EQUINE

Treatment with continuous intrasynovial antimicrobial infusion for septic synovitis in horses: 31 cases (2000–2003)

Timothy B. Lescun, BVSc, MS, DACVS; James R. Vasey, BVSc;
Michael P. Ward, BVSc, MSc, MPVM, PhD; Stephen B. Adams, DVM, MS, DACVS

Objective—To determine clinical findings, complications, and outcome of septic synovitis in which continuous intrasynovial antimicrobial infusion (CIAI) was used for local antimicrobial delivery in horses.

Design—Retrospective case series.

Animals—22 adult horses and 9 foals (horses < 1 year of age).

Procedures—Records of horses with septic synovitis that had CIAI during treatment were reviewed. The association between clinical variables and whether horses performed their intended use following treatment was determined.

Results—42 synovial cavities were treated via CIAI. Twenty-nine cases were chronic (> 7 days) in nature, 15 had been refractory to standard treatments, and 13 synovial infections had associated osteomyelitis. Mean duration from infection to initiation of CIAI was 19.7 days, and mean duration of CIAI was 6.1 days. Temporary discharge from the catheter site at the time of removal was evident in 8 horses. Dysfunction of the infusion system occurred in 2 horses and was corrected during the course of treatment. No long-term complications were reported. Thirty-nine (93%) synovial infections in 29 (94%) horses were resolved. Twenty adult horses and 8 foals were discharged from the hospital, and 19 of 24 horses with long-term follow-up performed their intended use.

Conclusions and Clinical Relevance—CIAI was a useful adjunctive treatment for septic synovitis and allowed intrasynovial antimicrobial delivery into a variety of synovial cavities. (*J Am Vet Med Assoc* 2006; 228:1922–1929)

Intrasynovial infection causes severe, debilitating lameness in horses.[1,2] The lowest reported estimates of mortality rates are 8% in adults[3] and 22% in foals.[4] Most commonly, septic synovitis occurs within a joint[1]; however, septic tenosynovitis and septic bursitis may also occur.[5–7] Successful treatment requires rapid elimination of the infecting organisms from the synovial cavity before irreversible damage occurs. Recommended treatments include systemic antimicrobial and anti-inflammatory medications, synovial lavage, endoscopic surgery, and open drainage.[8] Local antimicrobial administration has also been used to improve drug delivery to the site of infection. Intra-articular injections,[3,9] intraosseous and IV regional perfusion,[10,11] implantation of antimicrobial impregnated polymethylmethacrylate beads,[12] and antimicrobial impregnated collagen sponges[13] have all been used clinically for the treatment of septic synovitis in horses.

Abbreviations

MIC	Minimal inhibitory concentration
CIAI	Continuous intrasynovial antimicrobial infusion

A system for continuous intra-articular gentamicin delivery was developed with the aim of achieving high antimicrobial concentrations within the synovial cavity.[14] In that study, in normal tarsocrural joints, mean steady state synovial fluid gentamicin concentration achieved during continuous infusion was 1,069 µg/mL. This concentration is > 100 times the MIC of commonly isolated equine bacterial pathogens.[14] Local delivery of aminoglycosides at high concentrations utilizes their concentration-dependent action, enabling rapid killing of a greater percentage of bacteria than would be achieved during systemic administration alone.[9,15] This delivery method avoids repeated injections, articular damage resulting from antimicrobial impregnated beads, damage associated with retrieval of nonabsorbable beads,[12] and the anatomic limitations of regional limb perfusion.[10,11]

The purpose of the study reported here was to review hospital records of cases of septic synovitis in horses treated with CIAI and to report the clinical findings, complications associated with this method of treatment, and outcome. We hypothesized that CIAI would be suitable for local antimicrobial delivery during the treatment of septic synovitis in horses and have few clinical complications.

Criteria for Selection of Cases

Medical records of horses and foals (< 1 year of age) with septic synovitis that were treated via CIAI at Purdue University or the Goulburn Valley Equine Hospital during the period from January 2000 to December 2003 were reviewed. Diagnosis of septic synovitis was based on several factors. All cases included in the study had at least 3 of the following findings: a confirmed source of synovial penetration (wound or iatrogenic); physical findings consistent with septic synovitis (heat, localized signs of pain, synovial effusion, rectal temperature > 38.3°C [101°F], grade 4 or 5 lameness,[16] osteomyelitis associated with synovial sepsis, supportive synovial fluid cytologic results [WBC

From the Departments of Veterinary Clinical Sciences (Lescun, Adams) and Veterinary Pathobiology (Ward), School of Veterinary Medicine, Purdue University, West Lafayette, IN 47909-1248; and Goulburn Valley Equine Hospital, 905 Goulburn Valley Hwy, Congupna, VIC, 3633, Australia (Vasey). Dr. Ward's present address is Department of Veterinary Integrated Biomedical Sciences, College of Veterinary Medicine, Texas A&M University, College Station, TX 77843-4461.
Address correspondence to Dr. Lescun.

count > 20×10^9 cells/L], > 80% neutrophils, and total protein > 40 g/L); and positive results of bacterial culture of synovial fluid, synovial membrane, or bone. Typically, horses with synovial sepsis refractory to previous treatments or chronic in nature, or with associated osteomyelitis were selected to receive CIAI during the study period.

Procedures

Information retrieved from the medical record included signalment, time from initial lameness or injury to initial treatment, treatments instituted prior to referral, physical examination findings, synovial structures involved, degree of lameness at hospital admission, radiographic and ultrasonographic findings, results of CBC, synovial fluid cytologic evaluation and bacterial culture and susceptibility, duration and type of antimicrobial treatments, duration and type of anti-inflammatory treatments, and details of any surgical or other medical treatments performed. Follow-up information was obtained through clinical reevaluation; through contact with owners, trainers, and referring veterinarians; and from race records.

