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REVIEW ARTICLE
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Nadežda B. TEŠIN[1], *Zorana R. KOVAČEVIĆ*[*]

[1] University of Novi Sad, Faculty of Agriculture, Department of Veterinary Medicine
Trg Dositeja Obradovića 8, Novi Sad 21125, Serbia

ANTIMICROBIAL PRINCIPLES IN THE DIAGNOSIS AND THERAPY OF CANINE PYODERMA: A REVIEW

ABSTRACT: Although bacteria are normal inhabitants of the canine skin, they play an essential role in the pathogenesis of canine pyoderma. As this skin disease is commonly presented in the small animal practice, the use of antibiotics in its treatment is on high level, although it is often misused. Consequently, excessive and irrational use of antimicrobials leads to the growth of antimicrobial resistance (AMR) and resistant bacterial strains. Therefore, it is necessary to follow the right therapy guidelines to provide appropriate treatment management which is crucial in any policy for prudent and rational antimicrobial use (AMU). Hence, this review aimed to summarize established evidence-based antimicrobial guidelines in treating pyoderma in order to help veterinarians in the fight against development of AMR and its further growth, as one of the highest threats to the public health and topics of the global concern.

KEYWORDS: antimicrobial guidelines, antimicrobial resistance, dogs, pyoderma, skin

INTRODUCTION

Cutaneous microbiota consists of various types of bacteria that normally live on the skin and within the ear pinna and canal (Bradley et al., 2020) and any disturbance that results as an itch or break of the skin can provide perfect conditions for them to multiply and cause inflammation and infection (Secker et al., 2023). Furthermore, one of the most common inflammatory skin conditions of the bacterial origin is pyoderma. In canine, clinical manifestation of this disease can include a wide range of lesions from erythema, alopecia and pruritus to serious cases such as deep folliculitis, furunculosis, vasculitis (Summers et al., 2014). Moreover, the division of this disease is based on depth of the pathological lesions and implies surface, superficial and deep pyoderma (May, 2006; Guardabassi et al., 2008).

[*] Corresponding author. E-mail: zorana.kovacevic@polj.edu.rs

Antimicrobial drugs are often included in the canine cutaneous infections treatment, but in many cases this is not effective because of the antimicrobial resistance (AMR) occurrence (Ebani et al., 2020). Furthermore, improper and imprudent antimicrobial use (AMU) in the veterinary health care systems may contribute to the AMR evolvement and could be responsible for the loss of drug efficacy (Mateus et al., 2011). Generally speaking, the number of drug-resistant (DR), multidrug-resistant (MDR) and (MR) bacteria strains has grown over the years (Beco et al., 2013). Interestingly, the appearance of MR *Pseudomonas aeruginosa*, specifically those resistant to drug used in humans but not that frequently used in dogs, can also be indicator of the overuse of these antibiotics or might suggest human-to-dog transmission (Dégi et al., 2021). Moreover, the frequent use of antimicrobials in general may be associated with the development of MDR (Zur et al., 2016), which influences on the different results of local susceptibility testing, due to local habits of using certain antibiotic. The migration effect in the modern global world, as one of the recent One Health problems, through the global interchange of goods by human travelers, migrating animals and even through the help of natural phenomena, could cause spreading of AMR, as well (Hernando-Amado et al., 2019). The rational AMU in the veterinary medicine can prevent the development and spread of resistance to antibiotics (especially those used in human medicine). Furthermore, it also contributes to preserving the effectiveness of antimicrobial drugs. Therefore, records on how, why and which antibiotics are used in the common animal practice, and the circumstances of their consumption, are required to establish whether upgrades are needed (Murphy et al., 2012), as well in order to monitor AMR. Hence, the aim of this review article is to present the existing clinical and bacteriological aspects of the pyodermas to guide for the selection of adequate antimicrobials, especially in order to combat AMR.

