Review Article

What has changed in canine pyoderma? A narrative review

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Abstract

Canine pyoderma remains one of the main presentations in small animal practice and frequently leads to prescribing of systemic antimicrobials. A good foundation knowledge on pyoderma was established during the 1970s and 1980s when treatment of infection provided little challenge. However, our ability to treat canine pyoderma effectively is now limited substantially by the emergence of multidrug-resistant, methicillin-resistant staphylococci (MRS) and in some countries, by restrictions in antimicrobial prescribing for pets. The threat from rising antimicrobial resistance and the zoonotic potential of MRS add a new dimension of public health implications to the management of canine pyoderma and urge a revisit and the search for new best management strategies. This narrative review focusses on the impact of MRS on how we manage canine pyoderma, and how traditional treatment recommendations need to be updated in the interest of good antimicrobial stewardship. Background information on clinical characteristics, pathogens and appropriate clinical and microbiological diagnostic techniques are briefly reviewed in so far as they can support early identification of multidrug-resistant pathogens. We examine the potential of new approaches for the control and treatment of bacterial skin infections and highlight the role of owner education and hygiene. Pyoderma patients offer great opportunities for good antimicrobial stewardship by making use of the unique accessibility of the skin through cytology, bacterial culture and topical therapy. For long-term success and to limit the spread of multidrug-resistance, we need to focus on identification and correction of underlying diseases that trigger pyoderma in order to avoid repeated treatment.

Keywords: Antimicrobial resistance; Staphylococci; MRSA/MRSP; Cytology; Topical antimicrobial therapy

Introduction

Although good prevalence data for canine pyoderma are lacking, bacterial skin infections were the second most frequent cause for presentation to first opinion practice in a UK survey on canine skin problems (Hill et al., 2006). Rarely life-threatening, pyoderma substantially contributes to canine morbidity through associated pruritus or pain, and potentially widespread and severe inflammatory changes. Because pyoderma is always secondary to underlying disease, unless this is corrected, recurrence is likely requiring repeated therapy, and causing frustration and continuing expense.

Indeed, pyoderma is one of the main presentations leading to antimicrobial prescription in small animal practice (Hughes et al., 2012). A recent UK first opinion practice survey showed that 92% of 683 dogs with pyoderma, either suspected or confirmed, received systemic antibacterial therapy (Summers et al., 2014). With continuing emergence of methicillin-resistant staphylococci, mainly *S. aureus* (MRSA) and *S. pseudintermedius* (MRSP), it is necessary to reduce antimicrobial use as a principal driver of multidrug-resistance (MDR) and pyoderma provides excellent opportunities for good antimicrobial stewardship.

In this narrative review, we focus **on how the emergence of MRSP, MRSA and other MDR zoonotic pathogens has changed our approach to the management of canine pyoderma, and on how** traditional treatment recommendations need to be adapted to deal with this increasing threat to antimicrobial effectiveness and to public health.

Foundation knowledge and clinical disease

Aetiology and pathogenesis

Since publication of the first comprehensive veterinary dermatology text books in the 1960s (Muller and Kirk, 1969), pyoderma has consistently featured as one of the major diseases affecting

canine skin. It has been suggested that this is partly a consequence of the comparatively thin and compact canine stratum corneum, of the paucity of intracellular emulsion in canine epidermis and of the lack of a sebum plug in the canine hair follicle (Lloyd and Garthwaite, 1982; Mason and Lloyd, 1993).

The critical question of why pyoderma, particularly superficial pyoderma, develops and frequently recurs, is still incompletely understood. The major role of primary underlying disease in its aetiology is supported by the observation that the predominant staphylococcal pathogens are colonisers of healthy dogs and that most staphylococcal skin infections involve 'endogenous' strains, i.e. isolates genetically identical to those of the patient's healthy cutaneous and mucosal microflora (van Eiff et al., 2001; Pinchbeck et al., 2006 & 2007).

Common underlying triggers such as ectoparasite infestations, allergic skin diseases and endocrinopathies have long been associated with pyoderma, with allergic disease likely the main driver for recurrent forms (Mason and Lloyd, 1989; Colombo et al., 2007; Bloom, 2014). More specific concepts of quorum sensing, of a minimum infective dose and most recently findings from microbiome studies showing significant changes in diversity and composition during atopic dermatitis have provided new insights on why infection with opportunistic bacteria may develop in skin (Lloyd, 2014; Pierezan et al., 2016; Rodrigues Hoffman et al., 2017). Immunological defects in innate and adaptive immunity were identified in deep pyoderma of German shepherd dogs presenting with widespread, highly inflammatory infections during the 1980s and 1990s (e.g. Wisselink et al., 1988; Chabanne et al., 1995; Shearer and Day, 1997) but could not be conclusively linked to the breed or the occurrence of pyoderma (Rosser, 2006). Fortunately, this devastating disease now seems to be rare, possibly following targeted breeding.

The gaps in our understanding remain frustrating but it is important to remember that, when underlying causes are not identified, use of the term "idiopathic pyoderma" does not represent a diagnosis. In such cases diagnostic investigations need to be continued as failure to eliminate or control underlying disease **or predisposing factors** will lead to recurrence.

Classification and diagnosis of pyoderma

With its secondary aetiology and the need for responsible use of antimicrobials in mind, a diagnosis should always include i) recognition of suggestive skin lesions and likely depth of infection, ii) confirmation of bacterial infection through cytology and iii) identification of underlying primary disease.

