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Invited Review

What has changed in canine pyoderma? A narrative review

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ABSTRACT

Canine pyoderma is a common presentation in small animal practice and frequently leads to prescription of systemic antimicrobial agents. A good foundation of knowledge on pyoderma was established during the 1970s and 1980s, when treatment of infection provided relatively few challenges. However, the 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 on 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 necessitate a revisit and the search for new best management strategies. This narrative review focusses on the impact of MRS on how canine pyoderma is managed 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 reviewed in so far as they can support early identification of multidrug-resistant pathogens. The potential of new approaches for the control and treatment of bacterial skin infections is examined and the role of owner education and hygiene is highlighted. Dogs with pyoderma offer opportunities for good antimicrobial stewardship by making use of the unique accessibility of the skin through cytology, bacterial culture and topical therapy. In order to achieve long term success and to limit the spread of multidrug resistance, there is a need to focus on identification and correction of underlying diseases that trigger pyoderma in order to avoid repeated treatment.

Introduction

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

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 the continuing emergence of methicillin-resistant staphylococci, mainly *Staphylococcus aureus* (MRSA) and *Staphylococcus pseudintermedius* (MRSP), it is necessary to reduce antimicrobial, which is a principal driver of multidrug resistance; pyoderma provides excellent opportunities for good antimicrobial stewardship.

In this narrative review, we focus on how the emergence of MRSP, MRSA and other multidrug-resistant zoonotic pathogens has changed our approach to the management of canine pyoderma and 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 featured consistently 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 the

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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 as to why pyoderma, particularly superficial pyoderma, develops and frequently recurs, is still understood incompletely. The major role of primary underlying disease in its aetiology is supported by the observation that the predominant staphylococcal pathogens are colonisers of the skin of healthy dogs and that most staphylococcal skin infections involve 'endogenous' strains, i.e. isolates genetically identical to those of the dog's healthy cutaneous and mucosal microflora (von 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 being considered likely to be the main driver for recurrent forms of pyoderma (Mason and Lloyd, 1989; Colombo et al., 2007; Bloom, 2014). More specific concepts of quorum sensing (regulation of bacterial gene expression in response to fluctuations in population density), 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 as to why infection with opportunistic bacteria may develop in skin (Lloyd, 2014; Pierezan et al., 2016; Rodrigues Hoffmann, 2017).

Immunological defects in innate and adaptive immunity have been identified in deep pyoderma of German shepherd dogs presenting with widespread, highly inflammatory infections during the 1980s and 1990s (Wisselink et al., 1988; Chabanne et al., 1995; Shearer and Day, 1997), but could not be linked conclusively 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