A commercially available continuous infusion system[a] was used for intrasynovial antimicrobial delivery in all cases (**Figure 1**). The system was placed by several clinicians during the study period following the guidelines in the package insert. Intrasynovial catheter placement was performed after synovial lavage during general anesthesia or during sedation and local anesthesia. A synovial pouch was chosen that positioned the catheter away from weight-bearing surfaces wherever possible. The balloon of the continuous infusion system was filled with an antimicrobial solution prior to catheter placement to allow time for the solution to fill the delivery tubing. The concentration of antimicrobial within the balloon was prepared so that one third of the calculated daily systemic dose would be delivered by CIAI and the remaining two thirds were given systemically.[17] An estimate of the infusion flow rate was used for these calculations.[14,17] A 6-F peel-away introducer and needle were inserted into the synovial pouch. The needle was removed, and the catheter was passed through the introducer to a depth of approximately 5 cm. The introducer was peeled apart and removed while the catheter was advanced, leaving the catheter in place within the synovial cavity. The balloon and infusion tubing were attached to the catheter. Both catheter and tubing were sutured in place and affixed with cyanoacrylate prior to placement of a sterile dressing (**Figure 2**). A protective bandage was placed over the entire infusion system. For 1 horse, the balloon and infusion system were maintained beneath a stent bandage on the shoulder region.

Selection of antimicrobial for CIAI was based on bacterial culture and susceptibility data when available and knowledge of antimicrobial susceptibility of bacteria known to cause septic synovitis.[1,18] Intrasynovial infusion was discontinued when lameness or clinical signs of infection were improved, synovial fluid WBC count was < 20×10^9 cells/L, or both. All catheter sites were scrubbed with an antiseptic after catheter removal and covered with a sterile dressing.

Medical and surgical treatments other than CIAI were selected by the clinician in charge of the case. All horses received systemic antimicrobial and anti-inflammatory treatments. Other treatments included needle lavage, endoscopic lavage and debridement, IV regional antimicrobial perfusion, and arthrotomy.

Statistical analysis—Logistic regression models[b] and Fisher exact tests[b] were used to assess the association between clinical variables (continuous and categoric, respectively) and whether horses performed their intended use after treatment. Horses performing their intended use were defined as having resumed or attained expected activities as reported by owners or trainers. Bivariate analysis for survival could not be performed because of the low number (n = 3) of nonsurviving horses. Clinical variables evaluated were age, sex, breed, time from lameness or injury to initial treatment, time from lameness or

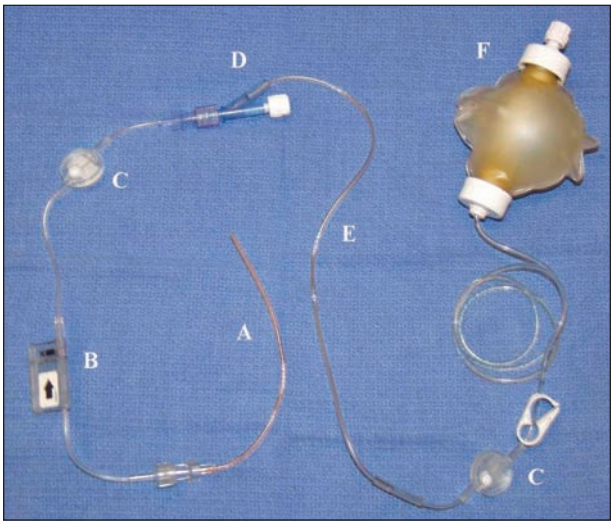

Figure 1—Photograph of a continuous intrasynovial antimicrobial infusion system used to treat horses and foals with septic synovitis. A = Intrasynovial catheter. B = Flow indicator. C = Air filters. D = Y-piece injection port. E = Flow control delivery tubing. F = Balloon reservoir.

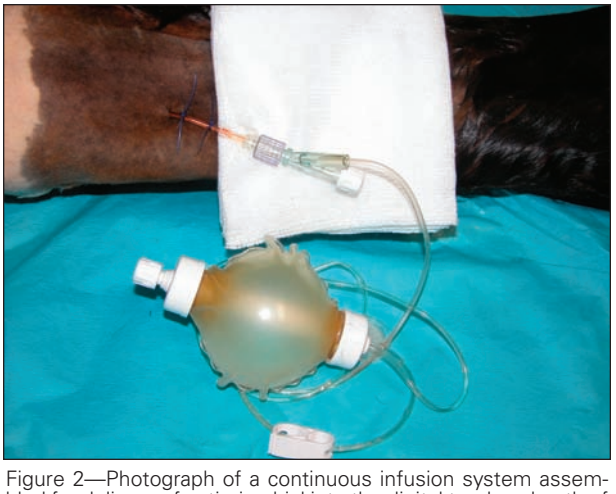

Figure 2—Photograph of a continuous infusion system assembled for delivery of antimicrobial into the digital tendon sheath of a horse. The intrasynovial catheter has been sutured in place, and the balloon and delivery tubing were filled with antimicrobial prior to being attached to the catheter.

injury to initiation of CIAI, degree of lameness on admission, source of infection, presence of osteomyelitis, number of joints affected, synovial fluid WBC count, synovial fluid total protein concentration, bacterial culture result, antimicrobial used for CIAI, total dose delivered by CIAI, daily dose delivered by CIAI, duration of CIAI, duration of hospitalization, and duration of systemic antimicrobial treatment. Thoroughbreds and Standardbreds were combined as racing breeds; all other breeds were nonracing. Infection source was categorized into those involving skin penetration (wound or iatrogenic) and those most likely arising from a hematogenous source (bacteremia or idiopathic). Total CIAI dose was categorized into synovial cavities that received ≥ 3,000 mg of antimicrobial and those that received < 3,000 mg. Daily CIAI dose was categorized into synovial cavities that received ≥ 600 mg of antimicrobial and those that received < 600 mg. The unit of analysis was the individual horse, and for horses with more than 1 joint affected, a "horse-level" variable was used for analysis. For example, foals with multiple synovial infections were counted once as hematogenous in origin in the analysis of infection source. For continuous variables associated with individual joints (synovial fluid WBC count and protein), the highest or "worst" values were chosen to represent the horse, as this was considered to be the most clinically relevant value for the individual horse. For purposes of analysis, osteomyelitis and bacterial culture results were considered at a horse-level also. That is, if osteomyelitis was present in an affected joint, the horse was considered to have osteomyelitis. A value of $P \leq 0.05$ was considered significant for bivariate analysis of whether horses performed their intended use. Multivariate analysis (logistic regression[b]) was attempted but could not be performed because of the low number of cases with complete follow-up information (n = 24).

