Introduction

The incidence of antimicrobial-resistant infections has been significantly increasing in the past decades. This phenomenon is partially due to the indiscriminate use of systemic antibiotics in both human and veterinary medicine. In particular, the prevalence of methicillin-resistant (MR) staphylococcal infections due to *Staphylococcus pseudintermedius* has almost quadrupled in certain regions of the United States in the past 10 years. In addition to this, multidrug-resistant (MDR) staphylococcal infection incidence is rising. The presence of MDR infections significantly decreases the armamentarium of systemic antibiotics available to general practitioners and specialists. Furthermore, the presence of bacterial biofilm even further limits the effectiveness of systemic antibiotics.

Topical treatment is the pillar for the management of bacterial skin infections in companion animals. However, it has always been seen as an adjunctive treatment to systemic antibiotics. Recent guidelines and consensus statements have highlighted the importance of topical antimicrobials for the successful management of resistant bacterial skin infections. Topical antimicrobials have also been positively seen for their activity against bacterial biofilm. Although lacking in supportive literature, topical antimicrobial therapy has been routinely used as a preventative method to limit the reoccurrence of superficial bacterial skin infections in dogs.

Topical antimicrobials are commercially available in several formulations. In veterinary dermatology, the most common delivery formulations include shampoos, sprays, mousses, wipes, leave-on conditioners, solutions, lotions, gels, creams, and ointments. However, because of the larger amount of studies performed using shampoos, this review will mainly focus on this type of formulation although other formulations will be discussed as appropriate. To guarantee the therapeutic success of these therapies, it is important to pay attention to both the active ingredients and the vehicle used to deliver it as well as to owner compliance. The ideal topical antimicrobial should be effective to treat the target organism(s), be easy to apply, have an effective delivery vehicle, have adequate contact time, and possess residual activity. This review will discuss the pros and cons of classic topical antimicrobial therapy as well as new treatment options for topically treating canine pyoderma. Because extensively treated in a previous review, the use of topical antibiotics, like mupirocin and fucidic acid, in veterinary medicine will not be discussed. Current clinical evidence will be discussed when available.

Classic Topical Antimicrobial Therapy for Canine Pyoderma

Traditionally, canine pyoderma has been treated with topical antimicrobials such as chlorhexidine, benzoyl peroxide, and ethyl lactate. These compounds
have been most commonly delivered in the form of shampoos. However, sprays, mousses, gels, and wipes also have a large usage. When possible, a multimodal user-friendly approach including the association of multiple formulations (eg, shampoo and mousse) can be used to potentially increase the effectiveness of the topical treatment to clear a skin infection. Although it may be very time consuming, shampoo therapy is specifically indicated when haired skin and/or large areas of the body need to be treated. Its efficacy depends on a variety of factors. Examples include frequency of application, pet-owner relationship, shampoo technique, and climate.6–8 The frequency of application varies based on owner compliance and the veterinarian’s personal experience. A common protocol of application includes a bath 2 to 3 times weekly until 7 days passed clinical resolution and then weekly afterward.

Chlorhexidine

Among the antimicrobials mentioned above, chlorhexidine is by far the most studied. Several studies have been published showing the powerful antimicrobial activity of chlorhexidine in dogs. Chlorhexidine is a bisbiguanide with potent antibacterial and antifungal activity, with an in vitro minimum bactericidal concentration for S pseudintermedius ranging from 7 µg/mL to 0.6247 µg/mL9–14 equal to a concentration of 0.0007% and 0.00006247%. Clinically, chlorhexidine has been shown to be effective for the treatment of superficial pyoderma when used at a dose of 19 mL/m² of body surface area.15 The mechanism of action of chlorhexidine is complex and spans from disruption of the bacterial cell wall, causing leakage of the cytoplasmic material leading to bacterial death, to the precipitation of ATP and nucleic acids. Chlorhexidine shampoos are available at concentrations between 2% and 4%, and although studies have shown that higher concentrations of chlorhexidine have a faster bactericidal activity, the formulation of the shampoo may equally affect bactericidal speed and activity.16