Despite its prevalence, canine pyoderma is often misdiagnosed (Gortel, 2013) leading to inappropriate treatment. Recognition of suggestive skin lesions and their distribution is essential and requires careful inspection of the skin. Since the number of ways skin can react to insult is limited, classifications have been proposed to facilitate morphological diagnosis. The most widely used is based on depth of infection and distinguishes surface, superficial and deep pyoderma, all three associated with typical clinical presentations (Ihrke, 1987; White and Ihrke, 1987) (Fig. 1).

Surface pyoderma remains the least understood group. It includes frequently seen presentations such as acute moist dermatitis ("hot spots", pyotraumatic dermatitis), fold pyoderma (intertrigo), and the more recently described microbial/bacterial overgrowth syndrome in which erythema is the only clinical sign but large numbers of bacteria on the inflamed skin can be demonstrated by cytology (Pin et al., 2006). Here, excessive multiplication of bacteria is confined to the skin surface and is seen as a minor player in the pathogenesis, triggered by a dominant inflammatory cause.

Superficial pyoderma involves invasion of the epidermis. Bacterial folliculitis extends into the follicular ostium and epidermal tissue and is likely the most frequent pyoderma type in dogs. It presents with papules, pustules and epidermal collarettes, typically on the ventral abdomen and medial thighs or on the trunk and often associated with areas of alopecia and varying degrees of pruritus; its interfollicular form (impetigo) occurs mostly in puppies. Coat type and immune-status can also influence clinical appearance as in the moth-eaten appearance of superficial pyoderma in short-coated breeds or in the large lesions (collarettes, pustules) associated with bullous impetigo or superficial spreading pyoderma in immune-compromised dogs (Bloom, 2014; Beco et al., 2013a). Mucocutaneous pyoderma is a disease of unknown aetiology. It primarily affects lips and perioral skin, with swelling, erythema and crusting which may lead to fissuring and erosion. It often responds slowly to therapy and can be confused with immune-mediated disease.

Deep pyoderma is less common but more serious, as its expansion into the dermis and proximity to blood vessels increases the risk of haematogenous spread and bacteraemia. It can be seen with any underlying trigger or acquired immuno-deficiency but is commonly associated with demodicosis (Kuznetsova et al., 2012; Mueller et al., 2012). Lesions include draining sinuses, fistulae, haemorrhagic crusts, nodules and varying degrees of erythema and swelling; pain is not infrequent. Common localised forms of deep pyoderma affect the head (chin acne, muzzle folliculitis and furunculosis) or limbs (interdigital nodules, callus pyoderma, acral lick granuloma). Nodular lesions quite often involve bacteria other than staphylococci and need to be differentiated from non-bacterial infected granulomas, sterile granulomatous disease, neoplasia and foreign body reactions by biopsy, special stains, macerated tissue culture and sometimes molecular techniques.

For initial diagnosis, cytology from slide or tape impressions, a frequent requirement of antimicrobial stewardship guidelines prior to antimicrobial prescription (e.g. BVA, 2015), is recommended to confirm bacterial involvement. Cytology of superficial pyoderma lesions is

142 reported to have 93% diagnostic sensitivity, based on presence of neutrophils and intracellular cocci
143 (Udenberg et al., 2014) but, despite being rapid and inexpensive (Curtis, 2001), remains underused
144 in general practice (Hill et al., 2006).
145
146 Bacterial culture, on the other hand, is of limited value in the initial diagnosis of pyoderma.
147 It is likely to yield staphylococci from infected and non-infected skin (Doelle et al., 2015), and can
148 therefore not distinguish infected from colonised skin. However, bacterial culture and antimicrobial
149 susceptibility testing are essential for selection of systemic therapy after a diagnosis has been
150 established. It is of note that sampling can be challenging, particularly in deep pyoderma for which
151 surface swabs have been shown to predict relevant pathogens from deep infection in only about
152 30% of cases (Shumaker et al., 2008) and submission of tissue (in saline, not formalin) obtained
153 through biopsy is preferred.
154
155 *Pathogens*
156 The predominant role of coagulase-positive staphylococci has been long recognised (Ihrke,
157 1987). Originally all such infections were ascribed to *S. aureus,* but refinement of microbiological
158 techniques allowed new species including *S. intermedius* and *S. pseudintermedius* to be described
159 (Table 1). *S. pseudintermedius* is recognised to be most commonly involved, particularly in
160 superficial pyoderma (Medleau et al., 1986; Shumaker et al., 2008). Other staphylococci, including
161 *S. aureus, S. schleiferi* and *S. hyicus* may be involved in up to 10% of cases.
162
163 Staphylococci have an array of potential virulence factors but despite detailed investigation
164 significant associations between specific virulence genes and disease have not yet been identified,
165 shifting attention again to host factors that may facilitate infection (Bannoehr et al., 2012; Tanabe et
166 al., 2013; Couto et al., 2015). However, biofilm production, which can promote resistance to host
167 defence mechanisms and greatly enhance antimicrobial resistance, has been confirmed in many

