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The increasing prevalence of staphylococcal antimicrobial resistance, particularly methicillin resistance, presents a challenge to veterinary practitioners treating clinical infections. Failure to recognize staphylococcal antimicrobial resistance frequently results in ineffective empiric therapeutic choices and protracted clinical disease. In addition, concern is developing regarding potential transmission of antimicrobial-resistant strains from humans to animals and vice versa.

METHICILLIN RESISTANCE
Methicillin-resistant staphylococci possess 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 low-affinity, penicillin-binding protein renders resistance to virtually all beta-lactam derivatives, including:
- Carbapenems (eg, imipenem, meropenem)
- Cephalosporins (eg, cephalexin, cefpodoxime, cefovecin)
- Penicillins (eg, penicillin, amoxicillin)
- Potentiated penicillins (eg, amoxicillin and clavulanic acid).

Although references to methicillin resistance are commonplace in the medical literature, oxacillin is often used by veterinary microbiology laboratories to screen for methicillin resistance in Staphylococcus aureus isolates, but may not reliably detect methicillin resistance in S pseudintermedius.

More recently, a mecA homologue—mecC—has been identified in some European staphylococcal isolates from humans and animals that exhibit methicillin resistance but lack the mecA gene. The prevalence of this gene in staphylococci is currently unknown.

METHICILLIN-RESISTANT STAPHYLOCOCCAL INFECTIONS
Recent Developments  Christine L. Cain, DVM, Diplomate ACVD

MULTIDRUG RESISTANCE
Although methicillin-resistant staphylococci are not necessarily more virulent than methicillin-susceptible staphylococci, treatment options are often severely limited by multidrug resistance. This is particularly true for infections caused by methicillin-resistant S pseudintermedius (MRSP); MRSP isolates are increasingly multidrug resistant.

Resistance to non–beta-lactam antimicrobials is common and conveyed by genetic mechanisms other than the mecA gene; these antimicrobials include:
- Fluoroquinolones
- Lincosamides
- Macrolides
- Potentiated sulfonamides
- Tetracyclines.

Due to the prevalence of multidrug resistance in methicillin-resistant strains, empirical switching of antimicrobial classes when treating staphylococcal infections that fail to respond to first-line antimicrobials (particularly beta-lactams) is NOT recommended. Treatment choices should be based on culture and susceptibility testing.
METHICILLIN-RESISTANT STAPHYLOCOCCAL INFECTIONS

Staphylococcus pseudintermedius

*S. pseudintermedius* colonizes the skin and mucosa of healthy dogs and is the most common cause of canine pyoderma.12 MRSP has been recognized as a cause of pyoderma, surgical site infections (particularly following orthopedic procedures), and urinary tract infections, among others.9,13

**Classification**

Investigators have recently used molecular techniques to classify 3 closely related staphylococcal species—*S. intermedius*, *S. pseudintermedius*, and *S. delphini*—as the *S. intermedius* group. It appears correct to assume that all previously classified *S. intermedius* isolates from dogs, cats, and humans were actually *S. pseudintermedius* isolates.12-15

**Prevalence**

The prevalence of MRSP infections in veterinary patients has increased substantially over the past decade. Although reported sporadically in the 1990s,16,17 MRSP infections are now commonly reported in the veterinary literature and increasingly isolated by veterinary microbiology laboratories.

**Colonization**

MRSP has also been isolated from carriage sites (skin and mucous membranes, including nares, oral mucosa, and rectal mucosa) of healthy dogs and cats.17,18 Several studies support a carriage rate of:

- 1.5% to 3% in healthy dogs19-21
- 0% to 4% in healthy cats.18,22

Overall, the literature suggests that MRSP isolation rates from clinical specimens may significantly exceed the prevalence of MRSP colonization in healthy animals, although prevalence may vary by sampled population and geographic area.

Staphylococcus schleiferi

*S. schleiferi* is an emerging cause of infections in veterinary patients.

**Classification**

Two variants have been described based on coagulase production:

- *S. schleiferi* subspecies *schleiferi* (coagulase negative)
- *S. schleiferi* subspecies *coagulans* (coagulase positive).

Recent studies suggest the 2 subspecies are not distinct by genotype or clinical behavior; therefore, both should be considered important pathogens.23,24 Coagulase-positive and coagulase-negative *S. schleiferi* are associated with pyoderma (especially recurrent pyoderma) and otitis in dogs with allergic dermatitis, although infections of other body sites in nonallergic dogs have also been reported.24

**Prevalence**

Methicillin resistance is particularly prevalent in clinical isolates of *S. schleiferi*, with reported rates often exceeding 50%.1,12-20 Fluoroquinolone resistance is also common in methicillin-resistant *S. schleiferi* (MRSS) isolates.9,23,24,27,29

MRSS has been isolated from:

- Dogs and cats with inflammatory skin disease18-20,30-32
- Carriage sites (skin or mucosal) of healthy dogs and cats.