In the past decade, several reviews2,5,17 have already been published on the effectiveness of chlorhexidine shampoo for the treatment of superficial pyoderma. Since then, 12 papers have been published on the in vitro (n = 7)18–25 and in vivo (4)26–29 efficacy of chlorhexidine against bacterial pyoderma in dogs. In addition, 2 publications have assessed the efficacy of chlorhexidine baths and scrubs to reduce the bacterial skin contamination for the prevention of surgical site infections in dogs undergoing elective surgeries.30,31 More in detail, 2 in vitro studies18,20 from the United Kingdom tested the efficacy of chlorhexidine monotherapy or in combination with either miconazole or Tris-EDTA. The first study by Clark et al20 showed a significantly higher minimum inhibitory concentration (MIC) for Staphylococcus aureus isolates (n = 50) when compared to S pseudintermedius isolates (49) with values ranging from 1 to 4 µg/mL. The same study20 tested the effect of a 1:1 combination of chlorhexidine/miconazole (at final concentrations of each varying from 256 to 0.03 µg/ml) showing a synergistic activity against 98%, 62%, 24.5%, and 47% of methicillin-resistant S aureus (MRSA), methicillin-susceptible S aureus (MSSA), S pseudintermedius (MRSP), and methicillin-susceptible S pseudintermedius (MSSP) isolates, respectively. Similar results were obtained from the second in vitro study20 conducted by the same authors showing an MIC₉₀ of 2 µg/mL and 0.5 µg/mL for the S pseudintermedius isolates tested (n = 196) with chlorhexidine alone and in combination with miconazole (1:1 ratio), respectively.

The third in vitro study19 evaluated the MICs of several antimicrobials (ie, chlorhexidine digluco- nate, benzalkonium chloride, triclosan, accelerated hydrogen peroxide, fidacid, bacitracin, mupirocin, geranium oil, tea tree oil, and grapefruit seed extract) against several isolates of MRSP (n = 25) and MSSP (25). The results of that study showed that there was no difference between MRSP and MSSP in terms of MIC for any of the antimicrobials tested. In particular, triclosan performed the best with an MIC₉₀ of 0.5 µg/mL and accelerated hydrogen peroxide performed the worst with an MIC₉₀ of 32 µg/mL (grapefruit seed extract MIC was ≥3.84 µg/mL), with chlorhexidine being in the middle with an MIC₉₀ of 8 µg/mL; these data are in line with previous studies.

More recently, the in vitro residual activity of chlorhexidine was tested on canine hairs and skin after in vivo application of chlorhexidine products. In these studies, hairs were treated with a shampoo containing chlorhexidine alone or followed by a 3% chlorhexidine conditioner,24 as well mousse21,25 or spray22 containing 1 to 4% chlorhexidine alone or in combination with other antimicrobials (eg, miconazole, clotrimazole, tromethamine USP/disodium EDTA, etc) or wipes23 containing 0.3% chlorhexidine, 0.5% clotrimazole, and Tris-EDTA. In the shampoo/conditioner, mousse, and spray studies dogs were treated with the topical products, and hairs were collected before, 1 hour after, and 4, 7, and 10 days (spray and mousse)21,22,25 and 14 days (only for the mousses)21,25 after treatment. In addition, in 1 study,25 skin swabs were also simultaneously collected to assess the post-treatment effect of mousses on the skin. In all studies, a significant residual effect of chlorhexidine was present on hairs up to 7 to 14 days posttreatment, although such an inhibitory effect was only present until day 4 on the skin. In the shampoo study,24 dogs were treated on days 1, 4, 7, and 10, and the hairs were collected on days 0, 10, 12, 14, and 17. At the end of the study, the greater bacterial inhibitory effect was seen with shampoos containing 2 and 3% chlorhexidine alone or in combination with a conditioner compared to other formulations of shampoos containing up to 4% chlorhexidine. This study demonstrated how the shampoo formulation is as important as the percentage of chlorhexidine in the determination of its antimicrobial action. In the mousse study,21 a 3% chlorhexidine mousse showed a significant antibacterial effect for up to 14 days. Similarly to mousse and spray, a single application of chlorhexidine as a wipe formulation has been shown to be effective as...
an antibacterial product and superior to acetic/boric acid wipes up to 3 days posttreatment. In regards to in vivo studies over the past 10 years, a total of 4 studies have assessed the clinical efficacy of chlorhexidine for the treatment of superficial pyoderma in dogs. The formulations used in these studies include a 4% shampoo and solution, 2% scrub, 3% shampoo, and 3% pads. The first study was a randomized, blinded, antibiotic-controlled study assessing the efficacy of a twice-weekly 4% chlorhexidine shampoo along with a daily 4% chlorhexidine lotion in dogs (n = 25) with superficial pyoderma over a 4-week period. In this study, chlorhexidine was compared to twice-daily amoxicillin-clavulanic acid antibiotic treatment (n = 16). After only 7 days of treatment, there was no statistical difference between the 2 treatments in terms of pyoderma score. These results were maintained over 56 days (28 days after discontinuation of the treatments) demonstrating that topical chlorhexidine therapy is not inferior to oral amoxicillin-clavulanic acid antibiotic therapy.