168 isolates of *S. pseudintermedius* and other veterinary staphylococci (Götz, 2002; Hall-Stoodley et al.,
169 2004).
170
171 Many other bacterial pathogens, including *Pseudomonas aeruginosa, Proteus spp.*,
172 streptococci, *Burkholderia* spp. and *Escherichia coli* may be difficult to distinguish clinically
173 (Rantala et al., 2004; Hillier et al., 2006; Cain et al., 2015; Tham et al., 2016). Isolation of
174 coagulase-negative staphylococci, such as *S. lugdunensis* and *S. schleiferi subsp. schleiferi,* and of
175 *Macrococcus* spp., can also cause confusion in laboratories that are looking for coagulase-positive
176 bacteria (Cain et al., 2011; Gobeli Brawand et al., 2016; Cotting et al., 2017). Surprisingly, the idea
177 that coagulase-negative staphylococci are non-pathogenic persists even though they are the most
178 common cause of nosocomial bacteraemia in human hospitals (von Eiff et al., 2002; Becker et al.,
179 2014) and are increasingly reported in animal infections (e.g. Rook et al., 2012; Frank et al., 2008;
180 Davis et al., 2013; Kern and Perreten, 2013; Ruzauskas et al., 2014).
181
182 **Emergence of multidrug-resistance**
183 Resistance to antimicrobials within bacterial populations is an ancient phenomenon, vital for
184 bacterial survival (D'Costa et al., 2011; Perron et al., 2015). However, the accumulation of multiple
185 resistance genes in bacterial pathogens, driven by overuse of antimicrobial drugs, has become a
186 chilling threat to human and animal health (Gossens et al., 2005; Costelloe et al., 2010).
187
188 First concerns about MDR in canine pyoderma emerged twenty years ago when MRSA
189 became recognised in sporadic skin and wound infections; later, the more epidemic spread of
190 MRSP overtook it and now presents major challenges to our management of canine pyoderma. In
191 addition, all key multidrug-resistant pathogens of relevance in human medicine, such as
192 *Enterococcus faecium, Klebsiella spp., Acinetobacter baumannii, Pseudomonas aeruginosa* and

193 *Enterobacter spp*. (Boucher et al., 2009), are now recognised to be associated with infection in pets
194 (Grobbel et al. 2007; Kuzi et al., 2016; Abdel-Moein et al., 2017).
195
196 *Meticillin-resistance in staphylococci*
197 Although methicillin is no longer available for clinical use, it still serves as a marker for
198 broad resistance to all β-lactams (excepting some of the latest anti-staphylococcal molecules) and as
199 an indicator of likely nosocomial epidemiology and additional multidrug-resistance. The genetic
200 basis underpinning methicillin-resistance is the presence of the *mecA* gene held on a large mobile
201 genetic element, the staphylococcal cassette chromosome (SCC). This is similar in all staphylococci
202 and has been extensively studied for MRSA (Lindsay and Holden, 2006).
203
204 Since the first identification of MRSA from pets, isolates from pets and humans have been
205 found genetically identical, providing indirect but good evidence that transmission between these
206 hosts can occur in both directions (reviewed by McCarthy et al., 2012). MRSA was the first
207 multidrug-resistant *Staphylococcus* to receive attention in animals when pets contaminated by
208 human MRSA patients were shown to be involved in perpetuating human infection or recurrent
209 outbreaks (Scott et al., 1988; Manian, 2003). Since then, sporadic infections, case series and
210 outbreaks have been reported, typically involving skin and wound infections in dogs (Tomlin et al.,
211 1999; Paterson et al., 2015; Morris et al., 2017). Most reports are from countries with a high MRSA
212 prevalence in human hospitals, indicating a spill-over from humans; epidemic spread beyond clinic
213 or kennel outbreaks has not been reported. Fortunately, the prognosis in such infections can be
214 considered good, depending on underlying causes, as the great majority of these human hospital-
215 associated MRSA remain susceptible to tetracyclines and potentiated sulphonamides and around
216 50% to clindamycin. A less predictable prognosis needs to be considered for rare infections
217 involving MRSA from human lineages that carry toxins such as Panton-Valentine-leucocidin

(Rankin et al., 2005; van Duikeren et al., 2005) and those associated with livestock-associated MRSA (Gómez-Sanz et al., 2013).

A much greater veterinary challenge is the emergence in dogs of MRSP, associated with even broader drug-resistance. Whole genome sequencing shows that only three genetic steps (acquisition of *mecA* on a SCC, acquisition of a large transposon (Tn5405-like element) carrying up to five resistance genes and genome point mutations for fluoroquinolone and sulphonamide resistance) are required for its rapid evolution to MDR, emphasising the important role of selection pressure (Loeffler et al., 2007; Perreten et al., 2010; Detwiler et al., 2014; McCarthy et al., 2015).

First reported from dogs in North America in the late 1990s (then MRSI), MRSP accounted for over 30% of staphylococcal isolates from American dogs within less than ten years (Gortel et al.,1999; Morris et al., 2006; Jones et al., 2007) and is now identified worldwide. An even higher prevalence was recently reported from China and Japan with nearly 50% and 70%, respectively (Feng et al., 2012; Kasai et al., 2016). In the UK, where MRSP was first recognised in 2009, the burden seems relatively low with rates below 5% of clinical *S. pseudintermedius* laboratory submissions reported in 2015 (Maluping et al., 2014; Beever et al., 2015). In contrast, studies from continental Europe, where MRSP had been identified three years earlier, prevalence was soon reported around 30% (Loeffler et al., 2007; DeLucia et al., 2011).

Substantial percentages of methicillin-resistance have also been reported in coagulase-variable *S. schleiferi* (subspecies *schleiferi* and subspecies *coagulans*), some from pyoderma but most from otitis (Cain et al., 2011).