COMMON BACTERIAL AGENTS OF THE SKIN INFECTIONS

The bacteria from staphylococci group are normal residents of the human and animal skin (Hoffmann, 2017), however they are also known as the most commonly associated pathogens with skin infections, especially to pyoderma (May, 2006). As for the humans, the most frequently isolated pathogen from pyoderma cases is *Staphylococcus aureus* (Venniyil et al., 2016). Furthermore, MR *Staphylococcus aureus* (MRSA) represents a major pathogen in health care management in humans, as well as in animals, primarily because a lot of these isolates manifest MDR (Beck et al., 2012). However, the incidence of MRSA was generally lower among pets than is reported for livestock (Graveland et al., 2011). Moreover, although these bacteria can colonize or infect dogs and cats, they are not considered as a reservoir host of this pathogen. MR *Staphylococcus pseudintermedius* (MRSP) is more substantial in the veterinary field (Binek et al., 2019) and represents an example of how AMR has a contri-

bution in the treatment failure (Bryan et al., 2012). Similarly to MRSA, MRSP tends to be clonally distributed within countries, meaning that certain clones can be isolated from epidemiologically unrelated dogs and even from veterinary hospitals located at the distant geographical areas within the same country (Bannoehr et al., 2007). Frequent isolation of biofilm-producing *S. pseudintermedius* strains and their resistance to antimicrobials can influence the outcome of infection treatment (Naziri and Majlesi, 2023). Therefore, it is not surprising that this causative agent has become one of the main topics in the modern veterinary medicine. Apart form the mentioned, *Staphylococcus schleiferi* has been registered as a frequent causative agent in animals on emerge (Davis et al., 2013). Although it does not appear to own factors of virulence as other staphylococci, it posses the ability to cause serious infections in some patients (May, 2006). The increased number of coagulase-negative staphylococcal infections is in correlation with evolving medical treatments and advances in human and veterinary medicine (May, 2006). Furthermore, *Pseudomonas aeruginosa* is a frequent canine pathogen isolated from chronic otitis externa and media cases (Secker et al., 2023). However, it is uncommonly associated with skin infections and usually has low incidence in pyoderma cases (Guardabassi et al., 2008). Actually, these bacteria are presiding in chronic, suppurative skin infections, isolated independently or in mix infections (Leonard et al., 2022; Bradley et al., 2020). Other causative agents that can be associated with pyoderma are *Streptococcus* spp., *Proteus* spp., *E. coli* and other *Enterobacterales* (Nocera et al., 2021).

UNDERLYING CAUSES OF THE SKIN INFECTIONS

Most skin infections are secondary to some underlying primary cause (May, 2006; Summers et al., 2012; Beco et al., 2013). Primary bacterial infections can happen, but much less frequently (Guardabassi et al., 2008). Therefore, predisposing factor must occur in order for the infection to develop. Usually these factors include allergies, skin injuries, endocrine or keratinous disorders and the presence of inflammation or ectoparasites (Summers et al., 2012; Beco et al., 2013). Conditions such as allergy can cause not only unpleasantness and agitation to the dog, but also stress and disturbance to its owners (Miller et al., 2023). Furthermore, prosperous management demands that these factors are addressed, so it is essential that history and clinical signs are well assessed to determine the underlying processes (Beco et al., 2013). These infections are more likely to happen without proper managing of the underlying causes (May, 2006). It is important to emphasize that repeated pyodermal infections caused by *S. pseudintermedius* isolates have shown significantly higher resistance than those isolated from previous cases, so identification and elimination of the predisposing factors are crucial to avoid recurrence of infections (Holm et al., 2002), as well as to mitigate AMR.

ANTIBIOTIC SUSCEPTIBILITY TESTS – YES OR NO?

When a medical condition exists, it is important to obtain an accurate clinical diagnosis whenever possible, including determining the likelihood of a bacterial infection that warrants AMU. Isolation and identification of microorganisms included in the canine skin diseases are a key and elementary step in both diagnostics and adequate treatment (Beier et al., 2015; Hillier et al., 2006). The incidence and constancy of isolation should be taken into account while distinguishing normal residents from the microorganisms that cause secondary settlement and contamination instead of the infection (May, 2006). This is essential in order to create an efficient treatment plan for a certain causative agents based on culture and susceptibility test results, particularly when various microorganisms are present (May, 2006).