Results

Continuous intrasynovial antimicrobial infusion was used during the treatment of 22 horses and 9 foals with septic synovitis. Fifteen horses were treated at Purdue University, and 16 horses were treated at the Goulburn Valley Equine Hospital. For Purdue University, this constituted 26% of the total number of horses with septic synovitis treated during the study period. The total number of horses treated at the Goulburn Valley Equine Hospital for septic synovitis was not determined. Fourteen females, 10 castrated males, and 7 sexually intact males were treated. Thirteen Thoroughbreds, 8 Standardbreds, 6 Quarter Horses, 1 Andalusian, 1 Belgian, 1 Appaloosa, and 1 horse of unknown breed were treated. Clinical findings, treatment details, and outcome were determined (**Tables 1 and 2**). Forty-two synovial cavities were treated, including 34 with septic arthritis, 6 with septic tenosynovitis, and 2 with septic bursitis. At the initiation of CIAI, all horses had received prior systemic antimicrobial administration, 29 (94%) horses had infection present for > 7 days, 15 (48%) horses had been refractory to aggressive standard treatments, and 13 (31%) synovial infections

Table 1—Clinical findings, treatments, and outcome for 22 adult horses with septic synovitis treated by use of CIAI.

Horse	Age (y)	Synovial structure infected	Bone infected	Duration of infection prior to CIAI (d)	Treatment prior to CIAI	Treatment with CIAI	CIAI (d)	CIAI drug	Dose (mg/d)	Outcome
1	6	Lateral femorotibial jt	No	8	A	C	6	GNT	250	Sound, resumed 3-day eventing
2	2	Tarsocrural jt	No	30	A	C	5	GNT	600	Sound riding horse
3	8	Tarsocrural jt	Yes	23	A	B	4	GNT	500	Sound riding horse
4	12	Femoropatellar jt	No	49	A	C	7	GNT	400	Sound broodmare
5	2	Tarsocrural jt	No	30	A	C	6	GNT	450	Resumed racing; 27 starts, 9 wins
6	2	Medial femorotibial jt	Yes	14	A, B, C, D	C	9	GNT	400	Euthanized, severe cartilage loss.
7	3	Digital flexor sheath	No	28	A, B (2), D, E	C	5	GNT	450	Resumed racing; 9 starts, 2 wins
8	8	Midcarpal jt	No	22	A, B (2), C, D	C	7	GNT	450	Discharged, did not race, no LTF
9	9	Tarsocrural jt	No	14	A, B (2), C, D, F	B, E	5	GNT	400	Discharged, mild lameness, no LTF
10	1	Tarsocrural jt	No	4	A	C, E, F	7	GNT	600	Training as 2-year-old
11	1	Bicipital bursa	No	21	A, B (2), C (2), D	C	5	GNT	550	Racing as 3-year-old; 2 starts
12	8	Metacarpophalangeal jt	No	11	A	C	7	GNT	450	Trained, did not race, sold for riding
13	4	Femoropatellar jt Medial femorotibial jt	No	8	A, D	C	6	GNT	1,200	Euthanized, infection resolved severe cartilage loss
14	15	Dist interphalangeal jt	Yes	66	A	B, E	6	GNT	500	Sound, resumed barrel racing
15	9	Prox interphalangeal jt	No	12	A, B, D, E	B, E	5	AM	250	Sound, returned to riding
16	6	Elbow jt	Yes	24	A	B, F	3	AM	2,500	Infection resolved, lame with osteoarthritis of elbow at 6 months
17	2	Dist interphalangeal jt Digital flexor sheath Navicular bursa	No	10	A	C, E	4	AM AM	3,000 3,000	Lame, did not race
18	15	Digital flexor sheath	Yes	14	A	B	6	GNT	800	Sound riding horse
19	5	Digital flexor sheath	No	9	A	C, E	11	GNT	550	Sound broodmare
20	6	Digital flexor sheath	No	33	A, B, C, E, F	C, E	4	TCN	300	Resumed dressage training
21	4	Tarsocrural jt	No	10	A	C	7	GNT	500	Resumed racing; 5 starts
22	11	Tarsocrural jt	Yes	56	A, C (2), D, E, F	C, F	14	AM	2,000	Infection resolved, lame, severe

jt = Joint. Dist = Distal. Prox = Proximal. A = Systemic antimicrobials. B = Synovial lavage. C = Endoscopic lavage. D = Intrasynovial antimicrobial injections. E = IV regional perfusion. F = Arthrotomy. GNT = Gentamicin. AM = Amikacin. TCN = Ticarcillin. LTF = Long-term follow-up.
Number in parentheses is the number of times a procedure was performed.

Table 2—Clinical findings, treatments, and outcome for 9 foals with septic synovitis treated by use of CIAI.

Foal	Age (wk)	Synovial structures infected	Bone infected	Duration of infection prior to CIAI (d)	Treatment prior to CIAI	Treatment with CIAI	CIAI (d)	CIAI drug	Dose (mg/d)	Outcome
1	2	L femoropatellar jt	No	9	A, B (2)	C	5	GNT	450	Euthanized, osteomyelitis of medial femoral condyles
		R femoropatellar jt	No					GNT	450	
		L med femorotibial jt	Yes							
		R med femorotibial jt	Yes							
2	6	L tarsocrural jt	Yes	5	A, B (2), D	C	4	GNT	400	Racing as 2-year-old; 1 start
		R tarsocrural jt	Yes					GNT	400	
3	4	Tarsocrural jt	Yes	24	A, B (3), D	B,E	6	AM	400	Sound, working horse
4	5	Femoropatellar jt	No	8	A	B	4	AM	600	Racing; 11 starts, 4 wins
		Med femorotibial jt	No							
5	2	L tarsocrural jt	Yes	12	A	C	3	AM	800	Training as 2-year-old
		R tarsocrural jt	Yes					AM	800	
6	4	Femoropatellar jt	No	10	A, B (2), D	C	6	AM	250	Sound, in training
		Med femorotibial jt	No							
7	28	Femoropatellar jt	No	33	A, C, D	C	6	GNT	500	Discharged, lame, no LTF
		Lateral femorotibial jt	No							
8	24	Tarsocrural jt	No	7	A	C	7	GNT	400	Discharged sound, no LTF
9	32	Tarsal sheath	No	8	A, B (2), D, E	C	9	CFT	750	Discharged sound, no LTF

