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# Bacterial isolates, antimicrobial susceptibility patterns, and factors associated with infection and outcome in foals with septic arthritis: 83 cases (1998–2013)

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**Abstract**

**Objective**—To determine clinical characteristics, clinicopathologic data, and bacterial culture and antimicrobial susceptibility results associated with septic arthritis in foals ≤ 180 days old.

**Design**—Retrospective case series.

**Animals**—83 foals with septic arthritis.

**Procedures**—Medical records at 2 teaching hospitals between 1998 and 2013 were searched to identify those for foals ≤ 180 days old with confirmed infection of ≥ 1 synovial structure. Data extracted from the records included signalment, clinicopathologic information, bacteriologic culture and antimicrobial susceptibility results, and outcome. Data were analyzed for all foals as a single population and for foals stratified into 3 age groups (≤ 7 days, 8 to 30 days, and 31 to 180 days).

**Results**—Mean ± SD age of all foals was 18.2 ± 25 days (range, 0 to 180 days). The median number of joints affected per foal was 2 (range, 1 to 10 joints). Forty-seven of 83 (56.6%) foals survived to discharge from the hospital. Seventy antemortem synovial fluid samples underwent bacteriologic culture, of which 60 (85.7%) yielded growth. Of the 72 bacterial isolates identified, 45 (62.5%) were gram negative and 27 (375%) were gram positive. Survival rate was positively associated with plasma fibrinogen concentration and negatively associated with number of affected joints.

**Conclusions and Clinical Relevance**—Results indicated the frequency with which certain bacterial agents were isolated from septic joints, which may be beneficial for the empirical treatment of septic arthritis in foals. Also, the positive association between survival rate and plasma fibrinogen concentration may have prognostic value in a clinical setting.

**Disciplines**

Large or Food Animal and Equine Medicine | Statistical Methodology | Veterinary Infectious Diseases | Veterinary Microbiology and Immunobiology | Veterinary Pathology and Pathobiology

**Comments**

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**Results**—Mean ± SD age of all foals was 18.2 ± 25 days (range, 0 to 180 days). The median number of joints affected per foal was 2 (range, 1 to 10 joints). Forty-seven of 83 (56.6%) foals survived to discharge from the hospital. Seventy antemortem synovial fluid samples underwent bacteriologic culture, of which 60 (85.7%) yielded growth. Of the 72 bacterial isolates identified, 45 (62.5%) were gram negative and 27 (37.5%) were gram positive. Survival rate was positively associated with plasma fibrinogen concentration and negatively associated with number of affected joints.

**Conclusions and Clinical Relevance**—Results indicated the frequency with which certain bacterial agents were isolated from septic joints, which may be beneficial for the empirical treatment of septic arthritis in foals. Also, the positive association between survival rate and plasma fibrinogen concentration may have prognostic value in a clinical setting. (*J Am Vet Med Assoc* 2015;246:785–793)

Septic arthritis is a common complication of sepsis in foals and results in prolonged treatment and substantial medical expense and is associated with a poor prognosis.[1,2] In neonatal foals, septic arthritis is most commonly caused by hematogenous dissemination of bacteria, but extension of an infection from adjacent infected soft tissues or penetrating wounds or infection by iatrogenic routes is also possible.[1,3] In older foals (> 7 days old), septic arthritis can be caused by various bacteria. Older foals are particularly susceptible to infection with *Rhodococcus equi*, which can cause extrapulmonary disorders. In 1 study,[4] 14 of 150 (9%) foals > 30 days old with confirmed *R equi* infection developed septic arthritis. Rates of survival to discharge for foals admitted to various veterinary hospitals for treatment of septic arthritis range from 45% to 84%.[2,5,6] Foals that recover from septic arthritis are at increased risk of developing degenerative joint disease that will impair athletic performance, compared with foals that did not have septic arthritis.[6,7]

**Abbreviation**

| | |
|---|---|
| TNCC | Total nucleated cell count |

Although foals with septic arthritis may have no overt signs of systemic illness, foals with lameness or joint effusion are considered to have infectious orthopedic disease until proven otherwise.[8,9] Early identification and treatment improve the odds for a successful outcome in foals with septic arthritis.[1] Foals with septic arthritis are routinely treated empirically with antimicrobials on the basis of the attending veterinarian's suspicion of the causative agent while awaiting the results of bacteriologic culture of synovial fluid samples and antimicrobial susceptibility testing. Because synovial infection in foals is generally the result of hematogenous bacterial dissemination, bacteria associated with bacteremia would presumably be the most common bacterial isolates from infected joints. In a 1989 retrospective study[10] of 47 foals < 8 days old with bacterial septicemia, gram-negative bacteria were isolated from all foals. However in subsequent studies[11,12] of critically ill foals < 1 month old, the percentage of foals from