The second study compared the efficacy of a 2-minute application of a 2% chlorhexidine scrub to an alcohol-based antiseptic scrub (80% ethyl alcohol) in reducing cutaneous bacterial populations in dogs. In this study, privately owned dogs (n = 50) were scrubbed with chlorhexidine in 1 area and alcohol in another area of the body, and culture was collected before and after application using contact plates. At the end of the study, the 2 treatments were equivalent with S. pseudintermedius being cultured in 36% of dogs pretreatment and only in 2% and 4% of dogs after chlorhexidine or alcohol, respectively.

The third study was a randomized, single-blinded controlled trial using a 3% chlorhexidine shampoo as a control treatment for the assessment of the efficacy of a new topical antimicrobial, olnexidine gluconate, for the treatment of superficial pyoderma in dogs. In this study, the authors enrolled 28 dogs with atopic dermatitis and superficial pyoderma. The dogs were treated with either once daily 1.5% olnexidine spray or a weekly 3% chlorhexidine shampoo for 14 days. At the end of the study, there was a significant decrease in the pyoderma score in both groups; the average clinical improvement was 54.8% with olnexidine and 42.6% with chlorhexidine.

Finally, the fourth study was an open-label trial, analyzing the effect of pads containing 3% chlorhexidine and ophiurny for focal bacterial overgrowth in dogs. In this study, dogs (n = 11) received daily pad application for 14 days. At the end of the study, an 84% bacterial count reduction was seen with 88.9% of dogs achieving a ≥ 70% microbial decrease.

Together, these in vitro and in vivo studies show relatively low MICs for clinical isolates of S. pseudintermedius, independently from the MR status, as well as a long-lasting residual activity on treated hairs. From the clinical standpoint, these concentrations are easily achievable using commercially available products independent from the formation (shampoo, lotions, sprays, mousse, etc). More importantly, the in vitro studies have been confirmed by several in vivo studies showing the clinical efficacy of chlorhexidine for the control of localized and generalized superficial pyoderma. This indicates that chlorhexidine is still an extremely valuable option for resistant bacterial skin infections in dogs.

**Benzoyl peroxide and ethyl lactate**

Benzoyl peroxide and ethyl lactate are the other 2 commonly used topical antibacterial agents in veterinary dermatology. These products are generally used as shampoos at 2.5 to 3% and 10%, respectively, although ethyl lactate is available as a mousse, whereas benzoyl peroxide is available as a human formulation as gel and creams up to a 10% concentration, with the latter characterized by a very powerful drying and keratolytic activity.

Clinically, benzoyl peroxide and ethyl lactate have in common the fact that they can be considered as pro-drugs. In fact, their major antibacterial activity is expressed after contact with the skin. Specifically, benzoyl peroxide is an oxidizing agent able to disrupt the bacterial cell membrane causing it to rupture. Once on the skin, benzoyl peroxide breaks down to benzoic acid and oxygen. The generation of highly reactive oxygen radicals and disruption of the bacterial cell membrane are the basis of the antibacterial action of this compound. Along with its antibacterial capabilities, benzoyl peroxide, thanks to the production of benzoic acid, is an efficient keratolytic product able to inhibit epidermal proliferation and sebum production. This characterizes its drying and potentially irritating activity on the skin if used too often. Similarly, ethyl lactate is lipid soluble and penetrates all skin layers, including hair follicles and sebaceous glands. When in contact with the skin, ethyl lactate is hydrolyzed by bacterial lipases into ethanol, which solubilizes lipids, and lactic acid, which lowers the skin pH, leading to its bacteriostatic and bactericidal action.