241

242 *Clinical implications and early identification*

243 Clinically, MRS infections in animals are no different from infections involving less
244 resistant staphylococci (Fig. 1) (Morris et al., 2017). In fact, early case-control studies showed that
245 clinical outcome was no worse for MRSA and MRSP infections in pets compared to those
246 involving their susceptible counterparts, provided that a safe antibacterial treatment option was
247 available (Weese et al., 2012; Lehner et al., 2014). Finding treatment options may be troublesome
248 and treatment has been shown to take longer than with susceptible staphylococci (Bryan et al.,
249 2012). However, the bigger concern with MRS pyoderma is its potential for spreading these
250 zoonotic, multidrug-resistant pathogens to other animals and people, and into the environment. For
251 MRSP, the risk of zoonotic transmission is generally considered low as low carriage rates of *S.*
252 *(pseud)intermedius* have been found in people regularly exposed to dogs (Havey et al. 1994;
253 Goodacre et al., 1997; Han et al., 2016). As for all staphylococci though, the risk is increased for
254 immune-compromised people and individual cases of zoonotic MRSP infection have been reported
255 (Stegman et al., 2010; Somayaji et al., 2016; Lozano et al., 2017).

256

257 Transmission of staphylococci is supported by their ability to survive on dry surfaces and at
258 healthy skin and mucosal carriage sites for many months, equipping them for nosocomial spread
259 (Wagenvoort et al., 2000; Windahl et al. 2016). Early identification of MRS by clinicians is
260 therefore crucial to limit outbreaks but it relies on awareness of risk factors. Risk factors for
261 multidrug-resistant infection in human medicine are well documented and include frequent
262 hospitalisation, length of stay in hospitals, surgical interventions and repeated antimicrobial therapy
263 (Sadfar and Maki, 2002). Unsurprisingly, the same risk factors have been identified for MRSA and
264 MRSP infections in dogs (Soares-Magalhães et al., 2010; Baker et al., 2012; Lehner et al. 2014;
265 Weese et al., 2012).

New focus on laboratory identification

Before the emergence of MRS, species identity of a coagulase-positive *Staphylococcus* was probably of little importance to most clinicians. When MRS are involved, accurate differentiation between MRSA and MRSP is critical for further management as important epidemiological differences exist. Isolation of MRSA from a dog will prompt a focus on human health concerns and the need to inform the owner's human physician. In contrast, isolation of the dog-adapted MRSP should initiate all appropriate infection control measures recommended for veterinary nosocomial pathogens and advice on limiting contagion to other animals, while only a lower zoonotic risk needs to be considered (Morris et al., 2017).

Unfortunately, it has also become clear that identification through phenotypic assessment alone is more difficult than text books suggest as subtle morphological and biochemical variation occurs within bacterial populations (Pottumarthy et al., 2004; Sasaki et al., 2007; Geraghty et al., 2013; Bond and Loeffler, 2012). Similarly, recognition and accurate identification of coagulase-negative staphylococci is important as their pathogenic potential is increasingly recognised; reporting such isolates as 'consistent with microflora organisms' is no longer sufficient. Semi-automated and automated laboratory procedures help with speciation but are commonly set up for human bacterial pathogens and may lack precision for veterinary isolates. Currently, best accuracy in a diagnostic setting is achieved by Matrix Assisted Laser Desorption/Ionisation Time of Flight Mass Spectrometry (MALDI-TOF) which has been validated for many veterinary pathogens including the very similar SIG species (Decristophoris et al., 2011; Sauget et al., 2016; Somayaji et al., 2016).

Susceptibility testing is most often done by traditional disk diffusion with clinical breakpoints guiding predictions on clinical efficacy. Dilution testing and minimum inhibitory

concentrations (MICs) were rarely needed for the management of skin infections in the past but will be helpful in multidrug-resistant infections when a borderline MIC may still be overcome with high doses of an authorised antimicrobial rather than choosing a less safe drug, or when calculating dosages for treatment with an unauthorised agent. Resistance testing against methicillin, nowadays replaced by oxacillin, can also been misleading since *mecA*-independent mechanisms (other *mec* types, hyper-penicillinase producers, incomplete expression) can lead to inconsistent results (Morris et al., 2017). Confirmation of phenotypic methicillin-resistance by additional tests (molecular for *mecA* or by agglutination tests detecting an altered penicillin-binding protein encoded by *mec*) is desirable before MRS management decisions are initiated (Becker et al., 2014b).

Management of canine pyoderma

In the past, treatment of canine pyoderma was rarely challenging as *S. pseudintermedius* (formerly *S. intermedius*) was widely susceptible and broad-spectrum antibacterial agents such as cephalexin, potentiated amoxicillin and enrofloxacin became licensed for use in dogs during the 1970s and 1980s, all with an indication for skin infection (Medleau et al., 1986; Kruse et al., 1996; Lloyd et al., 1996; Pellerin et al., 1998; Normand et al., 2000). It was already recognised that isolates from animals that had repeatedly received antimicrobials were likely to show more resistance (Noble and Kent, 1992; Holm et al., 2002) but empirical selection of drugs for systemic treatment of pyoderma was nearly always successful. This situation began to change around 20 years ago when methicillin-resistant, multidrug-resistant staphylococci were recognised amongst canine clinical isolates and, in the UK, there is now evidence that resistance to most antimicrobial classes is gradually increasing (Beever et al., 2015). Based on recent data for small animal pathogens, this trend of increasing AMR is likely to continue worldwide (Ludwig et al., 2016).