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which gram-negative bacteria were isolated from blood samples ranged from 57% to 66%, whereas the percentage of foals from which gram-positive bacteria were isolated from blood samples ranged from 34% to 40%. Gram-negative bacteria such as *Escherichia coli*, *Actinobacillus* spp, and *Klebsiella* spp are more commonly isolated from the joints of foals with septic arthritis than are gram-positive bacteria such as *Staphylococcus* spp and *Streptococcus* spp.[3,5] However, in 1 study,[2] gram-positive bacteria (26/34 [76%]) were isolated more frequently than were gram-negative bacteria (8/34 [24%]) from the joints of foals with septic arthritis. Differences in the ages of the foals evaluated in those studies[2,3,5] may account for the apparently conflicting results because, in foals, infections caused by gram-negative bacteria develop most frequently in the neonatal period, whereas infections caused by gram-positive bacteria generally occur after the neonatal period.[1]

Although studies[9,13] have been conducted to assess variables associated with bacterial isolates from adult horses with infectious orthopedic disease and foals with osteomyelitis, to our knowledge, studies to identify variables associated with septic arthritis in foals or evaluate the comprehensive antimicrobial susceptibility patterns for the bacteria that commonly cause septic arthritis in foals have not been performed. Information, including the antimicrobial susceptibility results, for bacterial pathogens commonly isolated from the joints of foals with septic arthritis and the age at which infections caused by a specific bacterium generally occur would help clinicians develop empirical treatment protocols for such foals. The objective of the study reported here was to determine the clinical characteristics, clinicopathologic data, and bacteriologic culture and antimicrobial susceptibility results associated with septic arthritis in foals of 3 age groups (≤ 7 days, 8 to 30 days, and 31 to 180 days).

## Materials and Methods

**Case selection**—The medical record databases of the Lloyd Veterinary Medical Center at Iowa State University and the Purdue University Veterinary Teaching Hospital were searched for records of foals ≤ 180 days old that were treated for septic arthritis between January 1998 and September 2013. Foals were included in the study if septic arthritis was definitively diagnosed on the basis of the currently recommended criteria.[1,3] Briefly, each foal had to have ≥ 1 of the following: bacterial growth from culture of a synovial fluid sample or biopsy specimen, synovial fluid TNCC ≥ 30,000 cells/µL, or the presence of suppurative or fibrinous inflammation within a joint during postmortem examination. Foals that were treated for septic arthritis on the basis of a high index of suspicion that did not meet the inclusion criteria or that had a history of trauma or other orthopedic conditions such as flexural or angular limb deformities and fractures were excluded from the study. Presumptive history from the owner that the mare stepped on the foal was not considered cause for exclusion from the study.

**Medical records review**—Only data that contributed to the diagnosis of septic arthritis were analyzed for each foal. Information extracted from each medical record included the foal's age, breed, sex, WBC count, segmented and band neutrophil counts, plasma fibrinogen concentration (determined by heat precipitation), synovial fluid TNCC and protein concentration, bacteriologic culture results of blood (if performed) and synovial samples, the number of affected joints, and whether the foal survived to discharge from the hospital. For samples from which bacteria were cultured, antimicrobial susceptibility results were also recorded.

**Bacterial culture and susceptibility testing**—For foals treated at Iowa State University, all synovial fluid samples were cultured directly on aerobic blood agar, MacConkey agar, anaerobic blood agar, and Columbia nalidixic acid agar; 50 to 100 µL of each sample was inoculated onto each agar plate. Additionally, 0.5 mL of each sample was added to 5 mL of brain-heart infusion broth for enrichment. In vitro antimicrobial susceptibility testing was performed with the Kirby-Bauer disk diffusion method until 2008 and a diagnostic microbiology system[a] thereafter.

For foals treated at Purdue University, 10 µL of each synovial fluid sample was inoculated onto a blood agar plate and a MacConkey agar plate. Enrichment was only performed on request, and information regarding which samples were enriched was not available. When performed, enrichment included inoculation of a tube of thioglycollate broth with 10 µL of synovial fluid, incubation for 7 days, and subculturing if growth was present. In vitro antimicrobial susceptibility testing was performed with a diagnostic microbiology system,[a] and the minimum inhibitory concentration for each isolate and antimicrobial combination was determined by a broth microdilution method in accordance with the National Accrediting Agency for Clinical Laboratory Sciences and Clinical and Laboratory Standards Institute guidelines.

