

Antimicrobial Resistance in Staphylococci in Small Animals

Christine L. Cain, DVM

KEYWORDS

- *Staphylococcus*
- Methicillin resistance
- Multidrug resistance
- Pyoderma
- Antimicrobial therapy

KEY POINTS

- Methicillin resistance is the most important mechanism of antimicrobial resistance in staphylococci and conveys resistance to all β -lactam derivatives.
- Methicillin-resistant staphylococci are frequently multidrug resistant by additional genetic mechanisms, making empiric antimicrobial selection difficult.
- Culture and susceptibility testing are often overlooked, but are increasingly indicated, in the clinical management of staphylococcal pyoderma.
- Systemic antimicrobial options for resistant staphylococcal pyoderma are often limited; potential adverse drug effects and drug interactions should be considered in treatment decisions.
- The medical literature suggests that transmission of methicillin-resistant staphylococci between humans and animals can occur; strict hygiene practices should be observed when handling infected patients.

INTRODUCTION

During the past several decades, the prevalence of staphylococcal antimicrobial resistance, particularly methicillin resistance, has risen substantially in both the human and the veterinary health care arenas. Infections associated with antimicrobial resistant *Staphylococcus* spp are increasingly encountered by veterinary practitioners. Staphylococcal resistance, in turn, presents significant challenges for successful empiric therapy, limits antimicrobial treatment options, and raises concerns of potential zoonotic transmission. This article will review common mechanisms of antimicrobial resistance in *Staphylococcus pseudintermedius*, *Staphylococcus aureus*, *Staphylococcus schleiferi*, and coagulase-negative staphylococci (CoNS). Implications of staphylococcal antimicrobial resistance for clinical practice, including rational antimicrobial selection and indications for culture and susceptibility testing, will be highlighted.

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Department of Clinical Studies - Philadelphia, School of Veterinary Medicine, University of Pennsylvania, 3900 Delancey Street, Philadelphia, PA 19104, USA

E-mail address: ccain@vet.upenn.edu

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METHICILLIN RESISTANCE

Methicillin resistance is the most important antimicrobial resistance mechanism in staphylococci. Methicillin resistance is conveyed by the *mecA* gene, carried on the mobile genetic element staphylococcal chromosome cassette *mec* (SCCmec), which encodes for an altered penicillin binding protein (PBP2a). Production of this altered penicillin binding protein renders resistance to all β -lactam derivatives, including penicillins, potentiated penicillins, cephalosporins, and carbapenems.¹ In veterinary staphylococcal isolates, the source of the *mecA* gene is unknown, although there is evidence in human medicine that the *mecA* gene likely originated in *Staphylococcus sciuri* (a CoNS) with possible horizontal transfer to *S aureus*.² Although references to methicillin resistance are pervasive in the medical literature, oxacillin is commonly used in veterinary microbiology laboratories as the correlate for testing antimicrobial resistance. Both drugs are semisynthetic penicillinase-resistant penicillins, but oxacillin possesses greater in vitro stability.^{3,4} In keeping with the common vernacular, “methicillin resistance” will be used throughout this article.

METHICILLIN-RESISTANT STAPHYLOCOCCI OF VETERINARY IMPORTANCE

Methicillin-Resistant S pseudintermedius

S pseudintermedius is the most common cause of pyoderma in dogs and also normally colonizes the skin and mucosal sites.⁵ This species was previously known as *S intermedius*. Recently, investigators used molecular techniques to more correctly classify 3 closely related staphylococcal species (*Staphylococcus intermedius*, *S pseudintermedius*, and *Staphylococcus delphini*) as the *S intermedius* group. Furthermore, it now seems that all previously classified *S. intermedius* isolates from dogs, cats, and humans were actually *S pseudintermedius* isolates.⁵⁻⁷ For simplification purposes, isolates from these species will be referred to as *S pseudintermedius* throughout this article, even in referencing results of studies published before the reclassification of the *S. intermedius* group.