Staphylococcus aureus

**Human Prevalence**

*S. aureus* colonizes approximately 30% of the human population worldwide and is a major cause of skin and soft tissue infections in humans.53 The number of human infections caused by methicillin-resistant *S. aureus* (MRSA) has increased dramatically since the 1960s.53 While human MRSA infections were once primarily nosocomial, community-associated MRSA infections of healthy individuals are being diagnosed more frequently.54,55

**Veterinary Prevalence**

MRSA infections have also been reported in a variety of companion and exotic animal species.9,46-41

- In dogs, prevalence of *S. aureus* colonization appears to be substantially lower than that of *S. pseudintermedius*.42
- In addition, *S. aureus* infections are far less common than *S. pseudintermedius* infections.9
- In cats, reports conflict as to whether *S. pseudintermedius* or *S. aureus* is the primary colonizing coagulase-positive staphylococcal species.15,46
- Healthy dogs and cats may be colonized by MRSA, although this colonization is likely transient.45,46

As is the case with MRSP, MRSA isolates are often resistant to non–beta-lactam antibiotics, especially:

- Fluoroquinolones
- Lincosamides
- Macrolides.

**Zoonotic Potential**

MRSA infections in companion and exotic animals are often associated with human hospital- or community-acquired clonal strains, suggesting, but not proving, human-to-animal transmission.38,39,49 Although the possibility of MRSA transmission from colonized or infected humans to animals, or vice versa, has frequently been suggested, the true direction of transmission is difficult to prove.30,49,50 While human-to-animal transmission is usually assumed, the infected or colonized human in the household may not be identified as the MRSA source for the pet.48

Coagulase-Negative Staphylococci

The clinical importance of coagulase-negative staphylococci (CoNS), other than the coagulase-negative variant of *S. schleiferi*, has not been well elucidated in veterinary patients. Historically, CoNS were considered commensal organisms or contaminants with limited pathogenic potential; however, they are becoming more frequently associated with nosocomial infections in humans.

CoNS are frequently methicillin resistant and may produce a number of virulence factors.57,58 When CoNS are isolated from clinical specimens, practitioners are encouraged to interpret results in light of culture technique: CoNS isolated from culture samples of closed sites, such as intact pustules or joints, are more likely to be true pathogens than those obtained by swabbing the skin’s surface.
RISK FACTORS
Recent antimicrobial exposure appears to be the most critical risk factor for acquisition of methicillin-resistant staphylococci.13
• In a recent prospective study, Beck and colleagues demonstrated that, following antimicrobial therapy, isolation of MRSP from the skin and mucosal sites of dogs with pyoderma caused by methicillin-susceptible S pseudintermedius (MSSP) is common.31
• Similarly, in a large retrospective study, recent administration of beta-lactam antimicrobials was found to be a risk factor for dogs with MRSS clinical isolates.24
• Recent administration of beta-lactams or fluoroquinolones is a risk factor for MRSA infection in dogs and cats.37,53
Additional risk factors for MRSA infection include: 37,53
• Contact with ill or hospitalized human
• Intravenous catheterization
• Multiple antimicrobial courses
• Prolonged hospitalization
• Surgical implants.

It is likely that alteration of commensal staphylococcal flora by systemic antimicrobial treatment, particularly beta-lactam antibiotics, allows for subsequent colonization by methicillin-resistant strains. With the increasing prevalence of antimicrobial resistant strains, practitioners are encouraged to consider the potential for infection associated with methicillin-resistant staphylococci even in the absence of risk factors, such as recent antimicrobial administration or hospitalization.

CULTURE & SUSCEPTIBILITY
Given the increasing prevalence of methicillin- and multidrug-resistant staphylococci, culture and susceptibility testing (Figure 1) is likely an underutilized tool, particularly in the management of pyoderma, urinary tract infections, wounds, and surgical site infections.

Clinical indications for performing culture and susceptibility testing include:
• Clinical lesions consistent with deep pyoderma, such as furuncles, nodules, and draining tracts
• Any surgical site infection, particularly those associated with orthopedic procedures15,54
• Presence of a nonhealing wound
• Cytologic evidence of mixed or nonstaphylococcal infection (eg, intracellular bacterial rods)
• History of prior antimicrobial-resistant staphylococcal infection
• History of recent antimicrobial-resistant staphylococcal infection
• Lack of response to appropriate empiric antimicrobial therapy
• Recurrent or relapsing infection.

