FOCUS ON PYODERMA

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CONTENTS

Page 4: Introduction

Page 5: History taking in canine pyoderma

Page 6–7: Clinical examination

Page 8–9: Diagnostic testing in canine pyoderma

Page 10–12: Antimicrobial therapy

Page 13: Summary

Page 14: References

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INTRODUCTION

Pyoderma is best defined as a cutaneous pyogenic infection. The dog seems particularly susceptible to bacterial skin disease amongst the veterinary species, and pyoderma is a common diagnosis in canine practice. Canine pyoderma commonly poses diagnostic challenges, due to its varied clinical presentation and tendency to be super-imposed on other skin diseases. Therapy is also potentially challenging, especially in relapsing cases, cases where concurrent diseases are not corrected, and/or where infection is associated with multidrug-resistant bacteria.

The majority of canine cases are associated with Staphylococcus pseudintermedius (formerly S. intermedius). This is a commensal organism on healthy canine mucosa / skin and perturbation of normal skin defence in the presence of strains of appropriate virulence is necessary for infection to develop. It therefore follows that dogs presenting with pyoderma should be carefully evaluated for diseases that impair immunity or skin barrier function because incomplete clinical response and/or relapsing infection can be anticipated if these are not diagnosed and treated. Other bacteria, including other staphylococci, streptococci and Gram-negative rods, are less frequently isolated.

It is traditional to classify pyoderma according to depth of infection into surface, superficial and deep forms of the disease. Whilst this is technically a histological classification, it is often possible to determine which form is most likely from the clinical signs (Table 1). This scheme has practical implications for therapy since response to topical treatments can be anticipated with surface and sometimes superficial infection (assuming correct application and compliance), whereas deep pyoderma cases most often require a systemic route of administration (Fig. 1).

In one survey of 428 dogs with skin disease seen in first opinion practice in the UK, pyoderma (62 cases, 14.5%) was second only to otitis (104, 24.3%) in cases with a specific dermatological diagnosis (Hill et al., 2006). In another review of 54,600 dogs presented to 73 UK veterinary practices in 2010, a diagnosis of pyoderma was retrieved from electronic patient records in 663 cases (1.3%) (Summers et al., 2014).

It is important to differentiate cases of persistent infection (suggesting poor compliance, wrong drug / dose / duration, resistance, or wrong diagnosis) from truly recurrent cases (as seen in cases where pyoderma has fully resolved but ongoing underlying disease or immune failure allows re-infection). Persistence of pruritus following successful treatment of pyoderma with antibiotics alone is a typical observation in dogs with underlying allergic diseases, and/or concurrent Malassezia dermatitis; dorso-lumbar pruritus is most common in flea allergy whereas a facial, aural, ventral and/or pedal distribution is reported routinely in cases of (food and non-food-induced) atopic dermatitis.

A combination of owner report and record scrutiny should establish the specific details of prescribed treatments and results of any sampling procedures. An assessment of general health is critical for the detection of systemic and metabolic diseases that might favour pyoderma. Review of ecto-parasite control measures and the likelihood of their reliable implementation, history of potential transmission of skin disease between other pet animals, wildlife and owners, along with reports of observed parasites, should help quantify the risk of a parasitic cause.

Table 1. Classification of canine pyoderma and associated histological and clinical features

<table>
<thead>
<tr>
<th>Type of pyoderma</th>
<th>Anatomical location</th>
<th>Histological inflammatory pattern</th>
<th>Typical clinical signs*</th>
<th>Route of treatment administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface</td>
<td>Inter-follicular epidermis</td>
<td>Erosive neutrophilic epidermitis#</td>
<td>Moist exudation and erosion, (e.g. hot spots, fold dermatitis)</td>
<td>Primarily topical</td>
</tr>
<tr>
<td>Superficial</td>
<td>Inter-follicular epidermis + within intact follicle</td>
<td>Neutrophilic luminal folliculitis</td>
<td>Pustule, preceded by papule, evolving to collarette/crust</td>
<td>Topical and/or systemic</td>
</tr>
<tr>
<td>Deep</td>
<td>Extension into dermis from ruptured follicle</td>
<td>Neutrophilic luminal folliculitis / furunculosis</td>
<td>Nodules, furuncles, sinus tracts</td>
<td>Primarily systemic</td>
</tr>
</tbody>
</table>

*Not comprehensive; # rarely biopsied

The goals in history-taking in cases of pyoderma are to establish the course and duration of disease (differentiating first episodes from recurrent or persistent cases), to ascertain outcomes of any previous diagnostic testing and treatments, and to evaluate the case for evidence of concurrent diseases that might increase likelihood of infection or interfere with the diagnostic or therapeutic plan.