Since 2012 clinical trials assessing the efficacy of benzoyl peroxide and ethyl lactate for the treatment of pyoderma in dogs have not been published. The only in vitro studies published after 2012 showed minimal to no antibacterial activity of mousses and shampoo containing ethyl lactate on treated hairs. In fact, mousse and shampoo containing 10% ethyl lactate had none to minimal residual effect on S. pseudintermedius; however, this could be explained because the antibacterial action of ethyl lactate is mainly due to its hydrolyzation into ethanol and lactic acid occurring on the skin. Similarly, an in vitro study comparing the efficacy and residual effect of chlorhexidine, ethyl lactate, and benzoyl peroxide shampoos showed a lack of immediate and residual antibacterial activity of the 2.5% benzoyl peroxide shampoo on treated hairs. These results are in agreement with a previously published a randomized, partially blinded study comparing the clinical efficacy of a twice-weekly application of 3% chlorhexidine versus 2.5% benzoyl peroxide shampoo on dogs (n = 20) with superficial pyoderma for 21 days. At the end of the study, there was a significant improvement in the clinical signs only in the chlorhexidine group. A lack of
efficacy was recorded for the benzoyl peroxide group. However, the results by Kloos et al.\textsuperscript{46} are partially comparable to the results from a previous in vitro study\textsuperscript{40} showing the antibacterial activity of benzoyl peroxide and ethyl lactate, although significantly reduced when compared to chlorhexidine. In the study by Young et al.\textsuperscript{41} bacteria were tested using a microbroth dilution method instead of testing residual activity on treated hair making the comparison among these studies not possible. As mentioned above, it is important to remember that these results could be due to the intrinsic limitation of the in vitro tests and the mechanism at the base of the antibacterial activity of ethyl lactate and benzoyl peroxide in the skin.

Azoles

Many topical formulations containing chlorhexidine are associated with an azole to boost its antifungal activity. The azoles most commonly present in such formulations include miconazole, clotrimazole, and econazole. Among others, miconazole has been historically accredited antibacterial activities against \textit{S. pseudintermedius}. Supporting this historical knowledge are 2 in vitro studies\textsuperscript{43,44} showing an MIC\textsubscript{90} of 2 \textmu g/mL for \textit{S. pseudintermedius} and an MIC\textsubscript{90} of 4 \textmu g/mL for \textit{S. aureus}, independently from their MR status. Unfortunately, the in vivo antibacterial activity of miconazole alone is hard to judge since, as mentioned above, most commercially available formulations are available as a combination of miconazole with another antibacterial compound(s). However, the direct antibacterial activity of miconazole on \textit{S. pseudintermedius}, \textit{Escherichia coli}, and \textit{Pseudomonas aeruginosa} has been recently assessed via transmission electron microscopy.\textsuperscript{41} In that study, the authors were able to show that miconazole, at 5 \textmu g/mL, is able to alter bacterial membrane permeability as demonstrated by a significant decrease in size of the \textit{S. pseudintermedius} and \textit{P. aeruginosa}, and an increase in size of \textit{E. coli}. These results were similar to what was observed for polymyxin B.\textsuperscript{44}

Similar to miconazole, the antibacterial activity of clotrimazole has been recently demonstrated in vitro against 50 clinical isolates of \textit{S. pseudintermedius} (MRSP = 25 and MSSS = 25).\textsuperscript{45} In that study, the authors were able to show an MIC\textsubscript{90} of 1 \textmu g/mL for all the isolates, independently from their MR status. In the same study, the authors compared the antibacterial activity of clotrimazole to isolates previously shown to have a variable sensitivity to miconazole, MSSP (n = 1), reference \textit{S. pseudintermedius} isolate (2), MRSA (1), and MSSA (1), and for this reason, it was used as quality control and for comparative purposes. After the comparison, the authors showed that clotrimazole performed the same or better than miconazole, specifically looking at MSSA isolates.