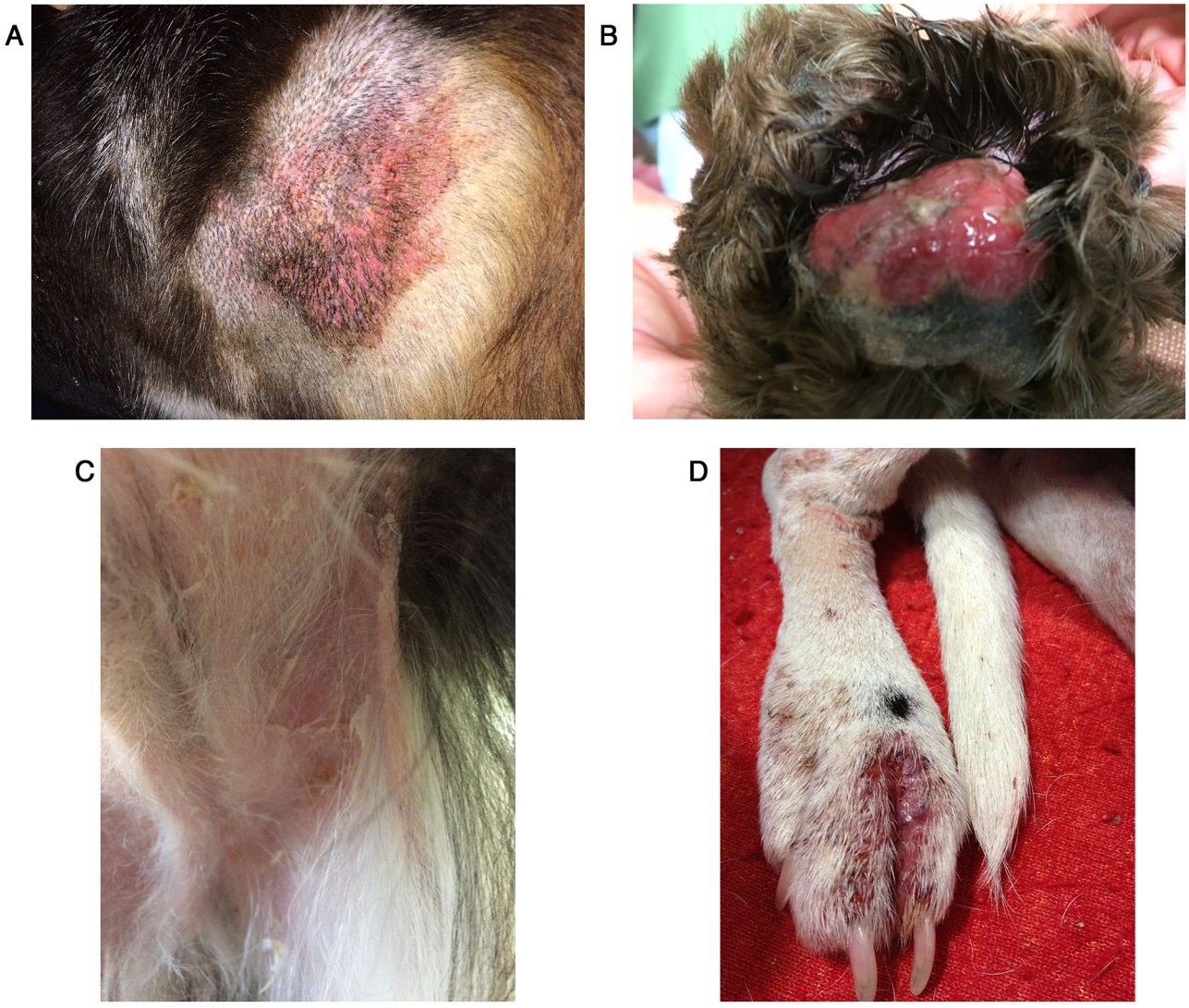

Fig. 1. Examples of recurrent or chronic (>3 months) pyoderma involving multidrug-resistant bacteria. All cases had received repeated courses of systemic antimicrobial agents with initial improvement. Pyoderma resolved when underlying triggering causes were diagnosed and treated in combination with antibacterial 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 methicillin-resistant *Staphylococcus aureus* (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.

represent a diagnosis. In such cases, diagnostic investigations need to be continued, since 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 antimicrobial agents in mind, a diagnosis should always include (1) recognition of suggestive skin lesions and the likely depth of infection; (2) confirmation of bacterial infection through cytology; and (3) identification of underlying primary disease.

Despite its relatively high prevalence, canine pyoderma is often misdiagnosed, leading to inappropriate treatment (Gortel, 2013). 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 insults 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 pyodermas; all three have typical clinical presentations (Fig. 1; Ihrke, 1987; White and Ihrke, 1987).

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 'microbial/bacterial overgrowth syndrome', in which erythema is the only clinical sign but in which large numbers of bacteria on the inflamed skin can be demonstrated by cytology (Pin et al., 2006). In this latter condition, excessive multiplication of bacteria is confined to the skin surface and is seen as a minor player in the pathogenesis, being triggered by a dominant inflammatory cause.

Superficial pyoderma is likely to be the most frequent type of pyoderma in dogs and involves invasion of the epidermis by bacteria; bacterial folliculitis extends into the follicular ostium and epidermal tissue. Dogs with superficial pyoderma are presented with papules, pustules and epidermal collarettes, typically on the ventral abdomen and medial thighs, or on the trunk, often associated with areas of alopecia and varying degrees of pruritus; the interfollicular form (impetigo) occurs mostly in puppies. Coat type and immune status can also influence appearance, as in the 'moth-eaten' appearance of superficial pyoderma in short-coated breeds or in large lesions (collarettes and 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 the 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, since 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 immunodeficiency, 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 and '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/or molecular techniques.

Cytology from slide or tape impressions is recommended for initial diagnosis to confirm bacterial involvement prior to prescription of antimicrobial agents. Cytology of superficial pyoderma lesions has a diagnostic sensitivity of 93%, based on the presence of neutrophils and intracellular cocci (Udenberg et al., 2014). However, although rapid and inexpensive (Curtis, 2001), cytology remains underused in general practice (Hill et al., 2006).