Skin infections of bacterial origin are frequent in the canine and the empiric choice of antimicrobial therapy is a general approach to reduce the clinical evolution (Dégi et al., 2021). In the case of empirical treatment, a rational approach should be chosen, selecting the prudent and economically acceptable drug that is efficient against expected microorganism (May, 2006). On the other hand, as reiterated episodes of empirically prescribed antibiotic therapy have been recognized as one of the most important risk factors for infections caused by MRSA in pets, failure in therapy should always be followed by reassessment, involving culture and antibiotic sensitivity tests, rather than switching to another empirically selected antimicrobial drug (Magalhães et al., 2010). In addition, in recurrent infections or with appearance of newly discovered lesions regardless of the application of adequate antimicrobial, adjustments in treatment should be made based on the culture and susceptibility data (May, 2006). In the severe cases of pyoderma, antimicrobial susceptibility should be considered imperative (Dégi et al., 2021).

THE TREATMENT APPROACHES IN THE CANINE PYODERMA

The treatment approach for canine pyoderma differs with the deepness of the infection (Loeffler et al., 2011). The vast majority of skin infections in the companion animals are associated with coagulase-positive staphylococci, especially with *S. pseudintermedius*. Hence, a broad spectrum of antibiotic groups has been recommended for therapy of pyoderma caused by staphylococci based on their in vitro efficacy testing, experience from in vivo studies and clinical trial results (Summers et al., 2012). Moreover, if inadequate smaller doses of antimicrobials are used or length of time is too brief, staphylococcal cultures are changing so that antibacterial-resistant isolates are selected, guiding to chronic cases of infections (Hnilica and May, 2004).

Although there are plenty of topical antimicrobial pharmaceutical formulations available and licensed for use in the veterinary practice against skin infections worldwide, superficial pyoderma still remains a frequent occurrence

in dogs (Loeffler et al., 2011; Mueller et al., 2012). Topical treatment by itself should be taken into consideration, especially in cases where long-term treatment is expected, such as recurrent infection of superficial pyoderma which, due to the underlying cause, were not detected and rectified on time (Loeffler et al., 2011).

Animals which are under antimicrobial therapy can be particularly at risk for acquisition resistant microorganisms, considering the fact that antimicrobial therapy may promote the transmission of microorganisms through antibiotic-induced reduction of the normal inhabitant population of staphylococci (Loyd, 2005). In addition, systemic antimicrobial treatment may not be ideal considering an enlargement of multiresistant organisms, cost and potential side effects (Mueller et al., 2012). Furthermore, conditions such as deep folliculitis, furunculosis and cellulitis usually require extend treatments. While cicatrization can make it even more complicated, these lesions may also be painful and microorganisms, such as *Pseudomonas* spp., *E. coli* or *Proteus* spp. may be included, besides staphylococci (May, 2006). Thus, systemic antimicrobial treatment is generally indicated in cases such as deep pyodermas, as well as in cases of unsuccessful topical therapy or when it can not be applied properly (Loeffler et al., 2011).

Beta-lactams are one of the most common classes of antimicrobials prescribed in pets for systemic administration (Beaudoin et al., 2023). Rantala et al. (Rantala et al., 2004) have established that cephalexin and amoxicillin with clavulanic acid accounted for 60% and 15%, respectively, of all the antibiotics prescribed for pyoderma infections, followed by clindamycin (10%). Beside mentioned antibiotics, fluoroquinolones (enrofloxacin, marbofloxacin, difloxacin and orbifloxacin) are very efficient in pyoderma treatment and are commonly used for empirical treatment in dogs because of their favorable safe profiles and assured clinical efficacy due to proven antimicrobial activity against *S. pseudintermedius* and skin distribution (Guardabassi et al., 2008). Moreover, the "OIE List of Antimicrobial Agents of Veterinary Importance" suggest that fluoroquinolones and the 3rd and 4th generation cephalosporins, as critically important antimicrobials in human and animal health, should not be used as preventive treatment and as the first line treatment unless they are justified, while when used as the second line, they should be based on the bacteriological tests results. The extra-label or off label use of antimicrobials should be restricted and restrained for cases where there are no alternatives available and should be in accordance with the applicable national legislation (OIE, 2021).