The prevalence of methicillin-resistant *S pseudintermedius* (MRSP) infections in veterinary patients has increased substantially during the past decade. Two reports of antimicrobial susceptibility of veterinary *S pseudintermedius* isolates in the mid-1980s failed to identify any methicillin-resistant isolates.^{8,9} Following sporadic reports of MRSP isolates in the 1990s,^{10,11} reports of MRSP infections are now commonplace in the veterinary literature. MRSP is a potential pathogen of dogs, cats, and horses; infection has been associated with pyoderma, otitis, urinary tract infections, wounds, surgical site infections, and septicemia.¹²⁻¹⁷ In the United States, 2 large retrospective studies of clinical submissions to veterinary microbiology laboratories documented an overall MRSP prevalence of 15.6% (Jones and colleagues; 2001–2005) and 17% (Morris and colleagues¹³; 2003–2004), respectively.¹⁸ Since that time, clinical isolation of MRSP seems to have increased; in 2008, nearly 30% of *S pseudintermedius* isolates from the University of Tennessee veterinary bacteriology laboratory were methicillin resistant.³ Reported frequency of MRSP isolation from canine pyoderma varies with geographic location. For example, one recent Japanese study reported an MRSP prevalence of 66.7% from dogs with pyoderma,¹⁹ whereas MRSP has only been more recently documented in Europe and isolation rates from clinical samples are low, but they may be increasing.^{12,14,20}

MRSP has also been isolated from carriage sites of healthy dogs and cats. Multiple recent studies have investigated MRSP carriage in healthy dogs and/or cats in different geographic areas; sampled sites vary but include the nares, oral mucosa, skin, and rectal mucosa.²¹⁻³³ Reported prevalence of MRSP carriage in healthy

dogs ranges from 0% to 30%, although several studies support a carriage rate in healthy dogs of 1.5% to 3%.^{21,22,24–33} One study by Griffith and colleagues²⁴ also investigated MRSP carriage in dogs with inflammatory skin disease; an overall prevalence of 7% was found, compared with 2% prevalence in healthy dogs. Far fewer investigators have examined MRSP carriage in cats. Abraham and colleagues²³ demonstrated a prevalence of MRSP carriage of 4% in healthy cats, but MRSP was not isolated from cats with inflammatory skin disease. Couto and colleagues²⁶ failed to isolate MRSP from the carriage sites of healthy cats. In a study of veterinary dermatology staff and their household pets, Morris and colleagues³³ found relatively high rates of MRSP carriage in dogs (6.2%) and cats (3.1%), suggesting that the pets of veterinary dermatology staff may be at increased risk for colonization by MRSP. Taken together, the literature suggests that reported prevalence of MRSP in clinical specimens may significantly exceed the prevalence of MRSP colonization in healthy animals, although there may be variation by geographic region and the sampled population.

As is the case for methicillin-resistant *S aureus* (MRSA), several closely related (clonal) MRSP lineages have been identified.^{6,12,15,34–36} Furthermore, epidemic clonal strain types may differ by geographic region, suggesting that multiple methicillin-susceptible *S pseudintermedius* (MSSP) strains have acquired the *mecA* gene and successfully proliferated among the canine population.^{6,34,36} For example, by the molecular technique of multilocus sequence typing, most MRSP isolates from North America have been classified as the clonal lineage ST68, whereas most European MRSP isolates are ST71.^{6,12,15,34,36}

Although methicillin-resistant staphylococci are not necessarily more virulent than methicillin-susceptible staphylococci,³⁷ treatment of MRSP infections may present a major clinical challenge because of the multidrug resistance of isolates. High rates of resistance to non- β -lactam antimicrobials, including macrolides, lincosamides, tetracyclines, fluoroquinolones, and potentiated sulfonamides, have been reported in the United States, Europe, and Asia.^{3,12–15,18–20,26,29,30,34,38–40} Resistance to these additional antimicrobials is mediated by genetic mechanisms other than the *mecA* gene. Antimicrobials to which MRSP isolates often exhibit susceptibility include fusidic acid, mupirocin, amikacin, rifampin, vancomycin, linezolid, and teicoplanin.^{12,14,20,29,39,40} Susceptibility to chloramphenicol is variable; many European isolates are resistant to chloramphenicol,^{15,39} whereas good susceptibility has been reported in MRSP isolates in the United States.^{3,13} In the author's experience, chloramphenicol resistance seems to be increasing in the United States and is dependent on the region of practice. In a study of 103 MRSP isolates from various countries in Europe, various regions of the United States, and Canada, Perreten and colleagues³⁴ showed that 57.3% of isolates showed resistance to chloramphenicol, whereas only 1.9% of isolates showed resistance to rifampin. Options for antimicrobial treatment of MRSP infections will be further discussed later in the article.