Conversely, bacterial culture is of limited value in the initial diagnosis of pyoderma. It is likely to yield staphylococci from infected and non-infected skin (Doelle et al., 2016), and can therefore not distinguish infected from colonised skin. However, bacterial culture and antimicrobial sensitivity testing are essential for selection of systemic therapy after a diagnosis has been established. It is of note that sampling can be challenging, particularly in deep pyoderma, for which surface swabs have been shown to predict relevant pathogens from deep infection in only about 30% of cases (Shumaker et al., 2008). Submission of fresh tissue (in saline, not formalin) obtained through biopsy is preferred for bacteriology.

Pathogens

The predominant role of coagulase-positive staphylococci in pyoderma is well recognised (Ihrke, 1987). Previously, all such infections were ascribed to *S. aureus,* but refinement of microbiological techniques has allowed new species, including *Staphylococcus intermedius* and *S. pseudintermedius* to be described (Table 1). *S. pseudintermedius* is the most commonly involved pathogen, particularly in superficial pyoderma (Medleau et al., 1986; Shumaker et al., 2008). Other staphylococci, including *S. aureus, Staphylococcus schleiferi* and *Staphylococcus hyicus* may be involved in up to 10% of cases.

Table 1
The changing nomenclature of *Staphylococcus* spp.

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

[a] Canine SIG isolates are always considered as *S. pseudintermedius* (Bannhoer et al., 2007).

Staphylococci have an array of potential virulence factors; however, despite detailed investigation, significant associations between specific virulence genes and disease have not yet been identified, shifting attention again to host factors that may facilitate infection (Bannhoer et al., 2007; Tanabe et al., 2013; Couto et al., 2015). Biofilm production, which can promote resistance to host defence mechanisms and greatly enhance antimicrobial resistance, has been confirmed in many isolates of *S. pseudintermedius* and other veterinary staphylococci (Götz, 2002; Hall-Stoodley et al., 2004).

Many other bacterial pathogens, including *Pseudomonas aeruginosa, Proteus* spp., *Streptococcus* spp., *Burkholderia* spp. and *Escherichia coli* may be difficult to distinguish clinically (Rantala et al., 2004; Hillier et al., 2006; Cain et al., 2011; Tham et al., 2016). Isolation of coagulase-negative staphylococci, such as *Staphylococcus lugdunensis* and *S. schleiferi subsp. schleiferi,* and *Macrococcus* spp., can also cause confusion in laboratories that are looking for coagulase-positive bacteria (Cain et al., 2011; Gobeli Brawand et al., 2016; Cotting et al., 2017). Surprisingly, the idea that coagulase-negative staphylococci are non-pathogenic persists, even though they are the most common cause of nosocomial bacteraemia in human hospitals (von Eiff et al., 2001; Becker et al., 2014) and are increasingly reported in animal infections (Frank et al., 2008; Rook et al., 2012; Davis et al., 2013; Kern and Perreten, 2013; Ruzauskas et al., 2014).

Emergence of multidrug resistance

The first concerns about multidrug resistance in canine pyoderma emerged around 20 years ago when MRSA became recognised in sporadic skin and wound infections; later, the more epidemic spread of MRSP overtook MRSA and now presents major challenges to management of canine pyoderma. In addition, all key multidrug-resistant pathogens of relevance in human medicine, such as *Enterococcus faecium, Klebsiella* spp., *Acinetobacter baumannii, P. aeruginosa* and *Enterobacter* spp., are now recognised to be associated with infection in pets (Grobbel et al., 2007; Kuzi et al., 2016; Abdel-Moein et al., 2017).

Meticillin resistance in staphylococci

Although methicillin is no longer available for clinical use, it still serves as a marker for broad resistance to all β-lactams (excepting some of the latest anti-staphylococcal molecules) and as an indicator of likely nosocomial epidemiology and additional multidrug resistance. The genetic basis underpinning methicillin-resistance is the presence of the *mecA* gene, which is carried by a large mobile genetic element, the staphylococcal cassette chromosome (SCC). This is similar in all staphylococci and has been extensively studied in MRSA (Lindsay and Holden, 2006).

