What Is The Evidence?

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Problem

A 10-year-old female Quarter Horse weighing 480 kg (1,055 lb) was referred to the Texas A&M University Large Animal Clinic for evaluation of non–weight-bearing grade 5 lameness (5-point scale)[1] of the right forelimb. A tentative diagnosis of heel abscess or ligament strain had been made, and the horse had been treated with phenylbutazone (8.3 mg/kg [3.8 mg/lb], PO, q 24 h) for 1 week. Physical examination revealed an increase in strength of digital pulse and heat over the hoof capsule on the right forelimb. Sensitivity to hoof testers was detected over the cuneus ungulae (frog) of the hoof of the right forelimb. All other physical examination findings were unremarkable. Palmar digital nerve block of the right forefoot with 1 mL of 2% mepivacaine improved the lameness to a grade of 4, and abaxial nerve block on the right forefoot improved the lameness to a grade of 3. Cytologic examination of fluid from the podotrochlear navicular bursa and distal interphalangeal (coffin) joint revealed suppurative inflammation. Radiographs of the right forefoot revealed a small focal defect just medial to the central eminence of the distal sesamoid navicular bone, with evidence of lysis of the flexor surface, a thin radiolucent line undermining the central eminence of the bone, and poor cortical medullary distinction with enlargement of several synovial invaginations. Bacterial culture of navicular bursa fluid resulted in the growth of α-hemolytic *Streptococcus* spp with susceptibility to amoxicillin–clavulanic acid, ampicillin, ceftiofur, chloramphenicol, clindamycin, doxycycline, erythromycin, and penicillin and intermediate susceptibility to trimethoprim-sulfonamide. A diagnosis was made of septic bursitis of the navicular bone of the right forefoot concurrent with chronic navicular bone degeneration on the basis of radiographic, cytologic, and clinical findings.

Formulation of the Clinical Question

The clinical question was formulated in retrospect on the basis of observations by one of the authors (AMV), who at that time was a fourth-year veterinary student with an interest in antimicrobial treatment of horses. Given that treatment of septic joints can be problematic in horses, and return to soundness can be of paramount importance, a clinical question was developed with the objective of obtaining information regarding the choice of antimicrobial for treatment in similar situations in the future. To narrow the focus of the question, it was assumed that the method of antimicrobial administration would be IV regional limb perfusion (IVRP), which is the procedure of placing a tourniquet proximal to the affected area, injecting a drug IV, and leaving the tourniquet in place for a short period to allow the drug to diffuse.

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Clinical Question

In horses with septic joints in which the infecting organism has not yet been identified, is IVRP with amikacin or cefotaxime likely to be effective in resolving the infection?

Evidentiary Search Strategy

A search was performed through the PubMed database and the proceedings of the Annual Meeting of the American Association of Equine Practitioners (AAEP) via the International Veterinary Information Service Web site. Keyword combinations (and their variants) included horse, joint or bursa, and regional perfusion; horse, joint or bursa, and antimicrobials, antibiotics, amikacin, or cefotaxime; horse, pharmacokinetics, and cefotaxime or amikacin; and horse, antimicrobial, and susceptibility.

The burden of finding evidence for treatment of bacterial infections with particular antimicrobials becomes particularly heavy when there are few or no randomized controlled clinical trials in animals with naturally occurring infections. In that situation, clinicians must then rely on weaker or less clinically applicable evidence by reviewing reports of findings from other types of study designs considered to yield lower evidentiary strength, including pharmacokinetic data, pharmacodynamic action of the antimicrobials, and susceptibility of the suspected or confirmed bacterial isolate. Another issue is determining the means by which to evaluate strength of evidence from multiple sources of low evidence. For example, one might consider the number of level 4 studies (eg, case series) or level 5 reports (eg, expert opinion) that could be considered equivalent to 1 good level 1 study (eg, systematic reviews or randomized controlled clinical trials).[2] Even with the combination of search terms used, the number of reports identified was small (**Table 1**) and the abstracts in the PubMed database and reports in AAEP proceedings were not particularly onerous to review for relevance to the clinical question.

Review of the Evidence

The strength of evidence for the articles reviewed was assigned on the basis of the hierarchy of evidence

Table 1—Results of keyword searches performed in 2 databases to obtain information on whether amikacin or cefotaxime is effective for treatment of septic joints in horses.

Database	Search Statement	Total No. of articles found
PubMed	horses AND (joint* OR bursa*) AND (regional perfusion)	14
	horses AND (joint* OR bursa*) AND (antimicrobial* OR antibiotic* OR amikacin OR cefotaxime)	71
	horses AND pharmacokinetic* AND (cefotaxime OR amikacin)	26
	horses AND susceptibility AND (antibiotic* OR antimicrobial*) AND (amikacin OR cefotaxime)	13
International Veterinary Information Service, AAEP Proceedings	Joint perfusion	47
	Amikacin cefotaxine	5
	Pharmacokinetics amikacin	17
	Pharmacokinetics cefotaxine	2

from the Oxford Centre for Evidence-Based Medicine.[2] Published in the AAEP proceedings[3–6,a,b] and peer-reviewed journals,[7–12] results of case-series studies designed to evaluate efficacy of amikacin for IVRP suggest that amikacin is effective, with a range of 57% to 100% of horses surviving after treatment for septic joints. The percentage of horses that return to athletic soundness is difficult to summarize from these reports but appears to be somewhat lower than the percentage that survive, depending on the clinical situation.

