


Susceptibility of Incisional Site *Staphylococcus* spp. to Three Common Perioperative Antimicrobials in Dogs Undergoing Clean Orthopaedic Procedures

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Abstract

Objectives The aim of this study was to evaluate the susceptibility pattern of the incisional site *Staphylococcus* spp. to three commonly used perioperative antimicrobials in dogs.

Materials and Methods A cohort of client-owned dogs was included in this prospective observational study. After induction of general anaesthesia and hair clipping, culture samples were collected from the incisional site of healthy dogs before orthopaedic surgery. The isolated colonies were identified. The susceptibility pattern of staphylococcal isolates was determined using Clinical and Laboratory Standard Institute standards. The staphylococcal susceptibilities to amoxicillin/clavulanic acid and cefpodoxime were compared with cefazolin using two-sided equality of proportions test.

Results A total of 391 bacterial isolates were identified in 115 dogs. *Bacillus* spp. ($n = 200$) and *Staphylococcus* spp. ($n = 95$) were the most common bacteria isolated. Coagulase-positive and -negative staphylococci were isolated in 44 and 38% of dogs respectively. Cefazolin, amoxicillin/clavulanic acid and cefpodoxime staphylococcal susceptibilities were 68, 77 and 76% respectively. There were no significant differences in *Staphylococcus* spp. susceptibility between amoxicillin/clavulanic acid or cefpodoxime and cefazolin ($p = 0.19$, $p = 0.25$). Thirty-six per cent of coagulase-negative staphylococci and 6% of coagulase-positive staphylococci isolated were methicillin resistant.

Conclusion Cefazolin, amoxicillin/clavulanic acid and cefpodoxime had similar susceptibilities for staphylococcal isolates. Routine use of amoxicillin/clavulanic acid or cefpodoxime in place of cefazolin should be practiced with caution.

Keywords

- ▶ methicillin susceptibility
- ▶ *Staphylococcus*
- ▶ dogs
- ▶ perioperative antimicrobial therapy

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Introduction

Cefazolin (CFZ) is the most commonly used perioperative antibiotic medication in human and veterinary orthopaedic surgery. It has low toxicity, high bone and joint tissue concentrations, and its use is associated with decreased rates of surgical site infections (SSI) compared with dogs that receive no perioperative antimicrobials.^{1–3} Second- and third-generation cephalosporins or potentiated penicillin are also used as perioperative antimicrobials.^{4,5} They may have the advantage over CFZ because they tend to be effective against β -lactamase producing *Staphylococcus*,⁶ whose prevalence is increasing.^{7,8} However, information about their effectiveness as perioperative prophylactic antibiotic medications for orthopaedic procedures in dogs is lacking.

Susceptibility patterns of potential bacteria at the surgical site are one of the considerations for selecting perioperative antimicrobials.⁹ To the author's knowledge, studies conducted for commensal staphylococci susceptibility patterns have specifically investigated methicillin-resistant staphylococci colonization, characterized by the presence of *mec A* gene or oxacillin resistance interpreted by the culture and sensitivity report.^{7,8} The susceptibility pattern of incisional site skin flora in dogs has not been evaluated in the literature. The purpose of the study was to evaluate the susceptibility of cutaneous staphylococci to commonly used prophylactic antimicrobials isolated from planned incision sites in dogs undergoing clean orthopaedic procedures. The null hypothesis tested was that staphylococcal isolates retrieved from planned incision sites would have no difference in susceptibility to cefpodoxime (CPD) and amoxicillin/clavulanic acid (AMC) than to CFZ.

Materials and Methods

This was a prospective observational study of healthy client-owned dogs. Dogs over a year of age that underwent clean orthopaedic surgery between November 2015 and May 2016 were eligible for inclusion. Dogs were excluded if they had received systemic or topical treatments for dermatological condition, systemic antimicrobial treatments within 4 weeks of presentation, had undergone a surgical procedure within 4 weeks of presentation, had a confirmed diagnosis of endocrine diseases or had skin lesions discovered after clipping. Signed informed owner consent was obtained. The study protocol was approved by the institutional animal care and use committee (protocol no 18309). Once enrolled, data collected included breed, sex, age, weight, urgency of surgery, classified as elective (surgeries for naturally occurring orthopaedic disease) or urgent (surgeries for fractures or luxations following a traumatic event), and anatomic site.