EMPIRIC THERAPY
Despite the importance of culture and susceptibility testing in management of staphylococcal infections, empiric antimicrobial therapy remains common practice for first-time infections or treatment-naïve patients, especially patients with pyoderma.
• Beta-lactam derivatives, especially cephalosporins, are frequently considered first-line choices in treatment of pyoderma due to their bactericidal activity, tissue penetration, and low incidence of adverse effects.55
• Preferential selection of other antimicrobials, such as macrolides, lincomycins, or potentiated sulfonamides, as first-line therapies for staphylococcal infections has been suggested due to concerns regarding potential colonization with methicillin-resistant strains due to beta-lactam antimicrobial

INDUCIBLE RESISTANCE & CLINDAMYCIN
Figure 2. Double disk diffusion test (b-test) for detection of inducible clindamycin resistance; note the D-shaped zone around the clindamycin disk (CC) due to its close proximity to the erythromycin disc (E)

• Inducible resistance, in which the presence of an inducing agent, such as erythromycin, promotes expression of a resistant phenotype, has been reported in MRSA isolates from humans and animals and some MRSP isolates.56,57
• Clindamycin use in infections caused by isolates exhibiting inducible resistance may result in treatment failure.56,57
• Microbiology laboratories can test for inducible clindamycin resistance using a double disk diffusion test (b-test) with adjacent erythromycin and clindamycin disks (Figure 2).
• In the absence of this test, clinicians may predict inducible resistance based on susceptibility results, indicating erythromycin resistance and clindamycin susceptibility.56

Figure 1. Collection of a sample for culture and susceptibility testing using a culturette swab; taken from a dog with superficial pyoderma
Due to frequent resistance in methicillin-resistant strains, especially MRSP, practitioners should be aware for the potential of empiric failure with these antimicrobials; changes in therapy should be based on culture and susceptibility results.

Use of systemic fluoroquinolones for treatment of staphylococcal infections should be reserved for cases in which:
» In vitro susceptibility is demonstrated
» A fluoroquinolone is considered the most appropriate antimicrobial choice for the patient.
Empiric use of fluoroquinolones is NOT recommended due to the potential for therapeutic failure if the infection is caused by methicillin-resistant strains, which frequently exhibit co-resistance to fluoroquinolones.

Due to the connection between systemic antimicrobial therapy and acquisition of methicillin-resistant strains, topical antimicrobial or antiseptic therapy for the treatment of canine pyoderma, especially for first-time, mild, or localized infections, is recommended.

**RESISTANT INFECTION THERAPY**

Table 1 lists antimicrobial options and dosing regimens for methicillin-resistant staphylococcal pyoderma, based on culture and susceptibility.

**Treatment Duration**

Recommended treatment duration for methicillin-resistant staphylococcal infections does not necessarily exceed that recommended for methicillin-susceptible infections, which is the case, for example, for methicillin-susceptible staphylococcal pyoderma:
- Superficial infections should be treated for a minimum of 3 to 4 weeks; then 1 week past clinical resolution
- Deep infections should be treated for a minimum of 6 to 8 weeks; then 2 weeks past clinical resolution.

Clinical resolution of MRSP-associated pyoderma may take longer than resolution of MSSP-associated pyoderma, but this is more likely due to empiric treatment failure, infection chronicity, or secondary pathologic changes to the skin rather than increased virulence of methicillin-resistant strains.

**Systemic Therapy**

Systemic antimicrobial options for treatment of methicillin- and multidrug-resistant staphylococcal infections are often limited to:
- Aminoglycosides, particularly amikacin
- Chloramphenicol
- Rifampin.

When prescribed for extended therapy, potential adverse effects of these medications must be considered (see Table 2).