New/Alternative Topical Therapies

Over the years the need for new topical antimicrobials has led many researchers to look beyond the “classic” antimicrobial compounds described above. This need for new antimicrobials has been dictated by the possibility of the insurgence of antimicrobial resistance to compounds like chlorhexidine.\textsuperscript{14,18,41} Resistance to antiseptics is associated with the expression of multidrug efflux pump genes (eg, qacA, qacB, and smr). However, such genes have not been identified in a cohort of 100 isolates of multidrug-resistant \textit{S. pseudintermedius} (MDRSP) in Japan.\textsuperscript{14} This study suggests that, although possible, the occurrence of resistance to commonly used antiseptics may be extremely low in veterinary medicine. Nevertheless, the search for alternative options to treat MDR organisms has led to a series of publications, mainly in vitro studies, testing the efficacy of several compounds against MDR organisms and biofilms. Particular interest has been seen toward the use of plant extracts and essential oils as topical antimicrobials. Other compounds of interest include sodium hypochlorite, sodium oxychlorosene, and nanosulfur.

Bleach or sodium hypochlorite

Bleach, or sodium hypochlorite (NaOCl), has been used as a topical antiseptic and disinfectant since the 18th century.\textsuperscript{33} Based on pH, sodium hypochlorite may exist as hypochlorous acid (HOCl), also present in neutrophils, or as a hypochlorite ion or as chlorine, its molecular form (Cl\textsubscript{2}).\textsuperscript{44} Sodium hypochlorite is broken down to hypochlorous acid when in contact with water. This reaction generates superoxide radicals extremely effective against bacteria, spores, fungi, and viruses.\textsuperscript{44} Hypochlorous acid has an inhered short shelf life, and until recently it was not commercially available. However, in 2007, a stabilized pure form of hypochlorous acid was described, adding this compound to the armamentarium of topical antimicrobials. In vitro, hypochlorous acid has been shown to be more effective (lower MIC and MBC) and faster (1 vs 5–15 minutes) than sodium hypochlorite to kill \textit{Staphylococcus aureus}, \textit{E. coli}, and \textit{P. aeruginosa}.\textsuperscript{45}

Despite the in vitro greater antimicrobial effect of hypochlorous acid, sodium hypochlorite has been routinely used in human and veterinary dermatology for its low cost and safety profile. Sodium hypochlorite has several beneficial effects on human skin.\textsuperscript{44} As recently reviewed,\textsuperscript{44} bleach is a powerful, well-tolerated antimicrobial. It does not disrupt the epidermal skin barrier, it has anti-inflammatory properties, and it is able to decrease pruritus in atopic human patients. In human dermatology, sodium hypochlorite is used at a concentration of 0.005%. An in vitro study\textsuperscript{46} showed that concentrations ranging from 0.005% to 0.01% are innocuous for human keratinocytes. However, the same authors tested the antimicrobial and antibiofilm activity of sodium hypochlorite against \textit{S. aureus} only at concentrations as low as 0.01%. This study\textsuperscript{46} confirmed sodium hypochlorite’s antistaphylococcal activity at such concentration. Whereas to act as antibiofilm compound, concentrations ranging from 0.01% to 0.16% may be needed.\textsuperscript{46} In veterinary medicine, the in vitro antimicrobial activity of sodium hypochlorite has been tested.
against clinical isolates of *S pseudintermedius*, *P aeruginosa*, and *Malassezia pachydermatis* showing a powerful antimicrobial activity. This was demonstrated with concentrations as low as 0.00156% able to kill such organisms in 3 to 5 minutes of contact time. Regarding safety, the same group tested the toxicity of sodium hypochlorite on primary canine keratinocytes showing a lack of significant toxicity for concentrations up to 0.01% of sodium hypochlorite, mirroring the human study previously reported. Furthermore, 0.005% sodium hypochlorite was associated with a significant reduction in inflammatory markers, with concentrations of 0.05% lacking negative effects on the epidermal skin barrier.