### HISTORY TAKING IN CANINE PYODERMA

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Surface pyoderma

Fold dermatitis (intertrigo) is clinically distinctive wherein inflammatory skin lesions are confined to facial, lip, neck, vulval (Fig. 2) or body folds. Accordingly specific breeds are most likely to be affected (for example, facial fold dermatitis in brachycephalic dogs (Fig. 3)). Lesions comprise erythema and varying degrees of exudation and erosion. Differential diagnoses are normally limited to Malassezia dermatitis (which may mimic or co-exist with bacterial infection), mucocutaneous pyoderma (usually involving the lips and face) and rare cases of immune-mediated erosive diseases, most often associated with the vulvar folds. When suspected, these disorders cannot be excluded on clinical grounds alone and further tests are necessary to confirm the diagnosis.

There is controversy whether pyotraumatic dermatitis (acute moist dermatitis, ‘hot spot’) represents a surface pyoderma (an infection by definition) or mere bacterial colonisation of an area of self-trauma (Holm et al., 2004, Cobb et al., 2005). These lesions typically develop rapidly in dogs that traumatise a single area, usually on the rump or neck, with intense pruritus, erosion and purulent exudation that mats overlying hair. These lesions must usually on the rump or neck, with intense pruritus, erosion and typically develop rapidly in dogs that traumatise a single area, deep pyoderma (Fig. 4).

Superficial pyoderma

The typical primary lesion of this most common form of canine pyoderma is a pustule that may occur in the interfollicular epidermis or centred on a hair follicle (hair emerges from lesion). These transient lesions are preceded by papules and evolve to crusts or epidermal collarettes; intact pustules are usually less frequently seen than the other lesions (Fig. 5). The groin and medial thighs are important sites although lesions commonly affect the dorsal and lateral trunk in some patients. Sterile pustular diseases are rare but important differential diagnoses, especially in cases where lesions occur on the face or pinnae, where bacteria are absent on cytology/culture, and when rational antibiotic therapy is ineffective.

Deep pyoderma

Deep pyoderma can present in a variety of different ways. Examples of localised disease include callus pyoderma (secondary infection of elbow and hock pressure calluses), pyotraumatic folliculitis (Fig. 4), and focal digital (Fig. 6) or interdigital lesions (most commonly a complication of conformational pododermatitis). More generalised disease can be seen in dogs with concurrent superficial lesions; important target sites include the trunk, although the feet are commonly infected in cases of pododermatitis. Typically purulent exudation can be expressed from inflamed, swollen or thickened skin. Some cases should be differentiated from infection caused by fungi or atypical bacteria, or immune-mediated processes such as perianal fistulae or panniculitis. All deep pyoderma cases in dogs must be systematically and thoroughly evaluated for underlying demodicosis.
Canine pyoderma commonly poses diagnostic challenges, due to its varied clinical presentation and tendency to be superimposed on other skin diseases. The goals of diagnostic testing are:

- to confirm the presence (thus supporting a clinical diagnosis) or absence of bacteria by cytological evaluation,
- to accurately identify the nature of the potential pathogen(s) by culture and likely effective therapy by sensitivity testing,
- to identify or exclude concurrent diseases likely to mimic or favour skin infection.

A key clinical step is the recognition of the lesion types displayed by the patient, as this then dictates what investigations are most appropriate. Interpretation of test results from skin samples is complicated by the presence of a commensal microbiota which includes common pathogens such as *Staphylococcus pseudintermedius* and *Malassezia* spp. yeasts. The nature and extent of the investigations are commonly modified according to duration and severity of clinical disease, as well as the wishes, expectations and resources of the owner.

Surveys indicate that cytological testing is infrequently done in dogs with skin disease in general veterinary practice; whereas it is routine in referral practice. The cytological techniques are rapid and inexpensive to perform, and require only basic laboratory facilities.

**Tape-stripping**

Tape-stripping is a versatile method for skin sampling and is especially indicated for the sampling of skin folds (surface pyoderma) and lichenified plaques (bacterial overgrowth). In either scenario, bacteria and or *Malassezia* spp. may be observed. In skin fold lesions, mixed infections with rods and cocci are often seen, whereas in bacterial overgrowth a monomorphous population of (staphylococci) cocci can be expected.