Dogs were anaesthetized, and the planned surgical incision site was clipped using a sterile no 40 clipper blade (Oster, Boca Raton, Florida, United States). The person preparing the site and taking the sample wore sterile gloves. Excess hair was vacuumed from the site without skin contact. A culture sample of the planned incision site was collected using a sterile contact agar plate (RODAC plate, ThermoFisher

Scientific, Waltham, Massachusetts, United States) containing 5% sheep blood.¹⁰ The entire surface of the agar plate was applied to the skin for 5 seconds. The plate was incubated in 5% CO₂ at 35°C for 24 hours, and the bacterial organisms were subcultured to obtain pure bacterial isolates. The pure bacterial isolates were used for identification and determination of antimicrobial susceptibility. Isolate identification utilized a combination of colony morphology characteristics, haemolytic reaction, Gram stain results, spot catalase testing and coagulase testing. Further characterization of isolate identity was based on results from conventional biochemical testing (API, BioMérieux, Durham, North Carolina, United States) (tubed media, catalase reaction, identification strips) or matrix-assisted time-of-flight mass spectrometry (Bio-typer 3.0, Bruker, Fremont, California, United States). The susceptibilities of identified bacteria were determined using a broth microdilution technique (Sensititre Companion Animal Gram Positive COMPGP1G Vet AST plate, ThermoFisher Scientific, Waltham, Massachusetts, United States). Quality control testing was performed weekly using the following organisms: *Staphylococcus aureus* ATCC 29213; *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, and *E. coli* ATCC 35218. Susceptibility, intermediate susceptibility and resistance of staphylococcal isolates were determined using standards established by the Clinical Laboratories Standards Institute for Animals.¹¹ *Staphylococcus intermedius* and *Staphylococcus pseudintermedius* identified with matrix-assisted time-of-flight mass spectrometry were reported together as *Staphylococcus intermedius* group (SIG). No CPD breakpoint has been established for coagulase-negative (CoNS), so the breakpoint for *S. pseudintermedius* was used to help determine susceptibility. Oxacillin-resistant isolates were reported to be resistant to methicillin and all other β -lactam antimicrobials, regardless of individual β -lactam antimicrobial susceptibility testing result.¹¹

Isolates interpreted to have intermediate susceptibility were considered resistant for statistical analysis. Descriptive statistics were calculated for all measured variables and reported as number (per cent), median (interquartile range) or mean (standard deviation); a combined test of skewness and kurtosis was used to evaluate normal distribution of continuous variables. Population rates of staphylococci susceptible to CFZ, CPD and AMC were estimated with surrounding exact binomial 95% confidence intervals (CI). Two-sided equality of proportions test was used to test the null hypotheses that the rate of staphylococci susceptibility to CFZ did not differ significantly from the rate of susceptibility to CPD or from the rate of susceptibility to AMC. Antimicrobial susceptibilities of CFZ, CPD and AMC were compared across staphylococcal species using Fisher's exact tests. Logistic regression was performed to explore dog variables (age, body weight, sex, anatomic surgical site and urgency of surgery [classified as elective or emergent]) associated with isolation of CFZ-resistant staphylococci. All tests were two-sided, with $p < 0.05$ considered significant. Analyses were performed with computer software (Stata Statistical Software: Release 14, College Station, Texas, United States).

Results

One-hundred-fifteen dogs that underwent clean orthopaedic surgery were enrolled in the study. The median age was 4 years (interquartile range: 1–8). Commonly represented breeds included mixed breeds (38/115, 33%), Labrador Retriever (19/115, 16%), Pitbull Terrier (6/115, 5%), German Shepherd dog (6/115, 5%) and Bulldog (4/115, 3%). Sex distribution was female spayed (54/115, 47%), male castrated (43/115, 37%), male intact (10/115, 9%) and female intact (8/115, 7%). Mean body weight was 25.9 ± 14.3 kg. The surgical orthopaedic disease were categorized as elective (77/115, 67%), which included cranial cruciate ligament disease (60/115, 52%) medial patella luxation (7/115, 6%) hip dysplasia (4/115, 3%), elbow dysplasia (6/115, 5%) and urgent (38/115, 33%), which included traumatic fracture (32/115, 28%) and luxation (6/115, 5%). Surgical sites sampled were stifle (68/115, 59%), elbow joint (17/115, 15%), radius/ulna (9/115, 8%), tibia/fibula (7/115, 6%), humerus (5/115, 4%), femur (5/115, 4%) and coxofemoral joint (4/115, 3%). The right limb was sampled in 59/115 (51%), and the left limb was sampled in 56/115 (49%) dogs.