Regarding the clinical applicability of sodium hypochlorite as a powerful antimicrobial, the data are scant with only 2 clinical studies published. In the first study, a single application of 0.05% diluted sodium hypochlorite or water was applied at a concentration of 0.8 mL per 5 cm² on the thorax of atopic dogs (*n* = 4) and bacteria were counted over a 7-day period. At the end of the 7 days, although a significant difference was not seen between sodium hypochlorite and water, a visual reduction of bacterial colonies was seen in the treated group. In addition, after a single application of 0.05% sodium hypochlorite, there was a complete lack of side effects, confirming the high safety profile of sodium hypochlorite in dogs. These data suggest that repeated daily applications of sodium hypochlorite, as anecdotally used, would make sodium hypochlorite an extremely viable, safe, and affordable treatment option for MDR bacterial infections in dogs.

This hypothesis was confirmed by a second clinical prospective, open-label pilot study, reported the effects of a commercially available shampoo (Command Shampoo for animals; VetriMax) containing sodium hypochlorite and salicylic acid against canine superficial pyoderma. Dogs (*n* = 17) were treated with essential oil spray (PYOclean shampoo) plus daily spray (PYOclean spray) or placebo (PYOclean spray) for 8 weeks. The assessment of pruritus, clinical, and cytological scores was performed every 2 weeks. At the end of the study, a significant reduction in all scores was seen. Specifically, the results of this study confirmed the powerful antimicrobial and anti-inflammatory activity of the sodium hypochlorite and salicylic acid combination as an alternative treatment option for canine superficial pyoderma.

**Essential oils/plant extracts**

Several in vitro studies have been published on the effects of essential oils and plant extracts against gram-positive and gram-negative bacteria. For some of these compounds, the antibacterial activity has also been tested and confirmed in vivo. Specifically, extracts of *Melaleuca alternifolia* (tea tree oil) have been proven to be highly effective in killing isolates of *S aureus* and *E coli* at concentrations of 4.34 mg/mL and 2.17 mg/mL, respectively. At these concentrations, such extracts were also able to inhibit bacterial adhesion and biofilm formation. Unfortunately, the bacteria demonstrated an adaptation to the essential oil treatment. This phenomenon was clearly replicated by a study testing the effects of sublethal doses of *Oreganum vulgare* (oregano), *Melaleuca alternifolia* (tea tree), *Cinnamomum cassia* (cassia), and *Thymus vulgaris* (white thyme) on several Gram-positive and Gram-negative bacteria. Specifically, the results of this study showed that bacteria can easily adapt to repeated exposure to sublethal doses of tea tree more commonly than white thyme. Bacteria were less commonly adapted to repeated exposure to sublethal concentrations of oregano.

More recently, a series of articles has been published on the clinical use of spot-on, shampoo, and spray formulations containing essential oils (PYOclean and PYOspot; Demoscent Laboratories, Castres) and hemp seeds. The first study was a double-blinded, placebo-controlled clinical trial in dogs (*n* = 12) with a superficial pyoderma. Dogs once enrolled were treated with oral cephalixin for 4 weeks. In addition, half of the dog was sprayed every 12 hours with essential oil spray (PYOclean spray) or placebo. Clinical, cytological, and total pyoderma scores were assessed at the beginning and at the end of the study. From day 7 to day 21, a significant reduction in total pyoderma score, but not in clinical and cytological scores, was seen between treatment and placebo. The authors concluded that the use of this spray accelerated the clinical cure of pyoderma when associated with systemic antimicrobial treatment.

The second study assessed the use of the spot-on formulation of this line of products against localized pyoderma in dogs. For this open-label study, dogs (*n* = 20) with localized pyoderma were enrolled and treated with weekly spot-on applications (PYOspot) for 8 weeks. The assessment of pruritus and clinical and cytological scores was performed every 2 weeks. At the end of the study, a significant reduction in all scores was seen. Specifically, a reduction of 83.4%, 74%, and 62% was seen for the pruritus, clinical, and cytological score, respectively.

The third study was presented as an abstract at the 9th World Congress of Veterinary Dermatology. In this double-blind, placebo-controlled clinical trial the authors assessed the use of the weekly spot-on formulation (PYOspot) (*n* = 14) or placebo (12) as a preventative option for dogs with recurrent superficial pyoderma. Dogs with ≥4 pyoderma outbreaks per year were enrolled in this 1-year-long study. At the end of the study, there was a statistically significant reduction (60%) in the number of relapses in the treatment group (79% reduction from baseline) when compared to placebo (50% reduction from baseline).