Risk factors for MRSP acquisition have been investigated in only a few veterinary studies. In a recent retrospective study by Bryan and colleagues,⁴¹ dogs with pyoderma caused by MRSP were no more likely to have a concurrent endocrinopathy, neoplasia, or to be receiving immunosuppressive drug therapy than dogs with MSSP isolated on skin culture. In a 2011 study by Huerta and colleagues,⁴² dogs with methicillin-resistant staphylococci isolated on skin culture, mainly belonging to the *S intermedius* group, were more likely to be housed in an urban setting and to have received systemic antimicrobial treatment within the year before culture. Prior antimicrobial therapy may play a significant role in the acquisition of MRSP. As shown by Beck and colleagues,⁴³ subsequent MRSP isolation from the skin and mucosal sites

of dogs with previous MSSP pyoderma following antimicrobial therapy is common. In this study, no association was found between prior antimicrobial exposure and MRSP isolation from infection or carriage sites, but treatment of pyoderma with clindamycin was associated with MRSP isolation on follow-up culture. Taken together, these results suggest that systemic antimicrobial therapy may alter the patient's commensal staphylococcal flora and thus allow for colonization by methicillin-resistant strains. This concept is supported by work in horses showing an increase in commensal staphylococci harboring drug-resistance genes, including *mecA*, following hospitalization and prophylactic penicillin treatment.⁴⁴

Given the increase in MRSP infections, as well as the frequent multidrug resistance of isolates, the risk of MRSP transmission to other in-contact pets and humans, and of environmental contamination, has been a topic of concern. MRSP colonization of dogs and cats residing in the same household as a dog with a clinical MRSP infection has been demonstrated. For the most part, risk of MRSP colonization for healthy in-contact pets seems to correspond with active clinical lesions in dogs with diagnosed MRSP infections and to decrease after clearance of the infection.^{45,46} Rare MRSP infections in humans have been reported; in most cases, dog-to-human transmission is suspected.^{47–49} Nasal colonization of humans with MSSP and MRSP has also been shown, particularly in veterinarians, veterinary personnel, and persons residing in households with dogs with *S pseudintermedius* infections.^{30,33,45,46,50–56} In several cases, MRSP isolates obtained from pets and from humans have been found to be identical on pulsed-field gel electrophoresis (PFGE), further supporting pet-to-human transmission.^{33,45,54,56} In one study, lack of handwashing after the handling of pets was found to be a risk factor for nasal MRSP isolation.⁵⁰ Human colonization with MRSP is likely transient and seems to clear after clinical resolution of the pet's infection.^{46,54,55} Environmental contamination of households and veterinary hospital with MRSP has also been demonstrated.^{45,46,52} Environmental isolation of MRSP also seems to be associated with active lesions in patients with MRSP infections, although the organism has been isolated from environmental samples even in the absence of MRSP isolation from household humans or pets.⁴⁶

MRSA

In humans, *S aureus* is a major cause of skin and soft tissue infections and colonizes approximately 30% of the human population worldwide.⁵⁷ Although *S aureus* colonization of healthy dogs has been reported,⁵⁸ the prevalence seems to be much lower than that of *S pseudintermedius* colonization.⁵⁹ In cats, there is conflicting evidence as to whether *S pseudintermedius* or *S aureus* is the primary colonizing coagulase-positive staphylococcal species.^{60–63}

There has been a dramatic increase in the number of infections caused by MRSA in human medicine since the 1960s.⁶⁴ Although human MRSA infections were once regarded as primarily hospital-associated and nosocomial in origin, community-associated MRSA infections of healthy individuals have rapidly emerged during the past decade.^{64,65} Both hospital-associated and community-associated MRSA infections are now recognized as major causes of human morbidity, mortality, and health care expenditures.^{64,66} With the increasing importance of MRSA in the human health care arena, there has been a great deal of interest in MRSA infections in animals. Prevalence of methicillin resistance in clinical veterinary *S aureus* isolates has been reported to approximate 25% to 35%.^{13,18} MRSA infections have been reported in a variety of companion and exotic animal species, including dogs, cats, horses, parrots, rabbits, guinea pigs, turtles, bats, elephants, and marine mammals.^{13,16,67–94} Most infections involve wounds, both postsurgical and traumatic, but MRSA has also

been isolated from cases of pyoderma, otitis, respiratory disease, cystitis, prostatitis, joint infections, and septicemia.^{13,16,67,69–94} MRSA infections in companion and exotic animals are most often associated with predominant hospital-acquired or community-acquired clonal strains in the surrounding human population; this supports, but does not prove, human-to-animal transmission.^{68–71,73–77,82–88,90–94}

Risk factors for MRSA infection in dogs and cats may include recent administration of antimicrobials, particularly β -lactams or fluoroquinolones; multiple antimicrobial courses; multiple-day hospitalization; surgical implants; intravenous catheterization; or contact with an ill or hospitalized human.^{78,95} As with MRSP infections, empiric therapy can be challenging because of potential drug resistance; MRSA isolates are often resistant to non- β -lactam antibiotics, particularly fluoroquinolones, macrolides, and lincosamides.¹³