Since the first identification of MRSA from pets, isolates from pets and human beings have been shown to be genetically identical, providing indirect but good evidence that transmission between these hosts can occur in both directions (McCarthy et al., 2012). MRSA was the first multidrug-resistant *Staphylococcus* spp. to receive attention in animals when pets contaminated by human MRSA patients were shown to be involved in perpetuating human infection or recurrent outbreaks (Scott et al., 1988; Manian, 2003). Since then, sporadic infections, case series and outbreaks have been reported, typically involving skin and wound infections in dogs (Tomlin et al., 1999; Paterson et al., 2015; Morris et al., 2017). Most reports are from countries with a high MRSA prevalence in human hospitals, consistent with spill-over from human beings; epidemic spread beyond clinic or kennel outbreaks has not been reported. Fortunately, the prognosis in such infections can be considered to be good, depending on underlying causes, since most of these human hospital-associated MRSA isolates remain sensitive to tetracyclines and potentiated sulphonamides, and around 50% are sensitive to clindamycin. A less predictable prognosis needs to be considered for rare infections involving MRSA from human lineages that carry toxins such as Panton–Valentine-leucocidin (Rankin et al., 2005; van Duijkeren et al., 2005) and livestock-associated MRSA (Gómez-Sanz et al., 2013).

A 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 are required for its rapid evolution to multidrug resistance, emphasising the important role of selection pressure: (1) acquisition of *mecA* on a SCC; (2) acquisition of a large transposon (Tn5405-like element) carrying up to five resistance genes; and (3) genome point mutations for fluoroquinolone and sulphonamide resistance (Loeffler et al., 2007; Perreten et al., 2010; Detwiler et al., 2013; McCarthy et al., 2015).

MRSP was first reported from dogs in North America in the late 1990s, initially as methicillin-resistant *S. intermedius* (MRSI), then accounted for >30% of staphylococcal isolates from American dogs within 10 years (Gortel et al., 1999; Morris et al., 2006; Jones et al., 2007). MRSP is now identified worldwide and high prevalences have been reported from China (~50%) and Japan (~70%) (Feng et al., 2012; Kasai et al., 2016). In the UK, where MRSP was first recognised in 2009, the burden seems to be relatively low, with MRSP representing 5% of clinical *S. pseudintermedius* laboratory submissions (Maluping et al., 2014; Beever et al., 2015). In continental Europe, where MRSP had been identified 3 years earlier, the prevalence is ~30% (Loeffler et al., 2007; De Lucia et al., 2011). Substantial percentages of methicillin resistance have also been reported in coagulase variable *S. schleiferi* subspecies *schleiferi* and *coagulans*, some from pyoderma but most from otitis (Cain et al., 2011).

Clinical implications and early identification

Clinically, MRS infections in animals are no different from infections involving less resistant staphylococci (Fig. 1; Morris et al., 2017). Early case-control studies showed that clinical outcome was no worse for MRSA and MRSP infections in pets compared to those involving their susceptible counterparts, provided that a safe antibacterial treatment option was available (Weese et al., 2012; Lehner et al., 2014). Finding treatment options may be troublesome and treatment has been shown to take longer than with sensitive staphylococci (Bryan et al., 2012). However, the bigger concern with MRS pyoderma is its potential for spreading these zoonotic, multidrug-resistant pathogens to other animals and people, and into the environment. The risk of zoonotic transmission of MRSP is generally considered to be low, since low carriage rates of *S. pseudintermedius*/*S. pseudintermedius* have been found in people regularly exposed to dogs (Harvey et al., 1994; Goodacre et al., 1997; Han et al., 2016). However, as for all staphylococci, the risk is increased for immunocompromised people and individual cases of zoonotic MRSP infection have been reported (Stegmann et al., 2010; Somayaji et al., 2016; Lozano et al., 2017).

Transmission of staphylococci is supported by their ability to survive on dry surfaces and at healthy skin and mucosal carriage sites for many months, equipping them for nosocomial spread (Wagenvoort et al., 2000; Windahl et al., 2012). Early identification of MRS by clinicians is therefore crucial to limit outbreaks, but it relies on awareness of risk factors. Risk factors for multidrug-resistant infection in human medicine are well documented and include frequency of hospitalisation, length of stay in hospitals, surgical interventions and repeated antimicrobial therapy (Safdar and Maki, 2002). Unsurprisingly, the same risk factors have been

identified for MRSA and MRSP infections in dogs (Soares-Magalhães et al., 2010; Baker et al., 2012; Lehner et al., 2014; Weese et al., 2012).

New focus on laboratory identification

When MRS are involved, accurate differentiation between MRSA and MRSP is critical for further management, since 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 medical physician. In contrast, isolation of canine-adapted MRSP should initiate all appropriate infection control measures recommended for veterinary nosocomial pathogens and advice on limiting contagion to other animals, while the zoonotic risk is considered to be lower (Morris et al., 2017).