Bacterial cultures resulted in a growth of 391 bacterial isolates in 115 dogs. One (1%) dog had no growth. Eight (7%) dogs grew one bacterial isolate, 27 (23%) dogs grew two different isolates, 27 (23%) dogs grew three different isolates, 27 (23%) dogs grew four different isolates, 16 (14%) dogs grew five different isolates and 9 (8%) dogs grew six or more isolates.

Staphylococcus spp. were isolated from culture samples of 83/115 (72%) dogs. Twelve dogs grew two different staphylococcal isolates, and the remaining 71 dogs grew a single staphylococcal isolate. Nine isolates identified as *S. intermedius* and 38 *S. pseudintermedius* isolates were reported as SIG. The prevalence of bacterial isolates is shown in ►Table 1.

On univariable logistic regression analysis, none of the following factors were significantly associated with growing a CFZ-resistant *Staphylococcus* spp.: age, sex, body weight, urgency of surgery or anatomic surgical site.

Among the 95 staphylococcal isolates, 65 (68%, 95% CI: 59.1–77.8) were susceptible to CFZ. In the 12 dogs that grew two different staphylococci, both isolates were susceptible in five dogs, both isolates were resistant in two dogs, and in the remaining five dogs, one isolate was susceptible, and the other was resistant. Among the 83 dogs from which *Staphylococcus* spp. were isolated, 28 (33.7%, 95% CI: 23.6–43.9) had at least one CFZ-resistant strain.

Among the 95 staphylococcal isolates, 73 (77%, 95% CI: 68.4–85.3) were susceptible to CPD. The difference in rate of staphylococcal susceptibility to CPD versus CFZ was 8.4% (95% CI: 4.2–21.0), which was not significant ($p = 0.19$). Among the 83 dogs from which *Staphylococcus* spp. were isolated, 20 (24%, 95% CI: 15.5–33.9) dogs grew at least one CPD-resistant strain, which did not differ significantly ($p = 0.17$) from the proportion of dogs that grew at least one CFZ-resistant strain.

Among the 88 staphylococcal isolates for which AMC susceptibility results were available, 67 (76%, 95% CI:

Table 1 Distribution of 391 bacterial isolates isolated from the skin of 115 dogs underwent orthopaedic surgical procedures

Isolate	No. of isolates	No. (%) of dogs
<i>Bacillus</i> spp.	200	90 (78)
<i>Staphylococcus</i> spp.	95	83 (72)
CoNS	44	44 (38)
CoPS	51	51 (44)
<i>S. intermedius</i> group	47	47 (41)
<i>S. aureus</i>	4	4 (3)
<i>Micrococcus</i> spp.	34	26 (23)
<i>Streptococcus</i> spp.	16	13 (11)
Non- <i>Enterobacteriaceae</i> spp.	15	14 (12)
<i>Enterococcus</i> spp.	11	11 (10)
<i>Corynebacterium</i> spp.	7	7 (6)
<i>Acinetobacter</i> spp.	6	6 (5)
<i>Klebsiella oxytoca</i>	1	1 (1)
<i>Pasteurella stomatis</i>	1	1 (1)
<i>Escherichia coli</i>	1	1 (1)
<i>Moraxella</i> spp.	1	1 (1)
<i>Streptomyces</i> spp.	1	1 (1)
<i>Ralstonia</i> spp.	1	1 (1)
<i>Pantoea</i> spp.	1	1 (1)

Abbreviations: CoNS, coagulase-negative staphylococci; CoPS, coagulase-positive staphylococci.

67.2–85.0) were susceptible to AMC. The difference in rate of staphylococcal susceptibility to AMC versus CFZ was 7.7% (95% CI: 5.2–20.6), which was not significant ($p = 0.25$). Among the 76 dogs that had at least one *Staphylococcus* spp. isolated with AMC susceptibility reported, 19 (25%, 95% CI: 15.3–34.7) dogs grew at least one AMC-resistant strain, which did not differ significantly ($p = 0.23$) from the proportion of dogs that grew at least one CFZ-resistant strain.

Among the 95 staphylococcal isolates, 36% (16/44) of CoNS and 6% (3/47) of SIG were resistant to oxacillin. No *Staphylococcus aureus* isolates were resistant to oxacillin. The oxacillin susceptibility differed significantly according to staphylococcal species; CoNS had a lower rate of oxacillin susceptibility compared with other strains ($p = 0.001$) (►Table 2).