Healthy dogs and cats may be colonized by MRSA, although this colonization may be transient, particularly in dogs, and the organism may not be isolated on repeated sampling.^{81,96,97} Reported prevalence of MRSA colonization in healthy dogs or on admission to veterinary hospitals ranges from 0% to approximately 3%, whereas reported prevalence in cats ranges from 0% to 4%.^{21–26,33,50,77,98} In one study, animals presenting for veterinary care were significant more likely to carry MRSA than were healthy animals.⁹⁸ Several studies have suggested the possibility of MRSA transmission from colonized or infected humans to animals, or vice versa, often via demonstration of genotypically identical strains.^{33,52,69,72,73,86,90,96,97,99–112} The true direction of transmission often cannot be proved, however. Although human-to-animal transmission is usually assumed, the epidemiologic relationships may be complex; even in households with infected or colonized humans, that person may not be identified as the MRSA source for the pet.^{96,113} The risk of direct pet-to-pet transmission seems to be low, especially among healthy colonized dogs.⁸¹

MRSA is an emerging pathogen in horses and farm animals, particularly pigs. In North America, horses may be colonized by or infected with a clonal MRSA strain known as USA500 (or Canadian epidemic MRSA-5).^{114–120} Although this strain was initially associated with nosocomial infections in humans, it has now become well adapted to horses, but it may colonize or cause infection in humans with close horse contact.^{115–118} Pigs may harbor a clonal MRSA strain known as ST398; this strain seems to have arisen in swine and may colonize large numbers of pigs in some herds, particularly in Europe.^{121,122} MRSA ST398 has been isolated from infections in dogs and humans,^{121,123} from commercial pork products in the United States and Canada,^{124,125} and from carriage sites of humans with pig contact.^{126,127}

Colonization by MRSA may be an occupational risk for veterinarians and veterinary staff. In 2001 through 2004, the prevalence of human nasal MRSA colonization in the United States was 1.5%.¹²⁸ By contrast, nasal colonization prevalence rates in veterinarians and veterinary staff of 3.5% to 21.4% have been reported in screening studies in North America, Europe, and Australia.^{33,129–132} Although some studies have reported a much higher prevalence of nasal colonization in large animal (including equine) practitioners,^{129,133} others have reported equal isolation from the nares of small and large animal practitioners.¹³⁰ MRSA may also be isolated from environmental sites in veterinary hospitals, although the role of the environment in MRSA transmission is not entirely clear.^{134–137}

Methicillin Resistant *S schleiferi*

S schleiferi is a unique staphylococcal species in that 2 variants have been described based on coagulase production: *S schleiferi* subsp *schleiferi* (coagulase negative) and *S schleiferi* subsp *coagulans* (coagulase positive). Recent work suggests that the 2

subspecies are not genotypically distinct and do not differ in clinical behavior.^{138,139} Coagulase-positive and coagulase-negative *S schleiferi* have been reported to cause infections in dogs and are mainly associated with pyoderma and otitis in dogs with allergic dermatitis.^{138–144} When isolated from dogs with pyoderma, there may be an association with recurrent pyoderma and prior or concurrent antimicrobial therapy.^{139,142}

Methicillin resistance seems to be particularly prevalent in clinical isolates of *S schleiferi* with rates of methicillin resistance exceeding 50% in several reports.^{1,138,139,142,145} Despite frequent methicillin resistance, *S schleiferi* isolates may maintain favorable susceptibility to non- β -lactam antimicrobials, especially to potentiated sulfonamides.^{13,138,139} Fluoroquinolone resistance is common in methicillin-resistant *S schleiferi* (MRSS) isolates.^{13,19,138,139,146,147} Risk factors for clinical isolation of MRSS identified in one retrospective study of 225 infections in dogs included recent (30 days to 6 months before culture) treatment with penicillins, potentiated penicillins, or first- and second-generation cephalosporins or treatment with third-generation cephalosporins within 30 days of culture.¹³⁹ These results suggest that alteration of the patients' methicillin-susceptible flora may have predisposed to colonization by MRSS, as has been found with *S pseudintermedius* after antimicrobial therapy.⁴³