Identification of MRS through phenotypic assessment alone is difficult, since subtle morphological and biochemical variation occurs within bacterial populations (Pottumarthy et al., 2004; Sasaki et al., 2007; Bond and Loeffler, 2012; Geraghty et al., 2013). Similarly, recognition and accurate identification of coagulase-negative staphylococci is important as their pathogenic potential is increasingly being 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, the 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 *Staphylococcus intermedius* group (SIG) species (Decristophoris et al., 2011; Sauget et al., 2016; Somayaji et al., 2016).

Sensitivity testing is most often performed using 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., 2014).

Management of canine pyoderma

In the past, treatment of canine pyoderma was rarely challenging, since *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 recognised that isolates from animals that had repeatedly received antimicrobial agents 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 evidence that resistance to most antimicrobial classes is gradually increasing (Beever et al., 2015). On the basis of recent data for small animal pathogens, this trend of increasing antimicrobial resistance is likely to continue worldwide (Ludwig et al., 2016).

Topical therapy

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

A wide range of different formulations, such as shampoos, creams, gels and ointments, and more recently foams, is marketed for dogs and includes a variety of antibacterial agents; this can be confusing. A systematic review of topical therapy for canine bacterial skin infections concluded that, while evidence from randomised controlled trials was sparse, good evidence supported the use of shampoos containing 2–3% chlorhexidine and, to a lesser extent, benzoyl peroxide (Mueller et al., 2012); these continue to be the mainstay of topical therapy, at least for widespread disease. Localised infections can also be treated with creams or gels containing antibiotics such as fusidic acid, which authorised for use in dogs in European countries and Canada, or mupirocin ointment, which is authorised in the USA for dogs, but reserved for use in human medicine in most of Europe (Cobb et al., 2005).[1]

Whilst there is concern over resistance to topically used antibacterial agents, there is no conclusive evidence of clinical treatment failure of topical anti-staphylococcal therapy; MICs for staphylococci from animals have been consistently low and are likely to be substantially exceeded by achievable topical drug concentrations (Loeffler et al., 2008; Valentine et al., 2012; Clark et al., 2015). However, continual monitoring of resistance and clinical efficacy, further evaluation of alternatives, such as hypochlorite (bleach), Manuka honey, anti-biofilm products and potentially synergistic combinations is required (Walker et al., 2016). Combinations of topical and systemic treatments are recommended whenever possible to potentially reduce the duration of systemic therapy and, in MRS infections, to reduce environmental contamination and the risk of transmission to other hosts.

Systemic therapy

Systemic therapy, which is required for deep pyoderma and for widespread or severe superficial infections, should follow the concept of 'as little as possible but as much as necessary' (RUMA, 2009). The efficacy of systemic therapy depends predominantly on bacterial susceptibility, but will also be determined by correct drug administration, appropriate dosing, owner compliance and clinical variables, such as severity of infection, and causative and concurrent diseases. Surprisingly, despite their universal use, evidence for the efficacy of systemic antimicrobial agents is sparse, since there are few adequate studies documenting outcome (Summers et al., 2012).

[1] See: https://www.medicinescomplete.com/mc/bnf/current/PHP7973-mupirocin.htm#PHP45895-indicationsAndDose-topic (accessed 14 October 2017).

Whilst bacterial culture and susceptibility testing would be desirable for every affected dog and is never contraindicated in pyoderma, realistically, cost, perceived delay of effective treatment and clinical time pressure often motivate empirical drug selection. In countries with a low prevalence of MRS, empirical selection may still be effective for most superficial pyodermas. In countries with a high prevalence of MRS, this can no longer be considered reliable or cost-effective. Furthermore, repeated testing may be required, since antimicrobial therapy has been shown to promote acquisition of MRSP in dogs not previously positive for MRSP (Beck et al., 2012). Recent pyoderma guidelines further specify that bacterial culture and sensitivity testing is essential in all dogs with deep pyoderma, those with a history of MRS or with owners reporting MRS in themselves, and in dogs where appropriate 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 World Health Organization (WHO) as 'critically important antimicrobials' or 'highly important for human medicine'.[2]

In cases of non-MRSP pyoderma, most antimicrobial agents authorised for use in dogs would be effective if prescribed appropriately. Treatment recommendations have been detailed in two free access publications, one on pyoderma by a group of veterinary dermatologists (Beco et al., 2013b) and the other on superficial bacterial folliculitis by the International Society for Companion Animal Infectious Disease (ISCAID; Hillier et al., 2014). 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 agent 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 patterns, since differences in resistance have been recognised between countries and between isolates from first time pyoderma vs. those from recurrent pyoderma (Holm et al., 2002; Beever et al., 2015; Larsen et al., 2015). Treatment with second tier agents, such as fluoroquinolones, should always be based on bacterial culture and sensitivity results.