For summary purposes, bacterial isolates were categorized as susceptible, intermediate, or resistant to individual antimicrobials. Isolates classified as susceptible were those that are inhibited by the usually achievable concentration of the antimicrobial under consideration when it is administered at the recommended dose for the site of infection. Isolates for which the minimum inhibitory concentration of the antimicrobial under consideration approached usually attainable concentrations in the target tissue following administration of the recommended dose, but for which the response rate might be lower than that for susceptible isolates were classified as intermediate. Isolates classified as resistant were those that were not inhibited by the usually achievable concentration of the antimicrobial under consideration when it is administered at the recommended dose for the target tissue.

**Statistical analysis**—For analysis purposes, all foals were assessed as a single population and then categorized by age into 3 groups (≤ 7 days old, 8 to 30 days old, and 31 to 180 days old). The ≤ 7 days old category was selected because bacteremia and septicemia are the most important risk factors for septic arthritis in neonatal foals and foals with confirmed sepsis are most commonly ≤ 7 days old.[1,14–16] The 8 to 30 days old category was selected because foals are at less risk of developing sepsis during this period, compared with the period from birth to ≤ 7 days old.[15,16] The 31 to 180

days old category was selected because septic arthritis caused by *R equi* most commonly occurs during this period.[17,18] No differentiation was made between foals that died and those that were euthanized, regardless of reason.

Outcomes of interest included the number of joints affected, WBC count, segmented and band neutrophil counts, plasma fibrinogen concentration, synovial fluid TNCC and protein concentration, bacteriologic culture and antimicrobial susceptibility results, and short-term survival rate (ie, survival to hospital discharge). Descriptive data were provided. The respective associations between age and each of the categorical variables were assessed by means of Fisher exact tests. Linear models were used to identify variables associated with each of the quantitative outcomes of interest. Prior to analysis, a logarithmic transformation was applied to the data for WBC count, segmented neutrophil count, plasma fibrinogen concentration, and synovial fluid TNCC to account for multiplicative variation in the distributions of those variables. Data for the band neutrophil count and the number of joints affected were analyzed by means of Wilcoxon score–based nonparametric tests (Wilcoxon 2-sample rank sum tests or Kruskal-Wallis multiple-sample tests) because they did not have normal distributions, even after transformation. Logistic regression was used to assess the association of various explanatory variables with survival to discharge (yes or no). Mixed models with a random effect for foal were used when necessary to account for repeated measures within the same animal. Post hoc pairwise comparisons were performed by means of Tukey *t* tests (for *F* tests in linear models) or Bonferroni-adjusted Wilcoxon rank sum tests (for nonparametric Kruskal-Wallis tests). Analyses were performed with statistical software,[b] and values of $P \leq 0.05$ were considered significant.

## Results

**Foals**—During the study period, 5,552 foals (3,992 from Iowa State University and 1,560 from Purdue University) ≤ 180 days old were examined, of which 83 were eligible for inclusion in the study. The study population included 36 male and 47 female foals. The mean ± SD age of all foals was 18.2 ± 25 days (range, < 1 to 180 days old); 5 foals were < 24 hours old at the time of hospital admission. At the time of admission, 34 foals were ≤ 7 days old, 36 were between 8 and 30 days old, and 13 were between 31 and 180 days old. Breeds represented included Quarter Horse (n = 33), Thoroughbred (11), Paint (10), Standardbred (7), Miniature (4), Percheron (3), Arabian (2), Belgian (2), Saddlebred (2), and Appaloosa, Clydesdale, Haflinger, Lusitano, Oldenburg, Pony of the Americas, Tennessee Walking Horse, warmblood, and mixed breed (1 each). The clinicopathologic variables for the foals were summarized (**Table 1**). The mean WBC count, segmented neutrophil count, and plasma fibrinogen concentration for foals ≤ 7 days old were significantly ($P < 0.001$) lower, compared with the corresponding values for foals between 8 and 30 days old and foals between 31 and 180 days old. The mean band neutrophil count and synovial fluid TNCC and protein concentration did not differ significantly among the age groups.