S schleiferi colonization of companion animals has been infrequently investigated in the veterinary literature. Coagulase-positive *S schleiferi* has been isolated from carriage sites of cats and dogs^{21,23,24,33} and may be found together with *S pseudintermedius*.¹⁴⁸ Prevalence of colonization with coagulase-positive MRSS has been reported to be 0.5% in a convenience sampled population of dogs entering a veterinary teaching hospital²¹; 2% in healthy dogs and dogs with inflammatory skin disease²⁴; and 0.4% in dogs belonging to veterinary dermatologists or staff.³³ Coagulase-positive MRSS was not isolated from healthy cats or cats with inflammatory skin disease in the study by Abraham and colleagues.²³ Coagulase-negative *S schleiferi* has been less frequently documented as a normal inhabitant of dogs and cats. This variant has been isolated from the ears of healthy dogs.¹⁴³ Coagulase-negative MRSS has been isolated from carriage sites of cats²³ and dogs²⁴ with inflammatory skin disease, with a 2% prevalence in both species, and from 1 of 258 dogs (0.4%) belonging to veterinary dermatology practice staff.³³ MRSS may also be isolated from carriage sites of dogs with pyoderma caused by MRSS, as well as dogs with other staphylococci isolated from skin lesions.⁴³

In humans, coagulase-negative *S schleiferi* is well documented as a normal component of preaxillary flora, although it has been associated with nosocomial infections, including surgical and pacemaker implantation site infections.^{149–151} By contrast, coagulase-positive *S schleiferi* is an infrequent cause of human infections; only 2 infections have been documented in the medical literature to date.^{152,153} In the second reported infection, a case of endocarditis in a human liver transplant recipient, a family dog with recurrent otitis was suspected as the source, but molecular characterization was not done to show identical strains from the person and the dog.¹⁵³ In the 2010 study by Morris and colleagues³³ of methicillin-resistant staphylococcal colonization in veterinary dermatology staff and pets, a higher prevalence of MRSS colonization, with a predominance of coagulase-positive isolates, was demonstrated in humans compared with dogs and cats. This finding suggests that MRSS colonization, particularly by the coagulase-positive variant, may be an occupational risk for veterinarians and veterinary staff.

Methicillin-Resistant CoNS

Both coagulase-negative and coagulase-positive *S schleiferi* are important pathogens in veterinary medicine. The clinical importance of other CoNS, which have historically

been considered to be commensal organisms or contaminants with limited pathogenic potential, is less well established. In human medicine, CoNS represent an emerging cause of opportunistic infections, particularly nosocomial infections. Isolates may produce a variety of different virulence factors and exhibit high levels of methicillin resistance.^{154–156} In veterinary medicine, CoNS may be isolated from the skin and mucosal sites of healthy animals,^{157–162} as well as from cultures of infection sites^{75,163–165} and from environmental sites in veterinary hospitals.^{158,166} Methicillin resistance in veterinary isolates of CoNS has been reported,^{75,157,158,160,161,167,168} highlighting their potential importance as both reservoirs of drug resistance and opportunistic pathogens.

OTHER MECHANISMS OF STAPHYLOCOCCAL ANTIMICROBIAL RESISTANCE

As discussed previously, methicillin-resistant staphylococci frequently exhibit core-sistance to non- β -lactam antimicrobials by mechanisms unrelated to acquisition of the *mecA* gene. Clindamycin resistance, resistance to tetracyclines, and fluoroquinolone resistance will be specifically discussed.

Clindamycin Resistance

Resistance to the related macrolides and lincosamides, including clindamycin, may be conveyed by the staphylococcal *msrA* gene, which encodes for antimicrobial efflux, or the *erm* genes, which encode for changes to the ribosomal antimicrobial target site. Clindamycin resistance encoded by the *erm* genes may be either constitutive, in which resistance is shown to all drugs in these related classes (ie, both erythromycin and clindamycin), or inducible, in which the presence of an inducing agent (eg, erythromycin) promotes expression of a resistant phenotype. Use of clindamycin in infections caused by isolates exhibiting inducible resistance may result in treatment failure.^{169,170} Inducible clindamycin resistance has been well documented in MRSA isolates from humans and animals and has been reported in some MRSP isolates as well.^{34,169–171} Microbiology laboratories can test for inducible clindamycin resistance using a double disc diffusion test (D-test) with adjacent erythromycin and clindamycin discs (**Fig. 1**).¹⁶⁹ In the absence of this test, clinicians may predict inducible resistance based on susceptibility reports indicating erythromycin resistance and clindamycin susceptibility. In these cases, clindamycin use should be avoided.^{169,171}



Fig. 1. The double disc diffusion test (D-test) for detection of inducible clindamycin resistance illustrating the D-shaped zone around the clindamycin disc ("CC") when in close proximity to the erythromycin disc ("E"). (Courtesy of Dr David A. Bemis and the University of Tennessee Veterinary Bacteriology Laboratory.)