315

316 *Topical therapy*

317 Topical antibacterial therapy has always been advised for surface infections and, in
318 combination with systemic therapy, for superficial and deep pyoderma (Ihrke, 1987; Curtis, 1998 &
319 1999). However, newer studies have provided good evidence that topical therapy can be effective as
320 sole antibacterial treatment in superficial pyoderma, including cases with MRS (Murayama et al.,
321 2010; Loeffler et al., 2011; Borio et al., 2015). In situations where pet and owner can be expected to
322 be compliant and where clinicians are prepared to convince owners of its merits, topical treatment
323 can help to reduce overall antimicrobial prescription.

324

325 A wide range of different formulations, such as shampoos, creams, gels and ointments, and
326 more recently foams, is marketed for dogs and includes a variety of antibacterial agents; this can be
327 confusing. A systematic review of topical therapy for canine bacterial skin infections concluded that
328 while evidence from randomised controlled trials was sparse, good evidence supported the use of
329 shampoos containing 2-3% chlorhexidine and, to a lesser extent, benzoyl peroxide (Mueller et al.,
330 2012) and these continue to be the mainstay of topical therapy, at least for widespread disease.
331 Localised infections can also be treated with creams or gels containing antibiotics such as fusidic
332 acid, authorised for use in dogs in European countries and in Canada, or mupirocin ointment
333 authorised in the USA for dogs but reserved for use in human medicine in most of Europe (Cobb et
334 al., 2005; BNF, 2017).

335

336 While concern over resistance to topically used antibacterial agents exists, clinical treatment
337 failure of topical anti-staphylococcal therapy has not been conclusively reported, to the authors'
338 knowledge; MICs for staphylococci from animals have been consistently low and are likely to be
339 substantially exceeded by achievable topical drug concentrations (Loeffler et al. 2008; Valentine et
340 al., 2012; Clark et al., 2015). However, continual monitoring of resistance and clinical efficacy,

341 further evaluation of alternatives such as hypochlorite (bleach), Manuka honey, of potentially
342 synergistic combinations and of anti-biofilm products will be critical (Walker et al., 2016).
343
344 Combination of topical treatment with systemic treatment is recommended whenever
345 possible to potentially reduce the duration of systemic therapy, and in MRS infections, to reduce
346 environmental contamination and risk of transmission to other hosts.
347
348 *Systemic therapy*
349 Systemic therapy, required for deep pyoderma and for widespread or severe superficial
350 infections, should follow the concept of 'as little as possible but as much as necessary' (RUMA
351 2009). Efficacy depends predominantly on bacterial susceptibility but will also be determined by
352 correct drug administration, appropriate dosing, owner compliance and clinical variables such as
353 severity of infection and causative and concurrent diseases. Surprisingly, despite their universal use,
354 evidence on efficacy of systemic antimicrobial agents is sparse as only few adequate studies
355 documenting outcome exist (Summers et al., 2012).
356
357 While bacterial culture and susceptibility testing would be desirable for every patient and is
358 never contraindicated in pyoderma, realistically, cost, perceived delay of effective treatment and
359 clinical time pressure often motivate empirical drug selection. In countries with low MRS
360 prevalence, empirical selection may still be effective for most superficial pyodermas. In high-MRS
361 prevalence countries, this can no longer be considered reliable or cost-effective. Indeed, repeated
362 testing may be required as antimicrobial therapy has been shown to promote acquisition of MRSP
363 in dogs not previously MRSP-positive (Beck et al., 2012). Recent pyoderma guidelines further
364 specify that culture and susceptibility testing is essential in all dogs with deep pyoderma, those with
365 a history of MRS or with owners reporting MRS in themselves, and in dogs where appropriate
366 empirical antibiosis has been ineffective. (Beco et al., 2013b; Hillier et al., 2014)

When prescribing antimicrobial drugs for dogs, it is important to remember that most are also used in human medicine, either as identical or related molecules, and that key agents for canine pyoderma are listed by the WHO as 'critically important antimicrobials' or 'highly important for human medicine' (WHO, 2011).

For non-MRSP pyoderma, most antimicrobials authorised for use in dogs would be effective if prescribed appropriately. Treatment recommendations have recently been detailed in two free access publications, one on pyoderma by a group of veterinary dermatologists (Beco et al., 2013b), the other on superficial bacterial folliculitis by the International Society for Companion Animal Infectious Disease (ISCAID)(Hillier et al., 2014). Briefly, antimicrobial drugs can be classified into first and second tier/line drugs, depending on the likelihood that they will be effective against staphylococci and their spectrum of activity against Gram-negative pathogens. First-tier drugs, such as **clindamycin,** first-generation cephalosporins, amoxicillin-clavulanate or **potentiated sulphonamides** may be chosen empirically in areas with a low prevalence of MRS. **Clindamycin, an antimicrobial with good efficacy against most staphylococci, can be considered as a responsible treatment choice due to its relatively narrow spectrum of activity. However, clinicians need to be familiar with their local *S. pseudintermedius* resistance pattern as differences in resistance have been recognised between countries and between isolates from first-time pyoderma versus those from recurrent pyoderma (Holm et al., 2002; Beever et al., 2015; Larsen et al., 2015).** Treatment with second-tier agents, such as for example fluoroquinolones, should always be based on bacterial culture and susceptibility results. Readers are referred to these guidelines for more detailed information on dose recommendations and adverse effects.