L = Left. R = Right. Med = Medial.
See Table 1 for remainder of key.

had associated osteomyelitis. Aggressive standard treatment was considered to be systemic antimicrobial treatment and synovial lavage (needle or endoscopic) combined with a method of local antimicrobial administration (intrasynovial injection or regional perfusion performed either daily or every other day).

Synovial cavities most commonly treated via CIAI included 13 (31%) tarsocrural joints, 7 (17%) femoropatellar joints, 6 (14%) medial femorotibial joints, and 5 (12%) digital flexor tendon sheaths. The source of synovial infection was bacteremia in 17 (40%) cases, a traumatic wound in 8 (19%) cases, iatrogenic in 7 (17%) cases (6 injections and 1 surgery), and unknown in 7 (17%) cases. Intrasynovial infusion catheters were positioned in the palmar-plantar or caudal pouch of the tarsocrural, metacarpophalangeal, midcarpal, distal interphalangeal, and elbow joints. They were positioned in the proximal aspect of the flexor tendon sheath, tarsal sheath, and bicipital bursa and in the dorsal or cranial pouch of the femorotibial, femoropatellar, proximal, and distal interphalangeal joints. The horse with septic navicular bursitis had communication between the distal interphalangeal joint, the flexor tendon sheath, and the navicular bursa. Two catheters were placed with arthroscopic visualization; 1 was placed into the palmar pouch of the distal interphalangeal joint and 1 into the flexor tendon sheath.

Synovial fluid cytologic evaluation was available from 34 synovial cavities. Mean synovial fluid WBC count was 34.5×10^9 cells/L (range, 7.6 to 100.0×10^9 cells/L). Percentage of neutrophils was > 90% in 19 (56%) horses, between 80% and 90% in 13 (38%) horses, and between 70% and 80% in 2 (6%) horses. Mean total protein concentration in synovial fluid was 40 g/L (range, 24 to 63 g/L). In 3 horses, purulent fluid was observed draining from a wound involving the affected synovial structure and cytologic evaluation was not performed.

Synovial fluid, tissue, or bone samples for bacterial cultures were submitted from 34 synovial cavities. Twenty-one organisms were cultured from 13 samples. The most common organisms isolated were *Staphylococcus* spp (38%), *Streptococcus* spp (24%), and *Escherichia coli* (14%). Eleven samples were taken when antimicrobials had not been administered within 24 hours, and 8 (73%) of these yielded a positive result. Twenty-three samples were taken while horses were still receiving systemic antimicrobial treatment, and only 5 (22%) of these yielded a positive result.

Radiographs were obtained of the affected synovial structures in all horses. Radiographic findings included subchondral lysis (14 cases), presence of an intrasynovial sequestrum (2 cases), periarticular proliferation (1 case), increased joint space (1 case), and decreased joint space (1 case). Osteomyelitis was associated with 13 synovial infections on the basis of radiographic, surgical, or necropsy findings. Seven tarsocrural joint infections (54%) and 3 medial femorotibial joint infections (50%) had associated osteomyelitis. Osteomyelitis was a result of bacteremia in 7 (54%) cases, a wound in 3 (23%) cases, and iatrogenic infection in 2 cases (15%).

Mean duration from onset of infection to initiation of CIAI was 19.7 days (range, 4 to 66 days). All horses received systemic antimicrobial treatment concurrent with CIAI. In surviving horses, systemic antimicrobials were administered for a mean of 27.9 days (range, 14 to 43 days) from the initiation of CIAI. Twenty-five horses received either penicillin[c,d] (22,000 U/kg [10,000 U/lb], IV, q 6 h or 22,000 U/kg, IM, q 12 h) or ampicillin[e] (22 mg/kg [10 mg/lb], IV, q 8 h) combined with either amikacin[f] (21 mg/kg [9.5 mg/lb], IV, q 24 h) or gentamicin[g] (6.6 mg/kg [3 mg/lb], IV, q 24 h) during CIAI. During CIAI with an aminoglycoside, the systemic aminoglycoside dose was reduced.[17,19] After CIAI, horses were typically administered an antimicrobial PO for a minimum of 2 weeks, most commonly trimethoprim-sulfamethoxazole[h] (30 mg/kg [13.6 mg/lb], PO, q 12 h). Other antimicrobials were used if bacterial culture and susceptibility results indicated a more appropriate choice. These included enrofloxacin[i] (7 mg/kg [3.2 mg/lb], IV, q 24 h or 2.5 mg/kg [1.1 mg/lb], IV, q 12 h) in 8 horses, chloramphenicol[j] (44 mg/kg [20 mg/lb], PO, q 6 h) in 1 foal, and vancomycin[k] (7 mg/kg

[3.2 mg/lb], IV, q 8 h) and doxycycline[l] (10 mg/kg [4.5 mg/lb], PO, q 12 h) in 1 horse.

Gentamicin, amikacin, ceftiofur,[m] and ticarcillin[n] were delivered via CIAI (Tables 1 and 2). Continuous intrasynovial antimicrobial infusion was performed for a mean of 6.1 days (range, 3 to 14 days). The infusion system delivered a mean volume of 9.5 mL/d (range, 6 to 15 mL/d) for all antimicrobials. Mean daily dose of gentamicin delivered via CIAI was 1.8 mg/kg (0.8 mg/lb), whereas for amikacin it was 5.5 mg/kg (2.5 mg/lb).