**Affected joints**—The study population had 196 affected synovial structures, with the tarsal joint being the structure most frequently affected (**Table 2**). Thirty-eight foals had 1 joint affected; 18 foals had 2 joints affected; 10 foals had 3 joints affected; 4 foals had 4 joints affected; 5 foals had 5 joints affected; 2 foals each had 6, 7, and 8 joints affected; and 1 foal had 10 joints affected. The number of joints affected for 1 foal was not available. The median number of joints affected per foal for foals between 31 and 180 days old was significantly ($P = 0.002$) less than that for foals ≤ 7 days old and foals between 8 and 30 days old.

**Bacteriologic culture and antimicrobial susceptibility testing**—One hundred seventeen synovial fluid samples were obtained for cytologic analysis or bacteriologic culture. Of the 70 antemortem synovial fluid samples that underwent bacteriologic culture, growth was detected in 60 (85.7%) samples and no growth was detected in 10 (14.3%) samples. Seventy-two bacte-

Table 1—Clinicopathologic variables for 83 foals with septic arthritis that were treated at 2 veterinary teaching hospitals between January 1998 and September 2013.

| | | Age category | | |
|---|---|---|---|---|
| **Variable** | **All foals** | **≤ 7 days old** | **8–30 days old** | **31–180 days old** |
| No. of foals | 83 | 34 | 36 | 13 |
| Age (d) | 18.2 ± 25 | 2 (0–7) | 17 (7–30) | 49 (31–180) |
| WBC count (cells/µL) | 15,786 ± 31,208 | 6,700 (636–20,900)[a] | 14,905 (2,080–281,000)[b] | 12,800 (5,380–45,600)[b] |
| Segmented neutrophil count (cells/µL) | 20,600 ± 7,918 | 4,869 (90–34,275)[a] | 12,618 (1,120–33,750)[b] | 9,728 (2,860–38,760)[b] |
| Band neutrophil count (cells/µL) | 432 ± 878 | 90 (0–3,410) | 0 (0–5,360) | 0 (0–1,290) |
| Fibrinogen (mg/dL) | 578 ± 257 | 400 (155–1,200)[a] | 600 (149–1,200)[b] | 616 (412–1,100)[b] |
| Synovial fluid TNCC (cells/µL) | 68,718 ± 74,276 | 31,500 (1,500–86,786) | 63,490 (560–343,000) | 37,015 (5,760–93,880) |
| Synovial fluid protein (g/dL) | 3.9 ±1.2 | 3.4 (2.2–7.5) | 3.7 (2.5–5.6) | 3.7 (2.7–5.3) |
| No. of gram-positive isolates | 18 | 7 | 7 | 4 |
| No. of gram-negative isolates | 37 | 16 | 17 | 4 |
| No. (%) of foals that survived to discharge | 47 (56.6) | 16 (47) | 22 (61) | 9 (69) |

Values in the all foals column represent the mean ± SD, and those in the other columns represent the median (range) unless otherwise indicated.

[a,b]Within a row, values with different superscripts differ significantly ($P < 0.05$).

To be included in the study, each foal had to have ≥ 1 of the following: bacterial growth from culture of a synovial fluid sample or biopsy specimen, synovial fluid TNCC ≥ 30,000 cells/µL, or the presence of suppurative or fibrinous inflammation within a joint during postmortem examination.

rial isolates were identified, of which 45 (62.5%) were gram-negative organisms and 27 (37.5%) were gram-positive organisms (**Table 3**). One bacterial isolate was cultured from each of 53 samples, 2 bacterial isolates were cultured from each of 7 samples, and 3 bacterial isolates were cultured from 1 sample. The number of gram-positive or gram-negative organisms cultured did not differ significantly among the 3 age groups. Infection with a gram-positive or gram-negative organism was not significantly associated with the WBC count, synovial fluid TNCC or protein concentration, number of joints affected per foal, or survival to hospital discharge. Results of antimicrobial susceptibility testing were summarized (**Table 4**).

Blood samples from 19 foals (age, < 1 to 21 days) were submitted for bacteriologic culture. Bacterial growth was detected in 13 of those samples, and 20 isolates were identified (data not shown). For foals that had bacteriologic cultures performed on both blood and synovial fluid samples that yielded growth, the same bacterial isolate was identified in both samples for 6 foals (*A equuli* [n = 2 foals], *Klebsiella* spp [2], *Salmonella* spp [1], and *Morganella morganii* [1]), whereas the bacteria isolated from the blood differed from that isolated from the synovial fluid for 7 foals. *Rhodococcus equi* was isolated from synovial samples from only 3 foals in the 31 to 180 days old group; those foals were 49, 61, and 74 days old when admitted to the hospital. Survival to discharge was not associated with positive results on bacteriologic culture of blood.