Clear adhesive tape is applied to the lesion of interest, removed, stained with Diff-GuiK, and examined using the x100 oil-immersion objective. Tape-stripping provides a semi-quantitative assessment of microbial populations; occasional bacteria might represent commensal bacteria whereas very large numbers can be expected in cases of infection. This method is also useful in monitoring the response to therapy.

**Bacterial culture**

Bacterial culture is normally performed using swabs from intact pustules (or epidermal collarettes) in superficial pyoderma, or discharging lesions in deep pyoderma. Culture and sensitivity testing is less often indicated in surface pyoderma where topical therapy with biocides is popular, and since in vitro culture results are not optimised for the high concentrations of drug achieved by the topical use of antibiotics.

International concern over the emergence of multi-drug resistant bacteria has led to an increased awareness for responsible antibiotic use, which in turn makes culture more desirable (“the right drug for the right bug”). Culture is especially indicated in deep pyoderma (often severe lesions, mixed infections), in superficial cases that relapse or are refractory to therapy, and when rods are identified in cytological specimens (Fig. 4), as these bacteria tend to have unpredictable sensitivity patterns.

Care should be taken to sample representative lesions, and to rapidly deliver a swab in transport medium to the laboratory with sufficient clinical history to enable the laboratory to select appropriate cultural conditions. In cases of pyoderma, routine procedures are likely to be sufficient but observation of unusual/rare organisms such as actinomycetes on cytology should be reported.

**Direct impression**

Direct impression with a glass slide is more appropriate for lesions of superficial pyoderma characterised by pustules and epidermal collarettes. Intact pustules are ideal lesions to sample: a fine needle is used to open the head and then the slide is applied to the bead of pus, air-dried and stained.

In cases of superficial pyoderma, large numbers of degenerate neutrophils with intra- and extracellular bacteria (usually cocci) are readily demonstrated (Fig. 7). When pustules cannot be identified, an impression of inflamed skin exposed by peeling back the scale at the margins of epidermal collarettes is a useful alternative. In deep pyoderma, impressions from furuncles and sinus tracts are likely to yield degenerate neutrophils and varying numbers of macrophages whereas bacteria can be expected to be much less abundant when compared with superficial lesions.

**Additional tests**

A variety of additional tests should be routinely considered in cases of superficial and deep pyoderma, in case of alternative diagnoses or concurrent diseases (see flowchart below).

In cases where dermatophytosis is possible, Wood’s lamp examination, direct microscopy and fungal culture should be considered. Evaluation for ectoparasitic infestation should be routinely considered, for example for fleas in superficial pyoderma, and for demodicosis in superficial and especially deep pyoderma. Coat brushings, skin scrapings and hair plucks are most useful in these circumstances.

**Skin biopsy**

Skin biopsy specimens might show inflammatory patterns that support a diagnosis of pyoderma. However, histopathology is arguably most useful for differentiating pyoderma from other inflammatory diseases when the latter are suspected, and in the search for underlying diseases once pyoderma has been resolved.
Are systemic antibacterial drugs necessary?

The traditional therapeutic approach to superficial and deep pyoderma was to provide oral antibiotics; in an extensive survey of primary-care prescribing practices conducted in the UK in 2010, 91.9% of 659 dogs received at least one systemic antimicrobial (Summers et al., 2014). The need to limit the emergence of antimicrobial resistance prompted a FECAVA working group on antimicrobial use to present guidelines for a more critical appraisal of their need (http://www.fecava.org/content/guidelines-policies); they suggest the use of antiseptics as a preferred alternative for conditions such as surface and superficial pyoderma, and when a delay to the use of a systemic antimicrobial will not negatively impact on the animal’s wellbeing.

Whilst the primary-care survey mentioned above showed that concurrent topical therapy was prescribed in 182 of 659 (27.7%) cases of pyoderma, topical therapy alone was used in only 31 dogs (4.7%) (Summers et al., 2014). These data indicate that a significant change in veterinary prescribing practice (and likely owner expectation and education) is needed if these guidelines are to be adopted.

Topical products of potential value include chlorhexidine alone or in combination with miconazole or EDTA, benzoyl peroxide, oxychlorine products (sodium hypochlorite and hypochlorous acid), and fusidic acid (Jeffers, 2013, Loeffler et al., 2012, Clark et al., 2015). In a recent evidence-based review (Mueller et al., 2012), good evidence of efficacy in canine pyoderma was identified for chlorhexidine, and to a lesser extent, benzoyl peroxide.

