Infection with methicillin-resistant 
Staphylococcus pseudintermedius masquerading as cefoxitin susceptible in a dog

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Case Description—A 2-year-old dog was evaluated because of complications that developed following tibial plateau leveling osteotomy. Infection of the surgical site developed following removal of the failed implant.

Clinical Findings—The dog was lame with evidence of a deep surgical site infection, and Staphylococcus pseudintermedius was isolated from the surgical site. Results of in vitro testing indicated that the isolate was resistant to multiple antimicrobials but susceptible to cefoxitin. Subsequent testing confirmed that the isolate was methicillin-resistant S pseudintermedius and was in fact resistant to cefoxitin.

Treatment and Outcome—On the basis of results of follow-up testing, doxycycline was administered before and after surgery to remove the surgical implant. The dog recovered without further complications.

Clinical Relevance—Findings suggested that certain strains of methicillin-resistant S pseudintermedius, which appears to be an emerging pathogen in dogs, may be falsely identified as methicillin susceptible on the basis of results of testing for cefoxitin susceptibility because cefoxitin may not induce the meca gene as reliably in S pseudintermedius as it does in Staphylococcus aureus. Isolates of S pseudintermedius should be considered to likely be methicillin resistant when multidrug resistance is identified, even if susceptibility to some β-lactam antimicrobials is reported. (J Am Vet Med Assoc 2009;235:1064–1066)

A 2-year-old castrated male Labrador Retriever was examined at the Ontario Veterinary Teaching Hospital because of complications that developed following tibial plateau leveling osteotomy surgery that had been performed on the left hind limb at another veterinary hospital 4 weeks earlier. The dog developed acute left hind limb lameness, tibial thrust, a cranial drawer sign, and effusion of the left stifle joint following the tibial plateau leveling osteotomy.

At the time of initial examination at the veterinary teaching hospital, radiography of the left hind limb revealed a fracture of the left fibula, a broken screw, and collapse of the osteotomy site. The bone plate and screws were removed, and a locking plate was inserted, along with a cancellous bone allograft. A single dose of cefazolin (20 mg/kg [9.1 mg/lb], IV) was administered immediately prior to surgery. Two screws could not be removed because the screwheads had fractured off, and the shafts of these 2 screws were left in the proximal aspect of the tibia. There was no clinical evidence of infection of the surgical site, and antimicrobial treatment was not prescribed.

The dog initially recovered well; however, lameness and a serous discharge from the incision site were identified by the referring veterinarian during scheduled reexaminations 2 and 4 weeks after surgery. On both occasions, bacterial culture of the discharge did not yield any growth. Empirical treatment with cephalixin was prescribed by the referring veterinarian at the time of the 4-week postoperative evaluation, but there was no change after 10 days of treatment, and administration was discontinued. Eight days later, treatment with cephalixin was reinstated for an additional 10 days because of ongoing discharge from the site. Again, however, there was little clinical change, and treatment was discontinued. Five days after treatment with cephalixin was discontinued, empirical treatment with amoxicillin-clavulanic acid for 21 days was prescribed. Mild clinical improvement was reported after treatment with amoxicillin-clavulanic acid was begun.

The dog was returned to the Ontario Veterinary College for reexamination 5 weeks after all antimicrobial treatment had been discontinued. Physical examination revealed a seropurulent discharge from an open wound along the incision site and joint effusion. A deep aspirate of the surgical site near the locking plate was obtained by aseptically inserting a needle through normal-appearing skin approximately 4 cm distal to the draining tract and was submitted for bacterial culture and antimicrobial susceptibility testing. A pure, heavy growth of Staphylococcus pseudintermedius was identi-
fied. Antimicrobial susceptibility testing was performed by means of the Kirby-Bauer disk diffusion method in accordance with standard guidelines. The isolate was reportedly resistant to ampicillin, amoxicillin-clavulanic acid, cephalexin, clindamycin, enrofloxacin, gentamicin, orbifloxacin, imipenem, and trimethoprim-sulfonamides but susceptible to cefoxitin and tetracycline. Infection control personnel were immediately informed by the diagnostic laboratory that a multidrug-resistant organism with an atypical antimicrobial susceptibility pattern (ie, susceptibility to cefoxitin despite resistance to all other tested β-lactam antimicrobials) had been isolated, and further testing of the isolate was advocated to determine whether results of cefoxitin susceptibility testing were erroneous and the organism was MRSP.

Subsequent testing confirmed that the isolate was MRSP and resistant to cefoxitin. On the basis of these additional testing results, treatment with doxycycline (400 mg, PO, q 12 h) was begun, and 3 days later, the locking plate was surgically removed. The dog recovered from surgery without complications and was discharged the following day with instructions to the owner to continue treatment with doxycycline for 14 days. The bandage was changed and the dog was re-evaluated 4, 6, 8, 13, and 16 days after surgery. The dog progressed well after surgery, with no signs of lameness. Sutures were removed on day 16. No further effusion or drainage was noted.

**Discussion**

Infection with methicillin-resistant staphylococci, including MRSP, appears to be an increasing problem in veterinary medicine. Traditionally, *Staphylococcus intermedius* sp in dogs and cats, however, has demonstrated that isolates from dogs previously identified by means of standard techniques as *S. intermedius* were usually, if not always, the closely related *S. pseudintermedius* and has suggested that *S. intermedius* infections are most likely rare or nonexistent in dogs. In the dog described in the present report, the isolate was confirmed to be *S. pseudintermedius* on the basis of results of sequencing of the *sodA* gene.