**Table 1. Systemic Antimicrobial Therapy for Dogs and Cats: Methicillin-Resistant Staphylococcal Infection**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE / ROUTE / INTERVAL</th>
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<tr>
<td>Amikacin</td>
<td>15–20 mg/kg IV or SC Q 24 H</td>
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<tr>
<td>Chloramphenicol</td>
<td>50 mg/kg PO Q 8 H (dogs) 50–100 mg (total) PO Q 12 H (cats)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>10 mg/kg PO Q 12 H 11 mg/kg PO Q 24 H</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>5–12 mg/kg PO Q 12 H</td>
</tr>
<tr>
<td>Enrofloxacin</td>
<td>5–20 mg/kg PO Q 24 H (dogs) 5 mg/kg (maximum dose) PO Q 24 H (cats)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>10–15 mg/kg PO Q 8 H</td>
</tr>
<tr>
<td>Lincomycin</td>
<td>22 mg/kg PO Q 12 H</td>
</tr>
<tr>
<td>Marbofloxacin</td>
<td>2.75–5.5 mg/kg PO Q 24 H</td>
</tr>
<tr>
<td>Minocycline</td>
<td>5–12 mg/kg PO Q 12 H</td>
</tr>
<tr>
<td>Ormetoprim- sulfuradimethoxine</td>
<td>Day 1: 55 mg/kg PO Following days: 27.5 mg/kg PO Q 24 H</td>
</tr>
<tr>
<td>Rifampin§</td>
<td>5–10 mg/kg PO Q 12–24 H</td>
</tr>
<tr>
<td>Trimethoprim- sulfamethoxazole</td>
<td>15–30 mg/kg PO Q 12 H</td>
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**Table 2. Potential Adverse Effects of Systemic Antimicrobial Therapy**

<table>
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<tr>
<th>ANTIMICROBIAL</th>
<th>POTENTIAL ADVERSE EFFECTS</th>
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<tr>
<td>Amikacin</td>
<td>• Nephrotoxicity due to proximal tubular necrosis&lt;br&gt;• Ototoxicity</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>• Irreversible pancytopenia (humans)&lt;br&gt;• Dose-dependent bone marrow suppression (dogs and cats)&lt;br&gt;• Gastrointestinal upset, inappetence, weight loss&lt;br&gt;• Drug interactions via inhibition of hepatic cytochrome P450 microenzymes</td>
</tr>
<tr>
<td>Rifampin</td>
<td>• Rapid resistance development when used alone&lt;br&gt;• Severe, potentially fatal hepatotoxicity&lt;br&gt;• Gastrointestinal upset&lt;br&gt;• Hemolytic anemia, thrombocytopenia&lt;br&gt;• Orange discoloration of body fluids&lt;br&gt;• Drug interactions via inhibition of hepatic cytochrome P450 microenzymes</td>
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</table>
Despite good in vitro susceptibility, administration of antimicrobials used in humans for serious MRSA infections, such as linezolid and vancomycin, should be avoided in veterinary patients due to ethical concerns (these drugs are reserved for use in humans with MRSA infections); cost of these medications is also prohibitive.

Topical Therapy

Topical antimicrobial therapy for resistant staphylococcal infections has increased due to:
- Limited options for systemic therapy
- Potential for adverse drug effects
- Rise of multidrug resistance.

Topical therapy alone has been found to be effective for treatment of pyoderma associated with methicillin-resistant staphylococci (Figures 3 and 4). Therapeutic options for sole or adjunctive therapy include:
- Hypochlorous acid and sodium hypochlorite based products (including dilute bleach baths)
- Mupirocin (2%) ointment
- Shampoos, conditioners, sprays, and wipes containing chlorhexidine (2%–4%), benzoyl peroxide, or ethyl lactate
- Wipes containing nisin, an antimicrobial protein.

INFECTION PREVENTION

Strict hygiene practices are critical to limit transmission of methicillin-resistant staphylococci. Prudent hygiene practices include:
- Barrier precautions, such as disposable gloves, when working with infected patients
- Covering open or draining wounds
- Frequent cleaning of dishes, washing of bedding, and environmental disinfection
- Regular hand washing, especially after handling infected patients and between patients
- Restricting infected pets from sleeping in bed with humans (or vice versa) and preventing pets from licking humans.

To learn more about preventing spread of infection, read Practical Strategies for Preventing Nosocomial Infections (March/April 2013 issue of Today’s Veterinary Practice), available at todaysveterinarypractice.com.
IN SUMMARY
Methicillin- and multidrug-resistant staphylococcal infections are becoming increasingly common in veterinary patients.
- **Empiric antimicrobial selection** is difficult and treatment failure is common.
- **Culture and susceptibility testing** is indicated for management of staphylococcal infections, particularly canine pyoderma and surgical site infections.
- **Topical antimicrobial therapy** may be useful for infection treatment and prevention in cases of limited systemic antimicrobial options or adverse drug effects.
- **Strict hygiene practices** should be observed to limit bacterial transmission.

CoNS = coagulase-negative staphylococci; MRSA = methicillin-resistant *Staphylococcus aureus*; MRSP = methicillin-resistant *Staphylococcus pseudointermedius*; MRSS = methicillin-resistant *Staphylococcus schleiferi*; MSSP = methicillin-susceptible *Staphylococcus pseudointermedius*

References
METHICILLIN-RESISTANT STAPHYLOCOCCAL INFECTIONS