The use of antimicrobial drugs in pets should be assessed based on infectious disease treated in the affected population, available regulations and guidelines, current scientific knowledge and licensed drugs available for veterinary use, research-based knowledge and licensed antimicrobials disposed for use in veterinary medicine (Mateus et al., 2011). The Antimicrobial Stewardship Guidelines in pets are designed to assist veterinarian clinicians in selecting the adequate antimicrobial therapy that will best serve their patients while mitigating the AMR growth and other side effects (Frey et al., 2022). For instance, the

guidelines for the treatment of canine pyoderma were already created by the different groups of experts in this field (Table 1). These guidelines should be followed when treating this disease. Based on these guidelines, topical treatment is recommended for treatment of superficial pyoderma, whereas for deep ones, there should be used systemic therapy based on sensitivity testing, supported by topical treatment with antiseptics. For mild, surface and/or focal infections, topical antiseptic preparation and topical antibiotics or locally applied antimicrobials are suggested (in case topical antiseptics do not clear the infection) (Frey et al., 2022; Beco et al., 2013). Topical antiseptic solutions can speed up infection resolution or will significantly reduce the need for systemic antimicrobials (Beco et al., 2013). In the study of Borio et al. (Borio et al., 2015) treatment with chlorhexidine products resulted in clearing of clinical signs of superficial pyoderma in all dogs (including those infected with MRSP). Actually, this study indicated that topical therapy with chlorhexidine may be as effective as systemic therapy with amoxicillin with clavulanic acid, which supports the recommendations of existing guidelines to use topical antiseptics alone for the management of superficial pyoderma (Borio et al., 2015).

The common fact for all guidelines is that systemic antimicrobials are classified in three tiers (lines). First-tier usually implies broad-spectrum drugs that are used when diagnosis is clear and risk factors for AMR do not exist, but they are not considered less-efficient than higher-tier drugs in the correct circumstances (Beco et al., 2013; Hillier et al., 2014). Clindamycin is one of the first-tier drugs in all suggested guidelines (Table 1). However, recent study conducted in Netherlands has shown the high level of resistance to clindamycin in *S. pseudintermedius* isolated from dogs with previous antimicrobial exposure, recommending that a bacterial culture and sensitivity test should be carried out before prescribing these drugs and it should be regarded as the preferred treatment option if susceptibility is confirmed (van Damme et al., 2020). These results indicate that clindamycin might be reconsidered as tier-two drugs which should be used when culture evidence exists. Furthermore, tier-three drugs are very important to animal and human health, especially for treatment of MR organisms, so they are reserved for highly resistant infections and their use should be in consultation with specialists (Beco et al., 2013; Hillier et al., 2014). In Table 1, it can also be seen that dissimilarities exist in the distribution of antimicrobials through group of different guidelines. Existence of the variation in the antibiotic susceptibility patterns of pyoderma causative agents on the local level and dissimilarities in accessibility of drugs, legal status and cost, these all can have influence on the drugs efficiency within various clinical populations and geographical area (Summers et al., 2012; Hillier et al., 2014). Therefore, it is difficult to provide adequate evidence to publish ultimate best practice guidelines for the empiric treatment of superficial and deep pyoderma in dogs (Summers et al., 2012). Thus, every country needs to implement their own guidelines for treating pyoderma cases, based on the national and regional records. In addition, surveys that provide these details should be conducted regularly in order to ensure valuable and updated data.

Table 1. Available referenced guidelines for the pyoderma treatment with suggested principles for rational antimicrobial use through their categorization