Synovial fluid samples from 9 synovial cavities were analyzed for aminoglycoside concentration during CIAI by use of established assay protocols.[14,20] Mean gentamicin concentration from 3 synovial fluid samples was 321.3 µg/mL (range, 176 to 567 µg/mL). Mean amikacin concentration from 6 synovial fluid samples was 460.7 µg/mL (range, 185 to 1,012 µg/mL). Twelve trough serum aminoglycoside concentration measurements were made during CIAI immediately prior to administration of the daily systemic aminoglycoside dose. The mean trough serum gentamicin concentration was 0.92 µg/mL (range, 0.77 to 1.4 µg/mL), and the mean trough serum amikacin concentration was 1.52 µg/mL (range, 0.79 to 2.71 µg/mL).

Complications directly related to CIAI were reported in 10 (32%) horses. Discharge from the catheter site after its removal was seen in 8 (26%) horses. The discharge was characterized as serous or clear in 5 horses and as purulent in 3 horses. These 8 catheter sites had become sealed and were not discharging within 48 hours of catheter removal. Leakage of antimicrobial from the air filter located in the delivery tubing of the infusion system occurred in 2 (6%) horses. This was detected by observing some moisture in the location of the delivery tubing on the bandage. In one of these horses, the intra-articular catheter became blocked, presumably from an air lock, and the entire infusion system was replaced.

Thirty-nine of 42 (93%) synovial infections in 29 of 31 (94%) horses resolved after treatment. The three unresolved infections were all in the medial femorotibial joint. Twenty (91%) horses and 8 (89%) foals were discharged from the hospital after treatment. Mean hospitalization time was 14.4 days (range, 6 to 56 days). Following initiation of CIAI, mean hospitalization time was 10.2 days (range, 3 to 35 days). Residual lameness was present in 12 (43%) horses at the time of hospital discharge. One foal and 2 horses in the hospital with stifle infections were euthanatized because of severe, ongoing lameness or failure to respond to treatment. The foal had bilateral osteomyelitis of the medial femoral condyles (**Figure 3**). Both adult horses had substantial cartilage loss from the medial femoral condyle at gross necropsy examination.

Long-term follow-up (> 6 months) was obtained for 24 horses during a mean period of 25.1 months (range, 6 to 52 months). No long-term complications were reported from the use of CIAI during treatment of septic synovitis. Nineteen (79%) horses were being used as their owners had intended, including 8 racehorses, 8 pleasure riding or show horses, 2 broodmares, and one 3-day event horse. Residual lameness was evident in 3 (13%) horses, and an intermittent lameness was reported in 1 (4%) horse. Follow-up information from race records was available for 11 of 14 racehorses or foals intended to be racehorses, and 8 (73%) of these horses raced or were in race training after treatment.

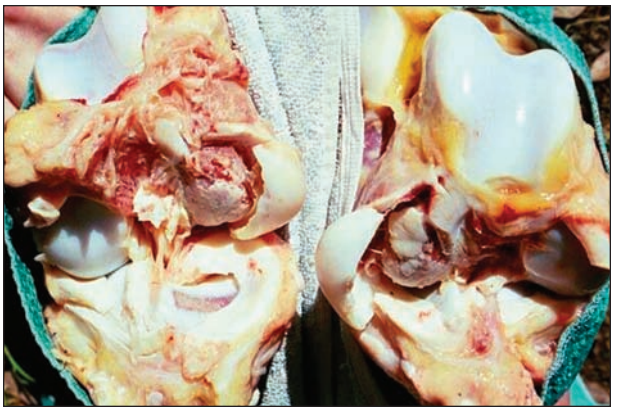

Figure 3—Photograph of the stifle joints of a foal at necropsy. Notice osteomyelitis of the medial femoral condyles and separation of articular cartilage from the infected subchondral bone.

Total CIAI dose ≥ 3,000 mg of antimicrobial (P = 0.04; odds ratio, 0.351; 95% confidence interval, 0.124 to 0.992), female sex (P = 0.05; from Fisher exact test), and wound or iatrogenic infection source (P = 0.05; odds ratio, 0.086; 95% confidence interval, 0.008 to 0.878) were associated with reduced likelihood of horses performing their intended use.

Discussion

The CIAI system was developed to attain sufficient antimicrobial concentrations in the synovial cavity and adjacent tissues to eliminate infecting organisms in horses with septic synovitis.[14] Horses in the study reported here predominantly had infections that were chronic in nature or refractory to prior treatments, or had associated osteomyelitis. Minor complications directly related to CIAI were overcome during the course of treatment, and no long-term complications were reported. Overall, the system was a reliable and effective method of intrasynovial antimicrobial delivery when used clinically.

Several factors have been reported to adversely affect survival, prognosis, or both in horses with septic synovitis. These include a delay in the initiation of treatment, involvement of more than 1 joint or synovial structure, and the presence of osteitis or osteomyelitis lesions.[2,4,21,22] In 1 study,[4] 85% of foals that were euthanatized had failed to respond to treatment or developed osteomyelitis. In another study,[21] osteitis or osteomyelitis was significantly associated with nonsurvival in horses treated for contaminated or infected synovial cavities by use of endoscopic surgery. Severe inflammation, local thrombosis, impaired synovial circulation, focal synovial necrosis, and bacteria-laden fibrin deposits all inhibit the ability of systemic antimicrobials to penetrate synovial tissues and kill bacteria.[2,8] Improving antimicrobial delivery into synovial tissues, thereby increasing bacterial killing and promoting a rapid resolution of infection, was the goal of

using CIAI during the treatment of horses in the present study.

Case selection and use of CIAI were based on several considerations. It was recognized that most cases of septic synovitis respond well to standard treatments,[1] and CIAI was not considered to be innocuous. An inflammatory response is incited when a catheter is maintained[23] and when gentamicin is injected[24] into a healthy synovial cavity. It is assumed that an intrasynovial catheter also has the potential to permit development of ascending sepsis, in a manner similar to other catheter-related infections.[25] However, in cases of septic synovitis, rapid elimination of infection is essential to normalize the synovial environment and allow it to return to a functional state in the long term.[1,21] Consequently, the use of CIAI in this study was primarily limited to chronic, unresponsive cases of septic synovitis or those complicated by osteomyelitis.