In MRS pyoderma, drugs predicted to be effective by *in vitro* testing are selected based on national licensing rules, their clinical and safety characteristics, dosing practicalities and cost, with no single drug shown to be better than another. Information specifically on MRS treatment is detailed in recently published open access Clinical Consensus Guidelines on MRS infections (Morris et al., 2017). Specifically on the interpretation of resistance testing, the guidelines point out that no representatives of β-lactam antibiotics should be used for MRS infections even if testing indicates susceptibility for individual agents of this class, that testing for inducible resistance to clindamycin is recommended for MRS to avoid treatment failure during therapy, that extrapolation of results for one type of tetracycline to another can be unreliable as resistance is mediated by a number of different genes and that resistance to one fluoroquinolone is likely to indicate resistance to others in MRSP; MIC determination may then help to inform treatment decisions (Kizerwetter-Świda et al., 2016).

When no susceptibilities to clinically relevant and authorised antimicrobials are reported, extended testing is required. Amikacin, rifampicin and chloramphenicol are most frequently mentioned for such infections (Frank and Loeffler, 2012; Papich, 2012) but their use should be preceded by appropriate dose calculations and toxicity monitoring, requires detailed owner education and compliance, and should include advice on infection control measures to limit spread (Morris et al., 2017). In the authors' opinion, glycopeptides, linezolid and potentially new compounds should be strictly reserved for use in humans. Some institutions may consider these under restriction-of-use protocols but this should rarely be necessary for pyoderma (Weese, 2008).

Recommendations on how long to treat pyoderma for remain controversial. Traditional advice, based on clinical expertise is three weeks or one week beyond clinical cure for superficial pyoderma, and four to eight weeks or two weeks beyond clinical cure for deep pyoderma (Ihrke, 1987). In addition, many datasheets now recommend several weeks of therapy. In human medicine,

antibiotic courses are typically shorter but recently, even the advice to patients to complete a course after clinical signs have resolved has been questioned (Llewelyn et al., 2017). In the absence of better data, it is prudent to follow advice from ISCAID and adhere to the traditional recommendations but where shorter treatment is prescribed, plans for close monitoring of progress by veterinarian rather than owner should be made (Hillier et al., 2014). In addition, resolution of clinical signs will not signal the end of case management for MRS pyoderma as dogs can become carriers and carry the risk of contagion, including zoonotic transmission, and of self-re-infection.

Correction of primary triggers, follow-up and prevention

After resolution of any type of pyoderma, prevention of recurrence is very important as multidrug-resistance may develop with repeated systemic treatment. Such prevention will depend on elimination or suppression of underlying triggers. A diagnosis of these triggers may not be a priority to owners compared to the urgency of resolving the pyoderma, and will present an extra challenge to communication during busy consultations. Most problematic, in the authors' experience, are those dogs that in the absence of pyoderma (i.e. when infection has been resolved) present either with no clinical signs suggestive of underlying triggers or with signs compatible with very mild allergic skin disease. In those cases, provided history and signalment are in line with allergic skin disease, empirical treatment with anti-inflammatory medication may help to prevent flares of bacterial infection. If successful, this approach can subsequently be optimised by further investigations into allergic skin disease (Olivry et al., 2015).

Importantly for MRS infections, once infection has resolved, animals will continue to harbour staphylococci on healthy skin and mucosae. For MRSP, a bacterium well adapted to dogs (Simou et al., 2005), carriage has been shown to continue for up to 11 months after infection has resolved (Windahl et al., 2012). Carriage and environmental contamination and the risk of subsequent self-re-infection have long been suspected as major contributors to the successful spread

444 of human MRSA and a similar epidemiology is suspected for MRSP in veterinary settings (Beck et
445 al., 2012; Morris et al., 2017).
446
447 **New approaches**
448 The growing problem of antimicrobial resistance and the lack of effective, new conventional
449 antimicrobial drugs has promoted the development of different approaches to prevention and
450 control of bacterial infections (Lloyd, 2012; Vale et al., 2016). Staphylococcal vaccines, either *S.*
451 *aureus* lysates or autogenous bacterin preparations have been assessed in small studies and warrant
452 further investigations (Glos and Mueller, 2006). Antimicrobial peptides, which are produced by the
453 skin and function as a vital part of cutaneous antimicrobial defence, are now being exploited in
454 veterinary products for dogs. Two promising approaches have been adopted. In the first, plant
455 extracts promoting production of endogenous antimicrobial peptides by the treated skin have been
456 incorporated in shampoos and ear cleaners (Marsella et al, 2013; Santoro et al, 2016). In the second,
457 a synthetic peptide (Cabassi et al, 2013) has been incorporated in shampoo, foam and an ear
458 treatment gel. A variety of other approaches are being investigated and developed (Lloyd, 2012) but
459 have not yet led to the development of veterinary products (Table 2).
460
461 It is likely that at least some of these new approaches will prove successful, however we
462 should not expect the development of agents which will allow us to ignore good drug stewardship
463 and the adoption of rigorous hygiene.
464
465 **Conclusions**
466 Canine pyoderma will need to be managed appropriately to reduce morbidity and to limit
467 the spread of potentially MDR pathogens amongst pets and humans. However, the availability of
468 effective and safe systemic antimicrobials will become - or already is in some countries -
469 substantially limited, either by continued selection of antimicrobial resistance amongst pathogens or

by legislative restrictions on prescribing by veterinary surgeons. We will likely need to adapt our prescribing practices for all animal species and all affected organs in the future. For canine pyoderma though, the skin as the infected organ can be easily accessed for examination and treatment monitoring, rapid in-house tests and topical therapy. This provides unique opportunities to combine relatively small achievable adaptations in our pyoderma management with good antimicrobial stewardship and effective treatment outcomes. Comprehensive owner education and rigorous hygiene measures need to become an integral part of pyoderma management and will help to limit the spread of antimicrobial resistance and delay the end the Golden Age of Antibiotics (Gould, 2009).