Discussion

When evaluating all bacterial isolates, *Staphylococcus* spp. were the second most commonly isolated bacteria from planned incision sites. The isolated staphylococci demonstrated similar susceptibility patterns to CFZ, AMC and CPD. Therefore, the null hypothesis was accepted. *In vitro* testing showed that dermal staphylococci isolates retrieved from

Table 2 Antimicrobial susceptibility for 95 *Staphylococcus* spp. isolated from the skin of 83 dogs underwent orthopaedic surgery. Amoxicillin/clavulanate susceptibility was not available for seven isolates

	CoNS n = 44 (%)	SIG n = 47 (%)	<i>S. aureus</i> n = 4 (%)	p-Value
Cefazolin	22/44 (50)	40/47 (85)	3/4 (75)	0.001
Cefpodoxime	27/44 (61)	43/47 (91)	3/4 (75)	0.002
Amoxicillin/Clavulanic acid	23/41 (56)	41/44 (93)	3/3 (100)	<0.001
Oxacillin	28/44 (64)	44/47 (94)	4/4 (100)	0.001

Abbreviations: CoNS, coagulase-negative staphylococci; SIG, *Staphylococcus intermedius* group; *S. aureus*, *Staphylococcus aureus*.
Note: p-Value < 0.05 indicates significant difference in susceptibility across CoNS, SIG and *S. aureus* group.

planned incision sites had no difference in susceptibility to CPD and AMC than to CFZ.

Breed, surgical site, age, sex, body weight, urgency of surgery or anatomic site did not have a significant effect on the CFZ susceptibility of staphylococcal isolates. In a previous study, bulldogs were identified to have a significantly higher risk of having methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) colonization and SSI. The differences in our results when compared with this previous study are likely due to different sample sizes and sampling methods.¹² In the present study, only cases referred to one institution were included, and samples from the incision site were collected. Additionally, only dogs that received prior antimicrobial treatment within 4 weeks or with skin lesions were excluded. A more detailed screening process including information such as antimicrobial treatment status of other animals and people in the same household, and husbandry environment, may have helped capture a more accurate image on the relationship between MRSP colonization status and incisional site bacteria.

Bacillus spp. were the most common incisional site bacteria isolated. A high prevalence of *Bacillus* spp. at these sites has been reported in previous studies using culture-based¹³ and molecular biology methods using 16s ribosomal ribonucleic acid amplification.¹⁴ *Bacillus* organisms are widely distributed in the environment and found in decaying organic matter, dust, vegetables and water. *Bacillus* spp. rarely causes orthopaedic SSIs. Except for *Bacillus cereus* and *Bacillus anthracis*, *Bacillus* spp. have low virulence and SSIs caused by *Bacillus* spp. were only reported in immunocompromised people,¹⁵ and SSIs caused by *Bacillus* spp. have not been reported in the veterinary literature.

The prevalence of coagulase-positive staphylococci (CoPS) and CoNS in this study was similar to those reported in previous veterinary studies. One study collected samples from multiple anatomic sites reported the isolation of CoPS in 37 of 50 (74%) dogs with healthy skin.¹⁶ Other veterinary studies reported 33 to 100% isolation rates of CoNS in healthy dogs.^{13,16,17} In a human study, CoNS comprised 59.6% of total isolates from planned incision sites.¹⁸ Differences between published studies are likely due to the variation in the sampling method, and the anatomic sites sampled. One previous study showed that *Staphylococcus* spp. demonstrated anatomic niche preferences, and *S. pseudintermedius* is more often isolated from the perineum area,

larynx and rectum.^{12,17} Samples from these other anatomic sites may have resulted in a higher isolation rate in the present study. However, the current study aimed to investigate the susceptibility of perioperative antimicrobial against bacteria present on incision sites; therefore, no samples were taken from other anatomic sites.

Six per cent of SIG isolated were oxacillin resistant. Due to the study design, a direct relationship between the MRSP colonization status and the bacteria present on the incision site could not be determined. In one previous study, the specificity of the incisional site sample for identifying MRSP carrier status was only 29.3%¹²; therefore, the actual number of dogs carrying methicillin-resistant SIG is likely to be higher. In addition, 36% of CoNS isolated in the present study were oxacillin resistant. This finding is similar to that in humans, where 28.6% of CoNS isolates were oxacillin resistant.¹⁸ Although traditionally regarded to be of low virulence, recognition of the role of CoNS as pathogens in veterinary dermatology is emerging,¹⁹ and the importance of CoNS in orthopaedic surgery should not be overlooked. Coagulase-negative staphylococci have been reported to be the causative bacteria in 12.7 to 14.2% of canine tibial plateau levelling osteotomy infections,^{20,21} in 22% of human fracture fixation infections,²² and up to 50% of human total hip arthroplasty infections.^{23,24} The high oxacillin resistance rate of CoNS observed in this study may provide one possible explanation for the high proportion of CoNS infections in human and veterinary orthopaedic surgery.