At the same international meeting, the fourth study was presented as another abstract. The study showed the equivalence of twice weekly shampoo (PYOclean shampoo) plus daily spray (PYOclean spray) or mousse (PYOclean mousse) formulation of essential oils when compared to twice weekly 2% chlorhexidine/2% miconazole with microsilver...
(Biohex shampoo; VetBioTek Inc) shampoo after 14 days of treatment for superficial pyoderma. For this study, dogs (n = 30) were assigned to 1 of the 3 groups and assessed weekly for pruritus, clinical, and cytological scores. After 14 days of treatment, all dogs showed a significant reduction in all assessed parameters with a lack of difference among treatments. These data indicate the equivalence between essential oil and chlorhexidine formulations for the treatment of superficial pyoderma in dogs. Altogether, these 4 studies suggest the possibility of essential oil formulations as possible alternatives to chlorhexidine treatments or a suitable adjuvant to systemic antibiotic therapy for the treatment of superficial pyoderma in dogs.

Another plant extract that has gained increasing interest for the treatment of bacterial infections is Aloe vera extract. Aloe vera extracts and gels have been shown to have significant in vitro antimicrobial activity against gram-positive and gram-negative bacteria. Recently, the use of a gel ointment containing 20% and 40% of Aloe vera was tested in dogs (n = 20) with experimentally induced staphylococcal pyoderma and compared to 1% gentamicin ointment. The ointments were applied twice daily for 2 weeks, and clinical scores as well as serological inflammatory, oxidant, and antioxidant parameters were measured. At the end of the study, there was a decrease in the size of the pyoderma lesions in all groups when compared to the nontreated group. A lack of difference was seen between Aloe vera and gentamycin formulations with dogs reaching clinical cures between 10 and 14 days posttreatment. Serologically, dogs treated with Aloe vera had lower haptoglobin and tumor necrosis factor alpha compared to the gentamicin group.

Plant extracts have also been investigated for their significant immunomodulatory effect on the natural immune defense in mammalians. In particular, the use of a spray containing Peumus boldus (wild mint) and Filipendula ulmaria (meadowsweet) extracts has been shown to significantly decrease the bacterial burden in a double-blinded, placebo-controlled clinical trial. In this study, atopic dogs (n = 20) were treated daily with either the spray containing plant extracts or placebo for 4 weeks. At the end of the study, a significant reduction in Staphylococcus sp organisms and total bacterial count was seen on days 14 and 28 with an overall reduction of 71% and 55% of staphylococcal bacteria in the treatment group against the 26.4% and 23.7% reduction in the placebo group on day 14, and 28, respectively.

Finally, a more recent study tested the antimicrobial activity of a Water Extract of Complex Mix of Edible Plants (WECMEP). The WECMEP is a solution of ingredients extracted from Arbutus unedo, Arctostaphylos uvaursi, Camellia sinensis, Combretum micranthum, Eugenia caryophyllus, Foeniculum vulgare, Fucus vesiculosus, Juniperus communis, Lippia citriodora, Rheum palmatum, Rosmarinus officinalis, Satureja montana, Spiraea ulmaria, Tanacetum parthenium, Valeriana officinalis, and Vitis vinifera. In this evaluator-blinded cross-over study, dogs (n = 9), with experimentally induced pyoderma, were treated twice daily with WECMEP or vehicle for 11 days and clinically assessed for 14 days. At the end of the study, treatment with WECMEP significantly reduced lesion development as quickly as 2 days when compared to placebo.

**Sodium oxychlorosene**

Sodium oxychlorosene (CLORPACTIN WCS-90; United-Guardian Inc) is a highly reactive chemical compound stabilized by the combination of the sodium salt of dodecylbenzenesulfonic acid and hypochlorous acid. When sodium oxychlorosene is dissolved in water, the hypochlorous acid is released acting as a detergent and oxidizing agent. Sodium oxychlorosene is extremely safe and has been used for decades in human medicine to treat a variety of infections. Sodium oxychlorosene is reconstituted to a concentration of 0.2% to 0.4% for topical use. With the 0.2% solution being safer perioricularly. Sodium oxychlorosene solution can be applied as irrigation, spray, wet wound packs, or as a bath rinse up to 4 times daily.