Should I perform a bacterial culture and susceptibility test in superficial and deep pyoderma?

Historically it was unusual for an empirically-selected anti-staphylococcal antibiotic to be ineffective in canine pyoderma but with the emergence of multidrug-resistant bacteria this is no longer the case. It has been usefully stated that a culture is ‘never contra-indicated’, and according to ISCAID guidelines (Hiller et al., 2014), culture is mandated in specific clinical circumstances in superficial pyoderma (Table 2.)

Culture mandated should any of the following apply:

- <50% improvement within 2 weeks of starting treatment
- New lesions developing 2 weeks after starting treatment
- Ongoing lesions with cocci in cytological specimens after 6 weeks of treatment
- (intracellular) rods in cytological specimens
- History of multidrug resistant organism in patient or in-contact animal

Empirical treatment without culture appropriate if:

- First episode of a superficial infection
- Following ineffective antiseptic therapy
- Only coccosid bacteria observed on cytology (not rods)
- No reasons to suspect antibiotic resistance

Empirical antibiotic choices

Various organisations have made recommendations on which antibiotics are appropriate for empirical use in canine pyoderma. FECAVA guidelines approve trimethoprim sulphonamide, clindamycin and cephalaxin for superficial pyoderma, and cephalaxin pending culture and sensitivity testing for deep pyoderma. ISCAID guidelines (which apply only to superficial pyoderma) refer to antibiotics suitable for empirical use as ‘first-tier drugs’; these include potentiated sulphonamides, clindamycin, first generation cephalosporins (includes cephalexin), and co-amoxiclav (Hiller et al., 2014). Anecdotal reports suggest that cephalaxin is strongly favoured by many dermatology specialists, although this approach is actively discouraged as a first-line approach in some countries due to the risk of selecting for methicillin-resistant staphylococci. The ISCAID working group was unable to reach consensus on whether cefovecin should be considered a ‘first-tier’ or ‘second-tier’ drug, in part due to concerns over potential for selection of extended-spectrum ß-lactamase-producing Escherichia coli (Hiller et al., 2014).

Duration of treatment

The majority of cases of superficial pyoderma show a rapid response to treatment within 1-2 weeks and are resolved within 3 weeks, although individual cases may take up to 6 weeks to recover (Hiller et al., 2014). Cases of deep pyoderma normally respond more slowly and may require 6-12 weeks of treatment. Regular re-examination by the veterinary surgeon is necessary to establish when infection has resolved as this is beyond the skills of most pet owners, especially when signs of concurrent disease may need to be differentiated from those of the pyoderma. Unfortunately, a recent review of prescribing practices showed that dogs with pyoderma were commonly under-dosed or given courses that were inappropriately short (Summers et al., 2014).
Use of fluoroquinolones in canine pyoderma.

Fluoroquinolones are considered by the World Health Organisation to be of ‘critical importance’ in the treatment of certain life-threatening bacterial infections of humans (WHO, 2011). Whilst several drugs of this class are currently licensed for use in veterinary medicine, there is an ethical imperative that their use in animal health is strictly limited.

Pradofloxacin

Pradofloxacin is a third-generation veterinary fluoroquinolone with proven activity against S. pseudintermedius (Korber-Ingang et al., 2012). Clinical trials have shown reliable efficacy in dogs with pyoderma. In one study of 107 dogs, clinical remission in pradofloxacin-treated dogs (86%) was higher than co-amoxiclav (73%); pradofloxacin was also more effective in preventing recurrence within 2 weeks of cessation (Mueller and Stephan, 2007). In pharmacokinetic-pharmacodynamic in vitro models, pradofloxacin showed faster and more sustained killing of 3 strains of S. intermedius than marbofloxacin. Pradofloxacin has also been shown to kill S. pseudintermedius more rapidly than cefazolin, cefovecin and doxycycline (Blondeau and Shebelski, 2016).

The ISCAID working group consider these to be ‘second tier’ treatment options to be considered only when topical therapy and ‘first tier’ antimicrobials are not appropriate and when cultures indicate susceptibility (Hiller et al., 2014). In the author’s clinic, they are most often used when deep pyoderma is complicated by Gram-negative pathogens such as Pseudomonas.

The diagnosis and management of canine pyoderma is challenging due to the varied clinical presentation and the frequent association with concurrent skin diseases. Therapy is evolving with a greater appreciation of the role of topical therapy, which may replace or enhance the efficacy of traditional oral antibacterial treatment.