Tetracycline Resistance

Staphylococcal resistance to tetracyclines may be mediated by plasmid-situated genes (*tetK* or *tetL*) encoding for antimicrobial efflux, or by the chromosomal or transposon-situated *tetM* or *tetO* genes, which encode for alteration of the ribosomal antimicrobial target site.¹⁷² The *tetK* and *tetM* genes seem to be the most important mediators of resistance in MRSP isolates.³⁴ Isolates possessing the *tetM* gene are considered to be resistant to all tetracyclines, including doxycycline and minocycline.¹⁷² Tetracycline-resistant isolates belonging to the ST68 lineage, the predominant MRSP clone in North America, have been found to carry the *tetM* gene.³⁴ Staphylococcal isolates possessing the *tetK* gene, by contrast, are considered to be resistant to tetracycline and susceptible to minocycline. Doxycycline resistance in both *tetM*- and *tetK*-positive MRSA isolates may be induced by incubation with subinhibitory concentrations of tetracyclines,¹⁷² suggesting that doxycycline may be a poor choice for any staphylococcal isolate exhibiting resistance to tetracycline by susceptibility testing. Tetracycline-resistant isolates belonging to the ST71 lineage, the predominant European MRSP clone, have been found to carry the *tetK* gene, indicating the minocycline may be an appropriate therapeutic option for MRSP infections in Europe if supported by susceptibility test results.³⁴

Fluoroquinolone Resistance

Fluoroquinolones exhibit rapid bactericidal activity via inhibition of bacterial topoisomerase (TP) II, also known as DNA gyrase, and TP-IV, thus preventing bacterial DNA synthesis.^{89,173,174} Staphylococcal resistance to fluoroquinolones may be mediated by chromosomal mutations in the genes encoding DNA gyrase and TP-IV. Both of these enzymes contain 2 subunits: DNA gyrase is made up of GyrA and GyrB (encoded by the *gyrA* and *gyrB* genes, respectively) and TP-IV is made up of GrlA and GrlB (encoded by the *grlA* and *grlB* genes, respectively). In *S aureus*, mutations encoding for amino acid substitutions in GyrA and GrlA, and subsequent fluoroquinolone resistance, occur most often in the well-conserved quinolone resistance determining regions of the *gyrA* and *grlA* genes.^{89,147} Mutations in genes encoding for DNA gyrase and topoisomerase IV have been demonstrated in veterinary isolates of fluoroquinolone-resistant MRSA, MRSP, and MRSS.^{29,38,89,147} Other potential mechanisms of staphylococcal fluoroquinolone resistance include drug efflux pumps and reduced intracellular accumulation caused by altered membrane diffusion channels.^{147,175} One study demonstrated that fluoroquinolone resistance may be induced in vitro by subinhibitory drug concentrations, although the molecular mechanism was not investigated.¹⁷⁵

IMPLICATIONS OF STAPHYLOCOCCAL ANTIMICROBIAL RESISTANCE

The increase in methicillin resistance in veterinary staphylococcal isolates presents significant challenges in clinical management of infections, particularly staphylococcal pyoderma, by limiting therapeutic options. Many methicillin-resistant isolates are also multidrug resistant, making successful empiric therapy difficult. The remainder of the article will discuss the changing face of clinical practice in the age of antimicrobial resistance, including indications for culture and susceptibility testing, rational empiric therapy for staphylococcal pyoderma, and potential treatment options for resistant staphylococcal infections.

Indications for Culture and Susceptibility Testing

The importance of bacterial culture and susceptibility testing is often overlooked in the management of staphylococcal pyoderma. Given the increasing prevalence of

methicillin resistance, as well as the unpredictable antimicrobial susceptibility of MRSP, MRSA, and MRSS isolates, culture and susceptibility testing are likely indicated much more than are routinely performed by practitioners. Indications for culture and susceptibility testing include:

- Infections that have failed to respond to appropriate empiric therapy¹⁷⁶
- Clinical lesions (nodules, hemorrhagic bullae, draining tracts, furuncles) consistent with deep pyoderma
- Cytologic evidence of mixed infection (such as intracellular rods and cocci)¹⁷⁶
- Recurrent or relapsing pyoderma^{42,95}
- Recent antimicrobial administration, which may predispose to colonization, and subsequent infection, by methicillin-resistant strains^{42,43,78,139}
- Prior methicillin-resistant staphylococcal infection, because colonization, particularly with MRSP, may persist for extended periods of time¹⁷⁷