Highlights

1. Management of canine pyoderma is increasingly complicated by multidrug-resistant pathogens such as MRSP and empirical selection therapy is no longer reliable in areas with a high MRSP prevalence.
2. Use of in-house cytology can rapidly confirm bacterial infection and support responsible antimicrobial prescribing.
3. Topical therapy can be effective on its own in cases of superficial pyoderma, even in those involving MRSP.
4. Awareness of risk factors, contagious and zoonotic characteristics, laboratory requirements and necessary hygiene measures are critical in the management of MRSP pyoderma.
5. Diagnosis and treatment of underlying diseases needs to replace our reliance on antimicrobial therapy in dogs with recurrent pyoderma.

Conflict of interest statement

The authors have no financial or personal relationship with other people or organisations that could inappropriately have influenced or biased the content of this manuscript.

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Table 1

The changing nomenclature of *Staphylococcus aureus*.

Name	Year	Comments
Staphylococcus pyogenes aureus	1886 (Rosenbach)	Representing golden (rather than white) staphylococcal colonies
S. aureus	1951 (Shaw et al.)	Representing all coagulase positive staphylococci
Methicillin-resistant *S. aureus* (MRSA)	1961 (Jevons)	First recognition of methicillin resistance in *S. aureus*
S. aureus	1971 (Hajek and Marsálek)	Differentiation of animal species-related biotypes A-F
S. intermedius	1976 (Hajek)	Differentiated from *S. aureus,* representing biotypes E and F
S.pseudintermedius	2005 (Devriese et al.)	Differentiated from *S. intermedius,* representing biotype E.
Staphylococcus intermedius group (SIG)	2007 (Sasaki et al.)	Includes *S. intermedius*, *S. pseudintermedius* and *S. delphini* which are difficult to differentiate in routine laboratory testing. *S. intermedius* shown to be mainly associated with wild pigeons.*
Methicillin-resistant *S. pseudintermedius* (MRSP)	2007 (Sasaki et al.)	First recognition of methicillin resistance in *S. pseudintermedius*

*Canine SIG isolates are always considered as *S. pseudintermedius* (Bannoehr et al., 2007).

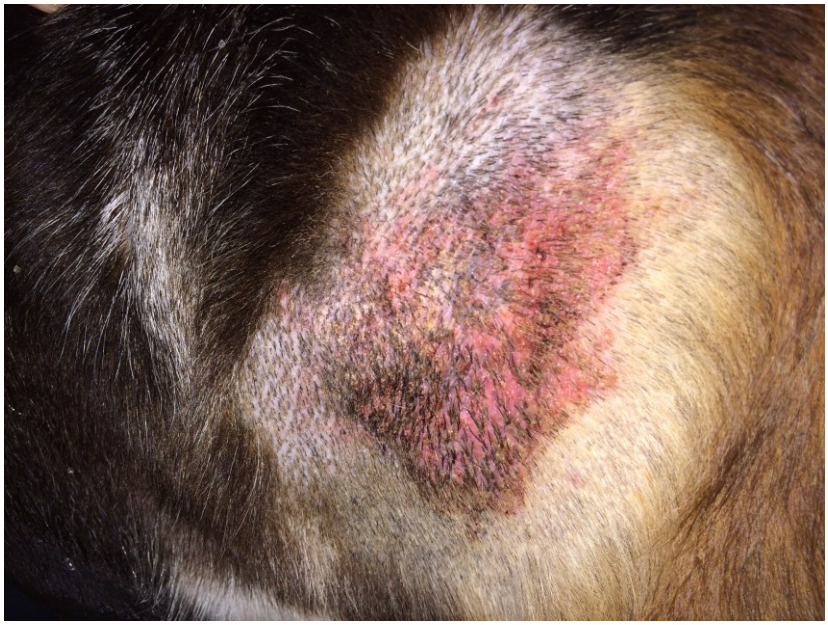
Table 2

New and alternative antimicrobial approaches.

Approach	Action
Efflux pump inhibitors	Suppress elimination of antimicrobial agents
Silencing of resistance and virulence genes	Antagonise function of specific genes
Quorum quenching	Agents suppressing virulence of pathogen
Probiotics and prebiotics	Provide or promote competitor bacteria
Microbial predation	Bacterial or fungal predators consume pathogen
Bacteriophages	Invade and destroy pathogen
Vaccines and immunoglobulins	Stimulate or passively provide immunity

Figure legend

Fig. 1. Examples of recurrent or chronic (> 3 months) pyoderma involving multidrug-resistant bacteria. All cases had received repeated courses of systemic antimicrobials with initial improvement. Pyoderma resolved when underlying triggering causes were diagnosed and treated in combination with antibacterial therapy. (A) Acute moist dermatitis with methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) on the neck of a young atopic Saint Bernard. (B) Purulent *Klebsiella* spp. infection complicating erosive pad lesions in a sterile granulomatous disease. Both dogs were treated and remained in remission with topical antibacterial and systemic anti-inflammatory treatment. (C) Recurrent superficial pyoderma with expanding epidermal collarettes and focal crusts due to MRSA in a dog with early hyperadrenocorticism; infection resolved with topical antibacterial washes alone when the endocrinopathy was treated. (D) Widespread deep pyoderma involving *Pseudomonas aeruginosa* in a young Dalmatian dog with juvenile-onset demodicosis; there was no evidence of pyoderma on cytology after 3 weeks of systemic antibacterial and acaricidal therapy.