In canine pyoderma due to MRS, drugs predicted to be effective by in vitro testing are selected on the basis national licensing rules, their clinical and safety characteristics, dosing practicalities and cost; no single drug has been shown to be better than another. Information specifically on treatment of MRS is detailed in open access Clinical Consensus Guidelines on MRS infections (Morris et al., 2017): (1) β-lactam antibiotics should not be used for MRS infections, even if testing indicates sensitivity to individual agents of this class; (2) testing for inducible resistance to clindamycin is recommended for MRS to avoid treatment failure during therapy; (3) extrapolation of results for one type of tetracycline to another can be unreliable, since resistance is mediated by a number of different genes; and (4) resistance to one fluoroquinolone is likely to indicate resistance to others in MRSP. Treatment decisions may be assisted if MICs are determined (Kizerwetter-Świda et al., 2016).

When no susceptibilities to clinically relevant and authorised antimicrobial agents 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, detailed owner education and compliance is required, and advice on infection control measures to limit spread should be provided (Morris et al., 2017). In the authors' opinion, glycopeptides, linezolid and potentially new compounds should be strictly reserved for use in human beings. Some institutions may consider these under restriction-of-use protocols, but this should be rarely necessary for canine pyoderma (Weese, 2008).

Recommendations on the duration of treatment of pyoderma remain controversial. Traditional advice, based on clinical expertise is to treat for 3 weeks (or 1 week beyond clinical cure) for superficial pyoderma and 4–8 weeks (or 2 weeks beyond clinical cure) for deep pyoderma (Ihrke, 1987). In human medicine, courses of antibiotic treatment are typically shorter and the advice to patients to complete a course of treatment 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 to adhere to the traditional recommendations; where shorter durations of treatment are prescribed, plans for close monitoring of progress by a veterinary surgeon rather than by the owner should be instituted (Hillier et al., 2014). In addition, resolution of clinical signs will not signal the end of case management for MRS pyoderma, since dogs can become carriers and there is a risk of spread, including zoonotic transmission and of self-reinfection.

Correction of primary triggers, follow-up and prevention

After resolution of any type of pyoderma, prevention of recurrence is very important, since 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. In the authors' experience, the most problematic cases are those dogs that, in the absence of pyoderma (i.e. when infection has 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 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-reinfection have long been suspected as major contributors to the successful spread of human MRSA and a similar epidemiology is suspected for MRSP in veterinary settings (Beck et al., 2012; Morris et al., 2017).

New approaches

The growing problem of antimicrobial resistance and the lack of effective, new, conventional antimicrobial drugs has promoted the development of different approaches to prevention and control of bacterial infections (Vale et al., 2016). Staphylococcal vaccines,

[2] See: http://www.who.int/foodsafety/publications/antimicrobials-third/en/ (accessed 25 October 2017).

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

either *S. aureus* lysates or autogenous bacterin preparations, have been assessed in small studies and warrant further investigation (Glos and Mueller, 2011). Antimicrobial peptides, which are produced by the skin and function as a vital part of cutaneous antimicrobial defences, are now being exploited in veterinary products for dogs. Two promising approaches have been adopted. In the first, plant extracts promoting production of endogenous antimicrobial peptides by the skin have been incorporated in shampoos and ear cleaners (Marsella et al., 2013; Santoro et al., 2016). In the second, a synthetic peptide (Cabassi et al., 2013) has been incorporated in shampoo, foam and an ear treatment gel. A variety of other approaches are being investigated and developed, but have not yet led to the development of veterinary products (Table 2). It is likely that at least some of these new approaches will prove successful; however, we should not expect the development of agents which will allow us to ignore good drug stewardship and the adoption of rigorous hygiene.

Conclusions

Canine pyoderma requires appropriate management to reduce morbidity and limit the spread of potentially multidrug-resistant pathogens amongst pets and human beings. However, the availability of effective and safe systemic antimicrobial agents will become, or already is in some countries, substantially limited, either by continued selection of antimicrobial resistance amongst pathogens or by legislative restrictions on prescribing by veterinary surgeons. 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 of the 'golden age of antibiotics'.

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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