Rational Empiric Therapy

Despite the increasing importance of culture and susceptibility testing in management of staphylococcal pyoderma, empiric therapy may be appropriate in selected cases, particularly first-time or treatment-naïve infections. β -Lactam derivatives, especially cephalosporins, are frequently considered to be first-line choices in the treatment of pyoderma because of their good tissue penetration, low risk of adverse effects, and bactericidal activity against methicillin-susceptible staphylococci.¹⁷⁸ Concerns about selection for colonization by methicillin-resistant strains may support the empiric choice of other antimicrobials, such as macrolides, lincosamides, or potentiated sulfonamides, instead of cephalosporins or potentiated penicillins, for treatment-naïve infections.¹³⁹ In the study by Beck and colleagues,⁴³ however, administration of clindamycin was associated with subsequent MRSP isolation from dogs with pyoderma. With recognition of the role of systemic antimicrobial therapy in the acquisition of methicillin-resistant strains, there may be a paradigm shift to increased reliance on topical antimicrobial therapy in the treatment of canine pyoderma, especially first-time, mild, or localized infections.⁴³

Systemic fluoroquinolone therapy may be indicated in selected instances, such as treatment of mixed infections according to culture and susceptibility results,¹⁷⁶ but their empiric use for canine pyoderma is not recommended. As discussed previously, many methicillin-resistant staphylococcal isolates exhibit coresistance to fluoroquinolones, often leading to therapeutic failure with empiric administration. Fluoroquinolone exposure is also a potential risk factor for MRSA isolation in humans¹⁷⁹ and in dogs,⁷⁸ possibly by increasing susceptibility to colonization by highly fluoroquinolones-resistant strains,¹⁷⁹ as well as by promoting adhesion of MRSA to host cells.¹⁸⁰

Treatment of Methicillin-Resistant Staphylococcal Infections

Potential antimicrobial options for methicillin-resistant staphylococcal pyoderma, as based on susceptibility test results, are listed in **Table 1**. Treatment duration, as for methicillin-susceptible staphylococcal pyoderma, should be a minimum of 3 to 4 weeks, with 1 week past clinical resolution, for superficial infections; and a minimum of 6 to 8 weeks, with 2 weeks past clinical resolution, for deep infections.¹⁷⁶ Clinical resolution of MRSP-associated pyoderma may take longer than clinical resolution of MSSP-associated pyoderma.⁴¹ This may be a result of infection chronicity and secondary pathologic changes to the skin, instead of an indication that methicillin resistant strains are more virulent than methicillin-susceptible strains.^{41,80}

Drug (Brand Name)	Dose, mg/kg	Dosing Interval	Typical Route
Erythromycin	10–15	q8 h	PO
Lincomycin (Lincocin)	22	q12 h	PO
Clindamycin (Antirobe)	10	q12 h	PO
	11	q24 h	
Trimethoprim-sulfa (Tribrissen, Bactrim, Septra)	15–30	q12 h	PO
Ormetoprim-sulfadimethoxine (Primor)	55 (d 1) 27.5 (subsequent d)	q24 h	PO
Doxycycline (Vibramycin)	5–12	q12 h	PO
Minocycline (Minocin)	5–12	q12 h	PO
Enrofloxacin (Baytril)	5–20	q24 h	PO
Marbofloxacin (Zeniquin)	2.75–5.5	q24 h	PO
Chloramphenicol (Viceton)	50	q8 h	PO
Rifampin (Rifadin, Rimactane)	5–10	q12–24 h	PO
Amikacin (Amiglyde-V)	15–20	q24 h	IV, SC

Antimicrobial options for treatment of pyoderma associated with multidrug-resistant staphylococci are often severely limited. Chloramphenicol, rifampin, and aminoglycosides, particularly amikacin, may be the only remaining effective systemic antimicrobial agents indicated by susceptibility tests.^{3,12–14} Despite good in vitro susceptibility,¹² use of antimicrobial agents that are more common for serious MRSA infections in humans, such as linezolid and vancomycin,¹⁸¹ should be avoided in veterinary patients because of ethical concerns.^{34,39} These drugs are also often prohibitively expensive in veterinary patients.¹⁸²

When prescribing chloramphenicol, rifampin, or amikacin, practitioners should be aware of potential adverse effects in treated patients. Chloramphenicol has the potential for dose-dependent bone marrow suppression, with cats more susceptible to this effect than dogs.¹⁸³ In humans, chloramphenicol may rarely cause idiosyncratic and irreversible pancytopenia^{182,183}; clients should be warned to take precautions when handling this medication. The most common side effects of chloramphenicol administration in dogs seem to be gastrointestinal upset, inappetence, and weight loss; these adverse effects may be severe enough to warrant drug discontinuation.⁴¹ Chloramphenicol may also interact with other drugs via inhibition of hepatic cytochrome P450 microenzymes.^{182,183} This effect must be kept in mind when prescribing chloramphenicol in combination with other cytochrome P450 substrates, particularly anticonvulsants.¹⁸³