Diagnosis of septic synovitis involves a combination of clinical and laboratory findings.[1,4,8,12] Although positive results of bacteriologic culture of synovium would be regarded as definitive, after inoculation in an experimental study[26] of septic arthritis in horses, only 70% of horses yielded positive results of culture with a combination of synovial fluid and synovial membrane samples. A recent prospective trial in humans revealed that the clinical and laboratory features and morbidity and mortality rates for humans with positive results of culture and septic arthritis and humans with a high degree of clinical suspicion of septic arthritis were comparable.[27] These findings support the use of broader inclusion criteria than positive results of culture alone for clinical studies[1,4,28] of the disease. In the present study, a higher proportion of cultures with positive results was detected in horses in which systemic antimicrobial treatment had been discontinued for at least 24 hours prior to sample collection. We believe that the overall low rate of cultures with positive results in this study (38%) could be attributable to the chronic nature of the cases and the high proportion of horses (68%) that received systemic antimicrobial treatment at the time of culture. Therefore, in cases of chronic, unresponsive septic synovitis in which antimicrobial treatment has been instituted previously, it may be advantageous to stop antimicrobial administration for at least 24 hours before taking samples, to improve the likelihood of obtaining positive results of a culture. Further evaluation of culture techniques and strategies in cases of chronic septic synovitis is warranted.

Continuous intrasynovial antimicrobial infusion was not used as a substitute for other treatments such as systemic antimicrobials, through-and-through synovial lavage, endoscopic lavage and debridement, or open drainage when deemed necessary. Continuous intrasynovial antimicrobial infusion was used for local antimicrobial delivery into the synovial environment.[14] Mean synovial fluid gentamicin concentration was 321.3 μg/mL, and mean synovial fluid amikacin concentration was 460.7 μg/mL during CIAI for those horses in which these values were measured in this study. These values are > 50 times the MIC of common equine pathogens for gentamicin and amikacin.[29] However, further investigation is required to determine the drug concentrations achieved in synovial tissues and in various synovial cavities by use of CIAI during the treatment of horses with septic synovitis.

The benefits of endoscopic surgery for treatment of horses with synovial infections have been reported.[21] Whenever possible, endoscopy was used to assess the synovial cavity, debride osteochondral and osteomyelitis lesions, remove pannus and infected synovial membrane, and perform directed lavage. We believe this approach optimizes the benefit of CIAI by reducing bacterial load in the synovial cavity and allowing antimicrobial penetration into fibrin deposits, freshly debrided synovial tissues, and osteomyelitis lesions. In 17 horses in the present study, synovial endoscopy was performed for the first time immediately prior to initiation of CIAI. Fifteen of these horses survived after treatment. It could be argued that synovial endoscopy was responsible for resolution of infection in these horses.[21] However, there were also 8 horses in which synovial endoscopy was not performed, of which all survived, and a further 7 horses in which synovial endoscopy had been previously performed without resolution of infection, of which 6 horses responded to treatment and survived after instituting CIAI. We believe from the clinical experience of treating these horses that CIAI was a valuable adjunctive treatment for horses with septic synovitis and provided effective antimicrobial delivery directly into the synovial cavity.

An advantage of CIAI was that it could be used in various synovial cavities. The stifle and elbow joints and bicipital bursa were locations where regional antimicrobial perfusion was not possible. An advantage of CIAI over daily antimicrobial intrasynovial injections was the ability to easily medicate swollen and painful joints, particularly in foals. Another advantage over daily injections may be a reduced amount of trauma associated with the catheter, compared with daily arthrocentesis. It was reported in a study[23] assessing the synovial effects of a continuous intra-articular gentamicin infusion that the dorsomedial arthrocentesis sites used for sample collections were associated with mild to moderate amounts of hemorrhage and edema and with moderate to severe neutrophilic inflammation histologically. The synovial membrane at the catheter sites in that study had a localized neutrophilic inflammatory response to the catheter, with mild fibrin accumulation and occasional blood clots adhered to the synovial surface. Another advantage of CIAI was the ability to place the catheter during sedation and local anesthesia in 2 foals with septicemia, obviating the risk and expense of general anesthesia. Potential complications that should be considered when using an indwelling intrasynovial catheter system include the effect on the articular surfaces and the ability to maintain a sterile environment to minimize any risk of ascending infection. In this study, catheters placed in distal limb locations, such as the distal and proximal interphalangeal joints, were maintained beneath a sterile dressing, padded bandage, and waterproof layer of impervious tape to minimize risk of contamination. To reduce the risk of catheter-related damage in high-motion joints, catheters should be placed in a synovial

pouch distant from the weight-bearing surfaces of the joint, preferably with endoscopic guidance to ensure accurate placement. In the present study, none of the catheters were dislodged during treatment and maintenance beneath a bandage was uncomplicated.

Gentamicin has no substantial effect on the glycosaminoglycan content of equine articular cartilage explants in vitro at concentrations up to 25,000 μg/mL[30] and has a mild inflammatory effect on the synovium when injected or infused in vivo.[23,24] Aminoglycosides such as gentamicin are concentration dependent. Their bacterial killing action is improved at higher concentrations. In humans, clinical efficacy is strongly correlated with the ratio of peak concentration to MIC of the infective organism,[15] and in vitro susceptibility patterns of bacteria cultured from horses reveal that there is a lower percentage of resistant bacteria at higher gentamicin concentrations.[31] Although gentamicin concentrations achieved with CIAI in healthy tarsocrural joints[14] and in the present study were greater than the MIC of common equine pathogens, the nature of a continuous infusion system may also be suited to the use of time-dependent antimicrobials. The time-dependent antimicrobials used in 2 horses of this series were chosen on the basis of culture and susceptibility results. Further investigation of time-dependent antimicrobials delivered in this fashion is warranted.