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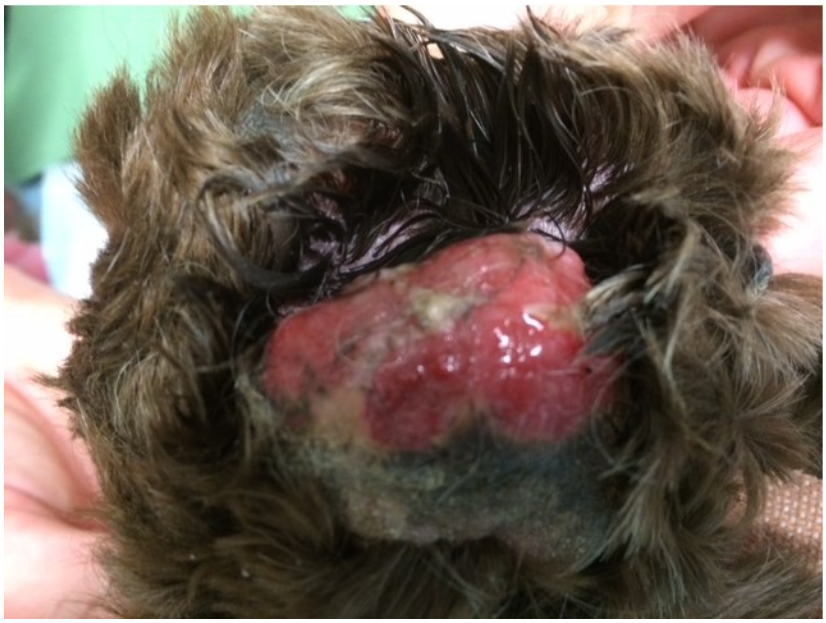

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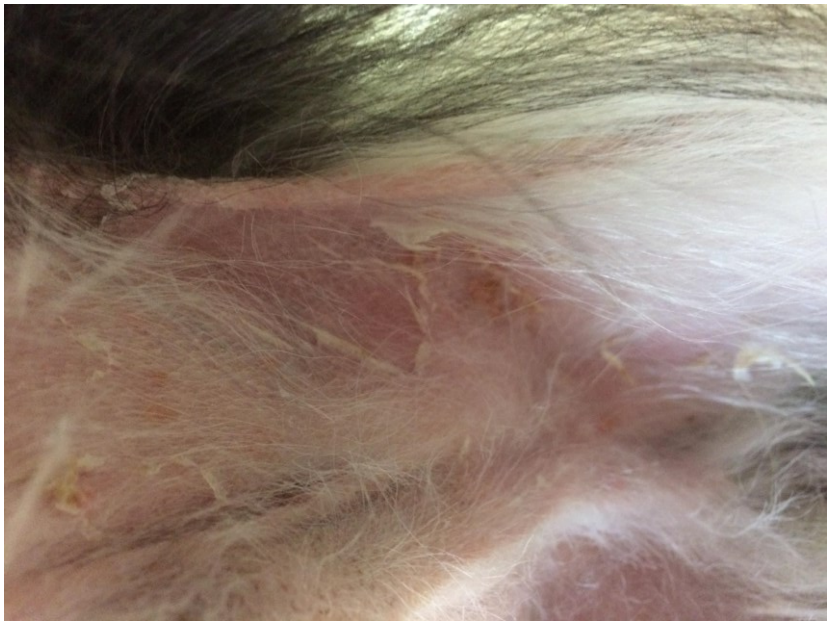
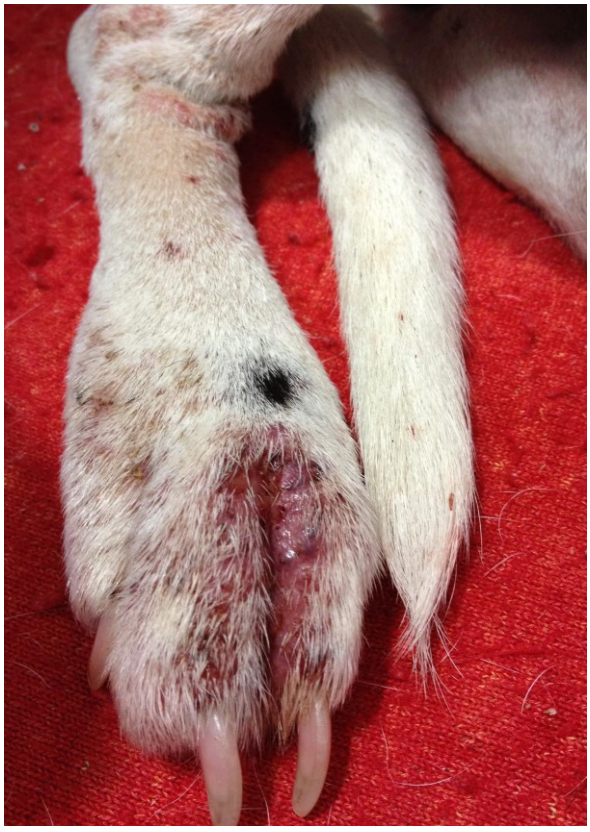
1075  C

1076  D