Rifampin is most often administered in combination with other antimicrobials for treatment of mycobacterial and rhodococcal infections,^{182,183} although it also exhibits antistaphylococcal activity.^{184,185} Resistance to rifampin is rare, even among methicillin-resistant strains.³⁴ Resistance may arise quickly, however, when rifampin is used as a monotherapy by mutations within the rifampin resistance-determining region of the staphylococcal *rpoB* gene.¹⁸⁶ Adverse effects of rifampin include hepatic enzyme induction and increase in hepatic enzyme activity, particularly alkaline phosphatase.¹⁸⁷ In some dogs, serious, and potentially fatal, hepatotoxicity may occur, with corresponding increases in hepatic enzyme activity indicting hepatocellular damage and hyperbilirubinemia.^{183,187} Other potential effects include gastrointestinal

upset, hemolytic anemia, thrombocytopenia, and orange discoloration of bodily fluids.^{182,183,187} To decrease the risk of adverse effects, it is recommended not to exceed a total daily dose of 10 mg/kg in dogs.¹⁸⁷ Rifampin is also a potent inducer of hepatic cytochrome P450 microenzymes and may, thus, reduce serum levels and activity of other cytochrome P450 substrates.^{182,183}

Like other aminoglycosides, amikacin must be administered parenterally.¹⁸³ When used for treatment of pyoderma, it may be administered subcutaneously by the client at home. The primary adverse effect of concern is nephrotoxicity, specifically renal proximal tubular necrosis.^{182,183} Amikacin may be less nephrotoxic than other aminoglycosides, particularly gentamicin.¹⁸³ Urinalyses should be frequently monitored for signs of nephrotoxicity; decreased specific gravity, casts, proteinuria, or glucosuria should precede azotemia.¹⁸³ When using amikacin, the author advises twice-weekly urinalyses. At the first sign of nephrotoxicity, amikacin administration should be discontinued; renal toxicity is generally reversible with early drug withdrawal.¹⁸⁸ Aminoglycosides also have the potential to cause ototoxicity via induction of inner ear hair cell apoptosis and may result in permanent deafness.¹⁸⁹

With the increase in staphylococcal multidrug resistance, limited options for systemic therapy, and potential for adverse drug effects, interest in the role of topical antimicrobial therapy for resistant staphylococcal infections has increased. Topical therapy alone has been found to be effective for treatment of pyoderma associated with methicillin-resistant staphylococci.^{14,41,190} Readers are referred to the article by Jeffers elsewhere in this issue for further exploration of topical therapy for drug-resistant pyoderma.

Infection Prevention and Decolonization

Standardized guidelines for preventing the spread of methicillin-resistant staphylococci have not been established in veterinary medicine. Strict hygiene practices seem to be of the utmost importance in limiting transmission of methicillin-resistant staphylococci from pets to pets, from pets to humans (or from infected humans to pets), and from pets to the environment. Recommended hygiene practices include regular handwashing, particularly after handling infected patients and between patients; covering open or draining wounds; preventing pets from licking human caretakers; restricting infected pets from sleeping in the bed with human caretakers (or vice versa); frequent environmental disinfection, washing of pet bedding, and cleaning of pet dishes; and barrier precautions within veterinary hospitals when working with infected patients (disposable gloves, etc).^{37,39,50,96,112,191,192}

Several case reports in the medical literature have discussed decolonization of pets by use of topical or systemic antimicrobials as a strategy for management of MRSA transmission in households.^{101,104,107,109} Fusidic acid application has also been reported to reduce *S pseudintermedius* colonization of mucosal sites in dogs.¹⁹³ Neither the efficacy nor the optimal types of decolonization strategies for methicillin resistant staphylococci have been well established in veterinary patients. Moreover, staphylococcal colonization seems to be widespread over the skin and mucosal sites,²⁴ making targeted decolonization difficult to impossible.

SUMMARY

In conclusion, methicillin- and multi-drug resistant staphylococci are increasingly isolated from veterinary patients, particularly from dogs with pyoderma and otitis. Practitioners should be aware of the most common mechanisms of staphylococcal antimicrobial resistance and the implications for successful clinical management of

resistant infections. Judicious antimicrobial usage, including basing treatment decisions on culture and susceptibility data when appropriate, should be encouraged.

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