The finding in this study that horses that received a total CIAI dose of antimicrobial ≥ 3,000 mg were less likely to perform their intended use should be interpreted with caution. This finding could reflect the requirement for an extended treatment period in chronic cases, resulting in greater articular and synovial damage during the infection process in these horses. However, there was no association between duration of CIAI or case chronicity and horses performing their intended use. The finding may also have been influenced by 3 horses with synovial infections (of 5 that did not perform their intended use) that received CIAI with amikacin at a concentration of 250 mg/mL. These 3 horses received a mean daily CIAI dose of 2,577 mg and a mean total CIAI dose of 16,917 mg of amikacin. Mean duration of infection prior to CIAI in these horses was 30 days, and 2 horses had associated osteomyelitis. All of these infections were resolved; however, the horses were lame at discharge and did not perform their intended use. The selection of a high concentration of amikacin (250 mg/mL) may have been made because of the severe nature of the cases. Alternatively, there may be a dose of intrasynovial antimicrobial that results in detrimental effects on the synovial cavity beyond that caused by synovial infection. The cutoff values for the statistical assessment were arbitrary and were chosen around the mean values for each category because this allowed an assessment of groups of similar number. A continuous variable evaluation was not performed on these categories, as the determination of fluid volume delivered through the continuous infusion system was made from the volume placed into the balloon minus that recovered at the end of treatment. This approach is an estimate that cannot account for the residual fluid remaining in the delivery tubing. Further investigation of individual antimicrobials and dosages for CIAI is warranted.

The unresolved infections in this report were all in the medial femorotibial joint and all had associated osteomyelitis. Studies that reveal a difference between affected joint and outcome in horses with septic synovitis are lacking, primarily because of an insufficient number of cases.[1] The number of cases in our report also precluded statistical comparison of affected joints. The size and complexity of the medial femorotibial joint, the intra-articular meniscus, and the variable communication with the other stifle joint pouches may have contributed to the persistent unresolved infections in this study.

A 6-month period was selected as a minimum for long-term follow-up evaluation in this study because some horses may take several months to fully resolve infection and optimally restore the synovial environment.[8] We believe that 6 months is a sufficient period for a horse with septic synovitis to be rehabilitated and assess whether the horse will be able to return to its intended use. The fact that our follow-up period extended to 52 months in some horses could alter the results in terms of horses successfully resuming activities and subsequently developing lameness secondary to the initial effects of septic synovitis (eg, osteoarthritis). The long-term assessment of horses in this study involved contact with trainers, owners, and referring veterinarians; clinical reevaluation by the attending clinician; and evaluation of available racing results. It was not possible to obtain follow-up information at the same time after treatment for each horse because of the methods of follow-up and the extended period over which the cases occurred and the horses were treated.

Results of recent studies evaluating septic synovitis in horses indicate survival rates in adults ranging from 81% to 92%[1,3,21,32] and survival rates in foals ranging from 42% to 78%.[1,4,32] Wright et al[21] treated contaminated and infected synovial cavities by use of endoscopic surgery, completing each procedure with an antimicrobial lavage of the synovial cavity. Osteomyelitis was diagnosed in 14% of those horses, wounds or punctures were evident in 79% of the horses treated, and 27% of the horses had duration of clinical signs > 1 week prior to surgery. In a study[3] of the use of open drainage and intra-articularly administered antimicrobials in treatment for septic synovitis, 73% of horses had an iatrogenic etiology, no horses had osteomyelitis, and 50% of horses had duration of disease > 1 week at the time of surgery. A report[1] of 192 cases of septic synovitis in horses had a more even representation of etiologies, with 35% iatrogenic, 34% hematogenous (foals), and 24% from wounds or punctures. The duration of clinical signs prior to treatment was not determined in that study; however, 52% of foals had evidence of osteomyelitis, and a variety of treatments were used during the study period. These studies are difficult to compare because of the varying etiology, chronicity, treatment approaches, and complicating factors in the treated horses. In view of the chronic, refractory nature of the cases in the present study, in which 94% of horses had duration of disease > 1 week at the time of initiating CIAI, 48% of horses had been refractory to standard treatments, and 31% of infections had associated osteomyelitis, we consider a 91%

survival rate in adults and an 89% survival rate in foals to support the use of intrasynovial antimicrobial administration during treatment of septic synovitis in horses. It should be recognized, however, that the present study did not have a controlled comparison group of horses in which CIAI was not used, and the historical perspective that the previously cited studies provided on the success of treating septic synovitis did not include a group of horses with chronic disease that were predominantly unresponsive to treatments used previously. We believe CIAI offers the advantage of convenience, enables maintenance of high intrasynovial antimicrobial concentrations, and should be considered as an alternative method of local antimicrobial delivery for chronic, refractory, or complicated cases of septic synovitis in horses.

a. Joint Infusion System, Mila International Inc, Florence, Ky.
b. SPSS, version 11.5, SPSS Inc, Chicago, Ill.
c. PfizerPen, Pfizer Inc, New York, NY.
d. Penicillin G Procaine Aqueous Suspension, GC Hanford Manufacturing Co, Syracuse, NY.
e. Ampicillin for injection, American Pharmaceutical Partners Inc, Schaumburg, Ill.
f. Amiglyde-V, Fort Dodge Animal Health, Fort Dodge, Iowa.
g. Gentamax 100, Phoenix Scientific Inc., St Joseph, Mo.
h. Sulfamethoxazole/trimethoprim, Mutual Pharmaceutical Co Inc, Philadelphia, Pa.
i. Baytril 100, Bayer Healthcare LLC, Shawnee Mission, Kan.
j. Viceton, Bimeda Inc, Riverside, Mo.
k. Vancoled, ESI Lederle Inc, Cherry Hill, NJ.
l. Doxycycline tablets, Ivax Laboratories Inc, Miami, Fla.
m. Naxcel, Pharmacia & Upjohn Co, Kalamazoo, Mich.
n. Ticar, Abbott Laboratories, Abbott Park, Ill.

