reduces the risk of flares and extends the time of remission. The long-term proactive application of hydrocortisone aceponate (Cortavance, Virbac) spray administered on two consecutive days each week or twice weekly was shown to be effective and well-tolerated in atopic dogs with skin and recurrent ear infections, prolonging

remission times of flares in comparison with reactive therapy (therapy only when clinical signs are visible) (Lourenco et al., 2016).

Improving epidermal barrier dysfunction in canine atopic dermatitis

The complex process of epidermal differentiation is disturbed in canine atopic dermatitis lesions, and the impaired skin barrier offers potential targets for therapeutic intervention, such as fatty acids (oral supplements or topical solutions) and various topical treatments (Olivry et al., 2010; Olivry et al., 2015). Weekly bathing with a mild nonirritating shampoo and postbathing topical moisturizers are recommended for each patient; this therapy provides a direct soothing effect to the skin, physically removes surface allergens, and increases skin hydration (Olivry et al., 2010; Olivry et al., 2015).

According to the systematic review of clinical trials, essential fatty acid supplementation is indicated only for long-term management of canine atopic dermatitis as an adjunctive treatment (Olivry et al., 2010; Olivry et al., 2015) the clinical benefit of essential fatty acid supplements on the skin may take up to 2 months to be seen. In recent years, some topical (spot-on, spray, shampoo, emulsion) formulations containing fatty acids and ceramides have been introduced for dogs with canine atopic dermatitis; however, their efficacy is inconsistent, and veterinarians should weigh their benefit and cost before deciding to use them (Olivry et al., 2010; Olivry et al., 2015).

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Topikalna terapija u veterinarskoj dermatologiji

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Topikalna ili lokalna terapija iznimno je važna u liječenju alergijskih, infektivnih i seboroičnih bolesti kože. Veterinarima su dostupne brojne komercijalne formulacije i mogu uključivati različite aktivne sastojke. Koža pasa često je osjetljivija od ljudske kože zbog anatomskih i fizioloških posebitosti, uključujući i razlike u debljini rožnatog sloja, pH kože i gustoće dlačnih folikula koji mogu također olakšati prodiranje aktivnih sastojaka lokalne terapije. Stoga je preporučljivo koristiti formulacije registrirane „samo za primjenu u pasa." U ovom preglednom članku naglašava se primjena lokalne terapije za liječenje površinske upale kože, keratoseboroičnih poremećaja i atopijskog dermatitisa u pasa.

Ključne riječi: *lokalna terapija, površinska upala kože, keratoseboroične bolesti, atopijski dermatitis*