Guidelines	Category	Antibiotics
Suggested guidelines for using systemic antimicrobials in bacterial skin infections: part 2 – antimicrobial choice, treatment regimens and compliance (Beco et al., 2013)	First-line	cefadroxil, cefalexin, clavulanate-amoxicillin, clindamycin, lincomycin
	Second-line	cefovecin, cefpodoxime, difloxacin, enrofloxacin, marbofloxacin, orbifloxacin, pradofloxacin
	Third-line	aminoglycosides, azithromycin, ceftazidime, chloramphenicol, clarithromycin, florphenicol, imipenem, phosphomycin, piperacillin, rifampin, tiamphenicol and ticarcillin
Australian Veterinary Prescribing Guidelines: Companion Animals Medical Guidelines-Skin	First-line	clindamycin
	Second-line	cephalexin, amoxycillin-clavulanate, trimethoprim-sulphonamide, doxycycline
	Third-line	enrofloxacin, marbofloxacin, cefovecin
2023 AAHA Management of Allergic Skin Diseases in Dogs and Cats Guidelines (Miller et al., 2023)	First-tier empiric	clindamycin, cephalexin, amoxicillin-clavulanate, trimetrorim-sulfadiazine/sulfamethoxazole
	First OR second tier	cefpodoxime, cefovecin
	Second tier ONLY with culture and susceptibility	minocycline, doxycycline, enrofloxacin, marbofloxacin, radofloxacin, chloramphenicol, rifampin
	Do NOT use for *Straphylococcus* spp. infections	amoxicillin, penicillin, nitrofurantoin
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) (Hillier et al., 2014)	First-tier	clindamycin or lincomycin cefalexin, cefadroxil, amoxicillin–clavulanate, trimethoprim- and ormetoprim-potentiated sulphonamides
	First or second tier	cefovecin, cefpodoxime
	Second tier	doxycycline or minocycline, hloramphenicol fluoroquinolones (such as enrofloxacin, marbofloxacin, orbifloxacin, pradofloxacin and ciprofloxacin), Aminoglycosides (gentamicin, amikacin), first tier drugs (clindamycin, lincomycin and potentiated sulphonamides) may also be considered
	Third tier	linezolid, teicoplanin, vancomycin

FUTURE OPTIONS OF PYODERMA TREATMENT

There are several new approaches under development for the management of skin and ear infections and inflammation. Although more clinical trials are needed to confirm efficacy, early results (especially *in vitro* studies) are promising (Nuttall, 2023). For instance, natural products, such as essential oils (EOs),

with antimicrobial properties, could represent a suitable alternative in the treatment of skin infections, mainly when conventional drugs resulted not effective (Ebani et al., 2020). The *in vitro* study conducted by Ebani et al. (Ebani et al., 2020) tested antimicrobial activity of nine EOs against staphylococcal skin isolates resulting in different antimicrobial activity degrees. *Origanum vulgare* and *Thymus vulgaris* EOs have shown the best antimicrobial activity, indicating that pharmaceutical formulation, based on these Eos, could be promising treatment to combat canine cutaneous infections caused by these pathogens.

CONCLUSION

As bacterial skin infections are one of the most common diseases presented in pets, responsible therapy approaches are crucial in order to prevent overuse of antimicrobials. A correct management of antimicrobial policy through the regular implementations of AMR patterns of the frequently isolated microorganisms is crucial to avert needless prescriptions and further emergence of resistant strains. Promoting responsible use of antimicrobial drugs through guidelines will ensure tenable access to the most efficient therapy. Furthermore, implementing best practical guidelines based on the national and regional records will improve human and animal health, while simultaneously providing reduce of emerge and spread of AMR.

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АНТИМИКРОБНИ ПРИНЦИПИ У ДИЈАГНОСТИЦИ И ТЕРАПИЈИ ПИОДЕРМЕ ПАСА: ПРЕГЛЕД

Надежда Б. ТЕШИН, Зорана Р. КОВАЧЕВИЋ

Универзитет у Новом Саду, Пољопривредни факултет,
Департман за ветеринарску медицину,
Трг Доситеја Обрадовића 8, Нови Сад 21125, Србија

РЕЗИМЕ: Иако су бактерије нормални становници коже паса, оне имају суштинску улогу у патогенези псеће пиодерме. Како се ова кожна болест често јавља у пракси малих животиња, употреба антибиотика у њеном лечењу је на високом нивоу, а често се може злоупотребити. Сходно томе, прекомерна и нерационална употреба антимикробних средстава доводи до раста антимикробне резистенције (АМР) и резистентних сојева бактерија. Због тога је неопходно пратити исправне смернице за терапију како би се обезбедио одговарајући третман који је кључан у свакој политици за разумну и рационалну употребу антими-

кробних средстава (АМУ). Стога је овај преглед имао за циљ да сумира утврђене антимикробне смернице засноване на доказима у лечењу пиодерме како би се помогло ветеринарима у борби против развоја АМР-а и његовог даљег раста, као једне од највећих претњи за јавно здравље и најзначајнијих тема од глобалног значаја.

КЉУЧНЕ РЕЧИ: антимикробне смернице, антимикробна резистенција, пси, пиодерма, кожа