References

1. Schneider RK, Bramlage LR, Moore RM, et al. A retrospective study of 192 horses affected with septic arthritis/tenosynovitis. *Equine Vet J* 1992;24:436–442.
2. Hague BA, Carter GK. Diseases of multiple bones and joints; inflammatory, infectious, and immune diseases. In: Colahan PT, Mayhew IG, Merritt AM, et al, eds. *Equine medicine and surgery*. 5th ed. St Louis: Mosby Inc, 1999;1447–1454.
3. Schneider RK, Bramlage LR, Mecklenburg LM, et al. Open drainage, intra-articular and systemic antibiotics in the treatment of septic arthritis/tenosynovitis in horses. *Equine Vet J* 1992;24:443–449.
4. Steel CM, Hunt AR, Adams PL, et al. Factors associated with prognosis for survival and athletic use in foals with septic arthritis: 93 cases (1987–1994). *J Am Vet Med Assoc* 1999;215:973–977.
5. Honnas CM, Schumacher J, Cohen ND, et al. Septic tenosynovitis in horses: 25 cases (1983–1989). *J Am Vet Med Assoc* 1991;199:1616–1622.
6. Vatistas NJ, Pascoe JR, Wright IM, et al. Infection of the intertubercular bursa in horses: four cases (1978–1991). *J Am Vet Med Assoc* 1996;208:1434–1437.
7. Wright IM, Phillips TJ, Walmsley JP. Endoscopy of the navicular bursa: a new technique for the treatment of contaminated and septic bursae. *Equine Vet J* 1999;31:5–11.
8. Bertone AL. Infectious arthritis. In: McIlwraith CW, Trotter GW, eds. *Joint disease in the horse*. Philadelphia: WB Saunders Co, 1996;397–409.
9. Lloyd KC, Stover SM, Pascoe JR, et al. Synovial fluid pH, cytologic characteristics, and gentamicin concentration after intra-articular administration of the drug in an experimental model of infectious arthritis in horses. *Am J Vet Res* 1990;51:1363–1369.
10. Whitehair KJ, Adams SB, Parker JE, et al. Regional limb perfusion with antibiotics in three horses. *Vet Surg* 1992;21:286–292.
11. Palmer SE, Hogan PM. How to perform regional limb perfusion in the standing horse, in *Proceedings*. 45th Annu Conv Am Assoc Equine Pract 1999;124–127.
12. Bertone AL. Update on infectious arthritis in horses. *Equine Vet Educ* 1999;11:143–152.
13. Summerhays GE. Treatment of traumatically induced synovial sepsis in horses with gentamicin-impregnated collagen sponges. *Vet Rec* 2000;147:184–188.
14. Lescun TB, Adams SB, Wu CC, et al. Continuous infusion of gentamicin into the tarsocrural joint of horses. *Am J Vet Res* 2000; 61:407–412.
15. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. *J Infect Dis* 1987;155:93–99.
16. Swanson TD. Guidelines for veterinary services and judging of endurance and competitive trail rides. In: *Guide for veterinary service and judging of equestrian events*. Lexington, Ky: American Association of Equine Practitioners, 1991;1–26.
17. Adams SB, Lescun TB. How to treat septic joints with constant intra-articular infusion of gentamicin or amikacin, in *Proceedings*. 46th Annu Conv Am Assoc Equine Pract 2000;188–192.
18. Moore RM, Schneider RK, Kowalski J, et al. Antimicrobial susceptibility of bacterial isolates from 233 horses with musculoskeletal infection during 1979–1989. *Equine Vet J* 1992;24:450–456.
19. Schurman DJ, Kajiyama G. Antibiotic absorption from infected and normal joints using a rabbit knee joint model. *J Orthop Res* 1985;3:185–188.
20. Murphey ED, Santschi EM, Papich MG. Regional intravenous perfusion of the distal limb of horses with amikacin sulfate. *J Vet Pharmacol Ther* 1999;22:68–71.
21. Wright IM, Smith MR, Humphrey DJ, et al. Endoscopic surgery in the treatment of contaminated and infected synovial cavities. *Equine Vet J* 2003;35:613–619.
22. Gibson KT, McIlwraith CW, Turner AS, et al. Open joint injuries in horses: 58 cases (1980–1986). *J Am Vet Med Assoc* 1989; 194:398–404.
23. Lescun TB, Adams SB, Wu CC, et al. Effects of continuous intra-articular infusion of gentamicin on synovial membrane and articular cartilage in the tarsocrural joint of horses. *Am J Vet Res* 2002;63:683–687.
24. Lloyd KC, Stover SM, Pascoe JR, et al. Effect of gentamicin sulfate and sodium bicarbonate on the synovium of clinically normal equine antebrachiocarpal joints. *Am J Vet Res* 1988;49:650–657.
25. von Eiff C, Jansen B, Kohnen W, et al. Infections associated with medical devices: pathogenesis, management and prophylaxis. *Drugs* 2005;65:179–214.
26. Bertone AL, McIlwraith CW, Jones RL, et al. Comparison of various treatments for experimentally induced equine infectious arthritis. *Am J Vet Res* 1987;48:519–529.
27. Gupta MN, Sturrock RD, Field M. Prospective comparative study of patients with culture proven and high suspicion of adult onset septic arthritis. *Ann Rheum Dis* 2003;62:327–331.
28. Madison JB, Sommer M, Spencer PA. Relations among synovial membrane histopathologic findings, synovial fluid cytologic findings, and bacterial culture results in horses with suspected infectious arthritis: 64 cases (1979–1987). *J Am Vet Med Assoc* 1991;198:1655–1661.
29. Adamson PJ, Wilson WD, Hirsh DC, et al. Susceptibility of equine bacterial isolates to antimicrobial agents. *Am J Vet Res* 1985; 46:447–450.
30. McCarthy HE, Singer ER, Davies MM. The effect of sodium heparin on equine articular cartilage. *Vet J* 2001;162:73–79.
31. Hirsh DC, Jang SS. Antimicrobic susceptibility of bacterial pathogens from horses. *Vet Clin North Am Equine Pract* 1987;3:181–190.
32. Meijer MC, van Weeren PR, Rijkenhuizen AB. Clinical experiences of treating septic arthritis in the equine by repeated joint lavage: a series of 39 cases. *J Vet Med A Physiol Pathol Clin Med* 2000;47:351–365.