Very recently, a pilot study testing the in vitro efficacy of 0.2% and 0.4% sodium oxychlorosene solution against MRSP isolates (n = 27) has been published. Sodium oxychlorosene was able to rapidly kill bacteria at both concentrations tested. The 0.2% solution was able to have a profound reduction (6.1-log reduction) of the bacteria load after only 1 minute of exposure, with a 3.4-log reduction achievable after only 5 seconds of exposure time. The 0.4% solution achieved a bacterial reduction equal to 4.9-log after only 5 seconds of exposure time, leading to a 100% bacterial killing after only 10 seconds of exposure.

The results of this study suggest that sodium oxychlorosene would be a great topical antimicrobial agent to be used in clinical practice. This compound has a long-standing history of use in human medicine, and because of its high safety profile and low cost, it would be a great compound to be further tested in the clinical setting.

**Nanosulfur**

Nanotechnology has been of extreme help in the advancement of medicine and engineering. Compounds like nano- and microsilver are known for their powerful antimicrobial activity. Elemental sulfur has been known for centuries for its antimicrobial activities. Very recently, the use of nanoclusters of sulfur (nanosulfur) has also been investigated in veterinary microbiology.

In this study, the authors tested the antibacterial and biofilm activity of nanosulfur against MDR isolates of S pseudintermedius (n = 10) and P aeruginosa (10) showing very promising results. Specifically, nanosulfur has been shown to be very well tolerated by canine keratinocytes indicating a very good safety profile. Nanosulfur has also been shown to be highly effective against S pseudintermedius with a concentration of 233.3 µg/mL solution able to kill 70% of the isolates tested (6-log reduction) after 24 hours of incubation. Unfortunately, nanosulfur
was not able to kill *P. aeruginosa* at the concentrations tested. In addition, when in the biofilm state 60% of the MDRSP isolates were killed at concentrations ranging from 233.33 to 1,866.7 μg/mL. In comparison, nanosilver was not effective against any of the isolates tested independently if in the planktonic or biofilm state showing a potential antimicrobial superiority of nanosulfur to nanosilver.

As with the sodium oxychlorosene, nanosulfur is extremely safe and low cost making it a very attractive alternative to other topical antimicrobials. The proven antibiofilm activity would be extremely useful in the treatment of resistant bacterial infections associated with biofilm production.

**Accelerated hydrogen peroxide and silver compounds**

Accelerated hydrogen peroxide and silver compounds are extremely attractive options for the treatment of superficial bacterial infections in dogs. However, since the previous review published in 2012, no studies have been published on the effect of such compounds on superficial pyoderma in dogs.

A recent clinical study compared the efficacy of twice-weekly shampoo plus daily spray or mousse formulation of essential oils to a twice-weekly 2% chlorhexidine/2% miconazole shampoo containing microsilver (Biohex shampoo) for the treatment of canine superficial pyoderma. In this study, the authors showed a 63% reduction in lesion score and a 70% reduction in pruritus score confirming the efficacy of microsilver with chlorhexidine against bacterial infections.

**Conclusions**

This review was designed to give the reader an idea of the breadth of compounds that are currently commercially available or have been tested for their antimicrobial properties. Unfortunately, MDR is in constant expansion and clinicians need alternative options to treat such infections. As reported here, many alternatives are available and ready to be tested in a clinical setting. Options like essential oils, bleach, sodium oxychlorosene, accelerated hydrogen peroxide, silver compounds, and nanosulfur offer attractive and cost-effective alternatives to the classic chlorhexidine-based products. That said, it is important to emphasize how chlorhexidine-, benzoyl peroxide-, and ethyl lactate-based products still represent extremely effective treatment options to treat MDR skin infections in dogs. In an era in which bacterial resistance is extremely common, topical antimicrobials with a low-resistance profile are essential for successfully managing superficial pyoderma in dogs. These antimicrobials allow for a significant reduction in the use of systemic (and topical) antibiotics to alleviate the antibiofilm pressure selecting for MDR bacteria. It is not possible to emphasize enough the need for better antimicrobial stewardship and reduction in the use of systemic (and topical) antibiotics in favor of compounds with a much lower resistance profile. To achieve such results more double-blinded, placebo-controlled clinical trials are needed for testing clinical applications of the extremely interesting compounds described in this review.

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**References**