According to results of pharmacokinetic studies,[13–15] IVRP with amikacin results in drug concentrations that may be effective against many pathogens in horses, with the exception of *Streptococcus zooepidemicus* and *Enterococcus* spp.[16–18] Because the effects of aminoglycosides are reportedly peak dependent (and perhaps also dependent on ratios of area under the curve to minimum inhibitory concentration because area under the curve and peak serum concentrations influence each other), establishment of a high serum concentration of aminoglycoside for a short period would be expected to be effective against many pathogens. On the other hand, as a β-lactam antimicrobial, cefotaxime is expected to require concentrations higher than the minimum inhibitory concentration for an adequate portion of the dosing interval. Because there are no reports of the efficacy of IVRP with cefotaxime, there is no evidence with which to confirm that the drug concentration after IVRP would be adequate. When injected IV (25 mg/kg [11.4 mg/lb]), cefotaxime had a mean elimination half-life of 58 minutes in serum,[19] and the active metabolite has a mean half-life of 1.7 hours,[20] with a mean peak concentration of 117 μg/mL,[19] but it is difficult to extrapolate these findings to IVRP.

The expert opinion of the clinician (level 5 evidence) tends to weigh heavily in clinical decision making for situations for which clinical trial data are lacking, and a quick search of the medical records at Texas A&M University Large Animal Clinic revealed that several horses had been treated with the combination of amikacin and cefotaxime over a 5-year period. However, even among the case-series studies, there were none in which comparisons were made among antimicrobial regimens to determine whether cefotaxime alone might be a better choice than amikacin alone.

Given the aforementioned evidence, what decision would you make?

Clinical Decision and Outcome

Given the lack of level 1, level 2, or level 3 evidence in favor of a particular antimicrobial regimen for treatment of septic joints in horses, results of case-series and in vitro studies must be used to guide clinical decisions, along with the experience of attending clinicians and their comfort with the administration procedures. The evidence indicated that neither amikacin nor cefotaxime is likely to cause harm to the joint structures, and they both appear to be effective in vitro against suspected infecting pathogens. However, given the unknown variables associated with cefotaxime (eg, elimination rate after IVRP injection, which then affects the pharmacodynamic likelihood of pathogen growth inhibition), its use might be questioned.

The selection of antimicrobial for treatment in the horse of this report was in fact made prior to the review of the evidence, as might be anticipated in many clinical settings. The horse's right front navicular bursa was injected with 375 mg of amikacin once a day for 3 days. Intravenous regional limb perfusion with 2 g of cefotaxime in 30 mL of sterile water was also performed once a day for 7 days on the right forelimb distal to the carpus. The horse was also treated with oxytetracycline (7 g in 35 mL of saline [0.9% NaCl] solution, IV, q 24 h for 5 days, then q 48 h for 10 days).

One month after diagnosis and hospitalization, the lameness was slightly improved but still grade 4. Radiographs revealed coarse trabeculation that was particularly evident in the proximal sesamoid bones, consistent with disuse osteopenia. There was also an erosive lesion on the flexor surface and medullary cavity of the navicular bone toward the medial aspect of the sagittal ridge, which was not seen previously. There had been no change in the distal phalanx of the proximal interphalangeal (pastern) joint. The radiologic diagnosis was disuse osteopenia and septic navicular bone. A wedge shoe was prescribed, and oxytetracycline was administered IV for 15 more days. Recommendations were to continue keeping the horse in its stall, allow it to graze only when led by hand, and continue oral administration of phenylbutazone.

Two months after the diagnosis and after 48 hours without phenylbutazone, the horse was sound when the wedge shoe was on but was still lame at a walk (lameness score not recorded) when the shoe was removed. Radiographs continued to reveal erosive lesions on the flexor surface of the navicular bone, but these lesions were not considered an active infection and were diagnosed as disuse osteopenia. Recommendations were to cease phenylbutazone administration unless the horse became lame at a walk and to keep the wedge shoe on for another 8 weeks. No other follow-up information was available.

Discussion

Although the literature search revealed limited data with which to answer the clinical question for the circumstances in the horse of this report, many of the findings could be applied in other situations, particularly those dealing with pharmacokinetics, pharmacodynamics (which are usually extrapolated from in vitro, retrospective, or laboratory animal studies), and antimicrobial susceptibility testing of bacterial isolates.

One might ask why there are not more randomized controlled clinical trials in which treatment of naturally occurring joint infections is evaluated, given that this condition is not uncommon in horses. At the very least, reports of case series in which the effects of various locally injected antimicrobials were compared or in which effects of systemically administered antimicrobials were compared with locally injected antimicrobials would be informative. Given the low evidentiary value of case-series studies, however, clinicians should be reluctant to have high confidence in the results. It is the authors' contention that evidence from several level 4 studies is not as strong as evidence from 1 well-done level 1 study.

One obvious advantage of locally administrated antimicrobials is the use of a lower dose than would be used via other routes, which may yield a lower likelihood of adverse gastrointestinal effects in horses, although there is no evidence that the risk of *Clostridium difficile*–associated disease is correlated with dose of cephalosporins in horses. Until more level 1 data are available, alternative types of data for making clinical decisions about treatment of joint infections include antimicrobial-susceptibility data (particularly when bacterial organisms are obtained from infected horses), pharmacokinetic and pharmacodynamic data, and predictions based on reported case series.

In summary, the evidence supporting any particular route of administration or selection of antimicrobial for the treatment of septic joints in horses is limited, and efforts to improve the database for decision making for these conditions would be welcome. Additionally, more up-to-date information is needed regarding minimum inhibitory concentrations of antimicrobials for pathogens associated with musculoskeletal infections.

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