Staphylococcal isolates tested in the study showed similar susceptibilities to CPD, CFZ and AMC. The result is likely due to the high proportion of methicillin-resistant staphylococci. The addition of clavulanic acid to amoxicillin and the development of CPD helped increase the inhibition of β -lactamase and therefore have an improved coverage of methicillin susceptible staphylococci.^{22,25,26} However, several bacterial adaptation to β -lactamase have been discovered over the past decades,⁶ with the *mec A* gene coded altered penicillin-binding protein 2a being the most important one. The presence of penicillin-binding protein 2a in staphylococci is responsible for the methicillin resistance phenotype and confers intrinsic resistance to all β -lactams.²⁷

The prevalence of multidrug-resistant staphylococcal colonization and infection is increasing,²⁸ but the susceptibility of incisional site *Staphylococcus* in dogs has not been reported to the authors' knowledge. The selection of

antimicrobial for perioperative prophylactic administration should consider multiple factors, and the results of the current study should only be a reference. Degree of contamination, prior antimicrobial usage, targeted pathogenic bacteria, tissue concentration, institutional antimicrobial resistance pattern, cost and side effects should all taken into consideration. Pharmacokinetic studies to determine the optimal dosage and interval for prophylactic administration in dogs are lacking for AMC and CPD, but are available for CFZ.^{1,25} However, a direct comparison of the use of different medications in dogs is lacking. Human studies showed no difference in the SSI rate between prophylactic AMC, CPD and CFZ in human hip arthroplasty, knee arthroplasty and laparoscopic gynaecology surgery.^{29,30}

Using the standard for interpreting cumulative antibiogram,³¹ the three antimicrobials evaluated would be classified as fair to good for *in vitro* efficacy against incisional site staphylococci. Although the antimicrobial susceptibility may seem low, the antimicrobials evaluated in the present study still have a high susceptibility against methicillin-susceptible staphylococci. The findings of this study may help to explain a previous study that shown the positive carrier status of MRSP being a risk factor for the development of SSI after tibial plateau levelling osteotomy.¹² Best practices to prevent SSI in patients colonized with a resistant staphylococci remain unknown. Preoperative decontamination for human patients with methicillin-resistant *Staphylococcus aureus* colonization has been shown to be effective in preventing SSIs.³² Comparable information is unavailable in veterinary medicine and would require further investigation.

This study had several limitations. The confidence intervals around susceptibility rates and rate differences suggest that significant differences could yet exist between antimicrobials, although such modest differences would need to be correlated with SSI rates to determine their clinical significance. In this study, short- and long-term patient follow-up was not conducted, and the relationship between skin culture status and SSI was not examined. Multi-site research over a broader geographic area might provide additional information to guide clinical practice. Dogs in this study had no pathologic skin lesions around the incision site, and cultures were collected before the skin was surgically scrubbed. Bacteria seen on the culture may have included bacteria residing on the residual hair after clipping. Additionally, the isolation rate and susceptibility to CFZ, AMC and CFD after skin closure may have been different since perioperative antimicrobial prophylaxis is used in an effort to decrease total bacterial load throughout the procedure. Only conventional agar-based culture methods were used to detect bacteria. Recent advancements in molecular biology allowed bacterial identification using gene sequencing,³³ which provides more detailed qualitative information to identify bacterial diversity. The currently used culture-based methods, although limited in breadth for the types of organisms detected and host-microbe interaction, have the advantage of quantifying absolute cell abundances of culturable microbes.

In conclusion, we found that 68% of staphylococci isolated from planned, clean, orthopaedic incision sites to be suscep-

tible to CFZ. Cefpodoxime and AMC did not provide additional susceptibility coverage for isolated staphylococci. Based on the result of the present study, the lack of pharmacokinetic data, unknown added benefit for preventing SSI and antimicrobial stewardship, routine use of AMC or CPD in replace of CFZ should be practiced with caution.

Authors' Contributions

All authors contributed to the conception of the study, study design, data acquisition, analysis and interpretation. All authors drafted the revised and approved the submitted manuscript.

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Conflict of Interest

None declared.

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