Methicillin resistance in staphylococci is mediated by the *mecA* gene, which encodes production of an altered penicillin-binding protein, PBP2a, and confers resistance to all β-lactam antimicrobials, including penicillins, cephalosporins, and carbapenems. The isolate obtained from the dog described in the present report was confirmed to be MRSP on the basis of a PCR assay that revealed the presence of the *mecA* gene and a latex agglutination test that confirmed the presence of PBP2a.

Infection with multidrug-resistant bacteria such as MRSP is complicated by the limited treatment options and the fact that the disease is often quite advanced at the time of diagnosis because of resistance to agents used for empirical treatment. Proper management requires prompt identification of the causative organism as methicillin resistant and commencement of appropriate antimicrobial treatment. However, identification of methicillin resistance can sometimes be complicated, as demonstrated in the case described in the present report. Importantly, not all methicillin-resistant staphylococci constitutively express the *mecA* gene, and different antimicrobials have different effects on *mecA* expression in vitro, which may alter results of in vitro susceptibility testing. The reason why different antimicrobials have different effects on *mecA* expression is unclear, but this phenomenon needs to be considered when developing testing methods and interpreting results. Oxacillin has been most commonly used to detect methicillin resistance in staphylococci, as it is more stable in vitro than methicillin. However, oxacillin may fail to adequately induce *mecA* expression during in vitro testing of some isolates, with the result that isolates are falsely reported as being susceptible to oxacillin and, by extension, methicillin. This has been identified as a problem during in vitro testing of MRSA in humans, and as a result, cefoxitin, rather than oxacillin, is increasingly being used for identification of MRSA because it is considered an excellent inducer of *mecA* expression.

Oxacillin susceptibility testing was not initially performed on the isolate obtained from the dog described in the present report because the diagnostic laboratory had previously switched to cefoxitin susceptibility testing on the basis of guidelines designed to detect MRSA. However, findings for this isolate suggested that although replacing oxacillin susceptibility testing with cefoxitin susceptibility testing was optimal for identifying MRSA, it may not be for identifying MRSP. Bemis et al have reported that, contrary to the situation with MRSA, oxacillin susceptibility testing is a sensitive indicator of methicillin resistance in *S. intermedius*, whereas cefoxitin susceptibility testing is a poor indicator. Following identification of this case, 17 MRSP isolates from the investigators’ collection that were confirmed to be methicillin resistant on the basis of detection of the *mecA* gene were tested in vitro oxacillin and cefoxitin susceptibility by means of a disk diffusion method. Fourteen of the 17 isolates were resistant to oxacillin in vitro, but none of the isolates were resistant to cefoxitin in vitro. It appeared, therefore, that cefoxitin did not adequately induce *meca* expression and that reliance on cefoxitin susceptibility testing as an indicator of methicillin resistance in *S. pseudintermedius* may be inadequate.

Anecdotally, MRSP infection appears to have become common internationally, and prompt and accurate identification will be critical for case management. Veterinary clinicians and microbiologists must be aware of the potential for misidentification of MRSP if cefoxitin is used as the indicator of methicillin resistance. Failure to do so could result in inappropriate treatment with cephalosporins and a high likelihood of treatment failure. Testing all *S. pseudintermedius* isolates for *meca* expression and that reliance on cefoxitin susceptibility testing as an indicator of methicillin resistance in *S. pseudintermedius* may be inadequate.

The origin of the MRSP infection in the dog described in the present report, including when and
where the organisms were acquired, is unclear. The dog received multiple courses of β-lactam antimicrobials, to which MRSP is resistant, which could have facilitated development of multidrug resistance. However, the role of antimicrobials as a risk factor for MRSP infection has not been adequately evaluated. It is unclear whether the discharge noted early in the disease process was associated with MRSP or MRSP infection developed secondarily as a result of administration of antimicrobials to which the organism was resistant. It is possible that the initial negative bacterial culture results were correct and that the disease process was not infectious initially. Alternatively, given the deep nature of the infection and the relatively consistent clinical picture during the initial treatment period, it is also possible that MRSP was present early in the process and was never eliminated because of inadequate antimicrobial treatment.

The present case highlights a few important points, including potential difficulties identifying and treating methicillin-resistant staphylococcal infections and the usefulness of close communication between clinicians, infection control personnel, and diagnostic laboratory personnel. Diagnostic laboratories need to ensure that they are using standardized and validated protocols wherever possible. Researchers and laboratory standards organizations need to ensure that proper scrutiny is applied to current testing methods and that these methods be continually reassessed in the light of emergence of organisms such as MRSP. Additionally, clinicians need to have a basic understanding of laboratory practices that produce the results they see, realize that there are limitations to all tests, and ensure that they adequately scrutinize results. As multidrug-resistant bacteria become more common, it is important that veterinary clinicians understand the limitations of diagnostic testing and the potential challenges posed by these organisms. Communication between clinicians and diagnostic laboratories must increase to prevent improper treatment decisions. Further, veterinary-specific evaluation of laboratory protocols is required, as protocols designed for important human pathogens may not be optimal for related, but different, veterinary pathogens.


References