Emergence of multidrug-resistant strains of Staphylococcus pseudintermedius represents a significant threat to the effectiveness of routine treatments. Recognition and correction where possible of underlying diseases is critical for successful control of relapsing cases, and is likely to limit the need for repeated courses of antibacterial treatments, and therefore selection pressure for resistance.

Summary

Bacterial genetic mutations resulting in antimicrobial resistance occur at a rate of around 1 in 10 million (10−7) bacteria. MIC testing utilises a standard inoculum of 100,000, or 105 bacterial colony forming units; this is a very useful test, but does not determine the concentration of antibiotic needed to kill spontaneously occurring mutant strains, as it isn’t evaluating large enough bacterial populations.

MPC testing uses larger inoculums of bacteria (106 CFU/ml) and as a result allows the identification of resistance arising from spontaneous mutations. This is an important concept as it allows the identification of the mutant selection window (MSW) which occurs at drug concentrations between the MIC and MPC.

The mutant prevention concentration (MPC) offers a novel approach for the treatment of infectious diseases (Dong et al. 1999). Essentially, the MPC-approach favours a dose selection that not only aims at clinical cure but also at reducing selection of bacterial resistance. Bacterial genetic mutations resulting in antimicrobial resistance occur at a rate of around 1 in 10 million (10−7) bacteria. MIC testing utilises a standard inoculum of 100,000, or 105 bacterial colony forming units; this is a very useful test, but does not determine the concentration of antibiotic needed to kill spontaneously occurring mutant strains, as it isn’t evaluating large enough bacterial populations.

Mutant Prevention Concentration (MPC) and Mutant Selection Window (MSW) (Blondeau et al. 2004)

Above MPC – both susceptible and first-step resistant cells inhibited – no selective amplification of resistant subpopulation

MPC

MSW

– susceptible cells inhibited

– first-step resistant cells not inhibited

– selective amplification of resistant subpopulation

MIC

Sub MIC – neither susceptible nor first-step resistant mutants inhibited – no selective amplification of resistant subpopulation

Time post-administration

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At drug concentrations above the MIC susceptible bacteria are killed but those that possess first-step mutations giving drug resistance are not, giving these isolates a selective advantage. Above the MPC, both susceptible bacteria and those with resistance are not, giving these isolates a selective advantage. At present MPC testing is technically challenging and is not commercially available, however theoretical knowledge still provides useful information for our patients. For example, the newer fluoroquinolone, pradofloxacin (Veraflox®), has the lowest available MPC values when compared to other generation fluoroquinolones such as marbofloxacin or enrofloxacin (Wetzstein 2005).

Pradofloxacin (Veraflex®) is therefore able to exceed MPC levels during therapeutic dosing in these cases, making it less likely that early, first-stage mutant strains will be left behind (Wetzstein 2005). This means that once a decision to use a fluoroquinolone has been made, pradofloxacin is the best choice in terms of limiting the development of resistance.

**FLUOROQUINOLONE MPC PROFILE**

<table>
<thead>
<tr>
<th>Fluoroquinolone</th>
<th>MPC (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradofloxacin</td>
<td>0.6</td>
</tr>
<tr>
<td>Marbofloxacin</td>
<td>3.5</td>
</tr>
<tr>
<td>Enrofloxacin</td>
<td>3.5</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>9</td>
</tr>
<tr>
<td>Difloxacin</td>
<td>18</td>
</tr>
</tbody>
</table>

**Comparative MPC values of veterinary fluoroquinolones against Staphylococcus sp. in relation to serum drug levels reached in dogs (Wetzstein 2005)**

**REFERENCES:**


REFERENCES: Simon Tappin

At drug concentrations above the MIC susceptible bacteria are killed but those that possess first-step mutations giving drug resistance are not, giving these isolates a selective advantage. Above the MPC, both susceptible bacteria and those with first-step mutations are killed, so there is no longer a selective advantage to the isolates with these first-step mutations.
VERAFLOX® 15 mg tablets contain 15 mg pradofloxacin. VERAFOX® 60 mg tablets contain 60 mg pradofloxacin. VERAFOX® 120 mg tablets contain 120 mg pradofloxacin. VERAFOX® 25 mg/ml oral suspension for cats contains 25 mg/ml pradofloxacin.

Further information is available from the datasheet at noahcompendium.co.uk or on request. Advice should be sought from the medicine prescriber.

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