Table 2—Frequency distribution of infected synovial structures for the foals of Table 1.

| | | Age group | | |
|---|---|---|---|---|
| **Synovial structure** | **All foals** | **≤ 7 days old** | **8–30 days old** | **31–180 days old** |
| Tarsal joint | 76 (38.8) | 40 (44.4) | 33 (35.5) | 3 (23.1) |
| Metacarpophalangeal or metatarsophalangeal joint | 31 (15.8) | 17 (18.9) | 11 (11.8) | 3 (23.1) |
| Stifle joint | 41 (20.9) | 14 (15.6) | 20 (21.5) | 7 (53.8) |
| Carpal joint | 24 (12.2) | 11 (12.2) | 13 (14.0) | 0 (0.0) |
| Proximal interphalangeal joint | 5 (2.6) | 3 (3.3) | 2 (2.2) | 0 (0.0) |
| Distal interphalangeal joint | 1 (0.5) | 1 (1.1) | 0 (0.0) | 0 (0.0) |
| Hip joint | 3 (1.5) | 1 (1.1) | 2 (2.2) | 0 (0.0) |
| Shoulder joint | 5 (2.6) | 0 (0.0) | 5 (5.4) | 0 (0.0) |
| Elbow joint | 4 (2.0) | 0 (0.0) | 4 (4.3) | 0 (0.0) |
| Tendon sheath | 5 (2.6) | 2 (2.2) | 3 (3.2) | 0 (0.0) |
| Unidentified or unavailable in medical record | 1 (0.5) | 1 (1.1) | 0 (0.0) | 0 (0.0) |
| **Total No. of structures affected** | **196** | **90** | **93** | **13** |
| Median (range) No. of structures affected/foal | 2 (1–10) | 2 (1–8)[a] | 1.5 (1–10)[a] | 1 (1–2)[b] |

Values represent the No. (%) unless otherwise indicated.
Within a column, percentages may not sum to 100 because of rounding.
*See* Table 1 for remainder of key.

Table 3—Frequency distribution of 72 bacterial isolates cultured from the infected synovial structures of the foals of Table 1.

| **Gram stain result** | **Category** | **Isolate** | **No. (%)** |
|---|---|---|---|
| Gram negative | Enterobacteriaceae | *Escherichia coli* | 13 (18.1) |
| | | *Proteus* spp | 1 (1.4) |
| | | *Enterobacter aerogenes* | 2 (2.8) |
| | | *Enterobacter cloacae* | 2 (2.8) |
| | | Unspeciated *Enterobacter* spp | 2 (2.8) |
| | | *Klebsiella pneumoniae* | 2 (2.8) |
| | | *Klebsiella oxytoca* | 4 (5.6) |
| | | *Salmonella enterica* serovar Typhimurium | 1 (1.4) |
| | | Unspeciated salmonellae | 2 (2.8) |
| | | *Morganella morganii* | 1 (1.4) |
| | | *Raoultella planticola* | 1 (1.4) |
| | Other gram-negative isolates | *Actinobacillus equuli* | 9 (12.5) |
| | | *Actinobacillus suis* | 2 (2.8) |
| | | *Pasteurella multocida* | 1 (1.4) |
| | | *Bacteroides fragilis* | 1 (1.4) |
| | | *Chryseobacterium meningosepticum* | 1 (1.4) |
| Gram positive | Coagulase-negative staphylococci | *Staphylococcus epidermidis* | 6 (8.3) |
| | | Unspeciated staphylococci | 2 (2.8) |
| | Streptococci | α-Hemolytic streptococci | 5 (6.9) |
| | | Unspeciated β-hemolytic streptococci | 1 (1.4) |
| | | *Streptococcus zooepidemicus* | 4 (5.6) |
| | Other gram-positive isolates | *Enterococcus* spp | 3 (4.2) |
| | | *Rhodococcus equi* | 3 (4.2) |
| | | *Clostridium perfringens* | 1 (1.4) |
| | | *Corynebacterium* spp | 1 (1.4) |
| | | *Micrococcus* spp | 1 (1.4) |

Percentages do not sum to 100% because of rounding.
*See* Table 1 for remainder of key.

Table 4—Number (%) of bacterial isolates cultured from the synovial structures of the foals of Table 1 that were classified as susceptible, intermediate, or resistant to various antimicrobials.

| | Gram-negative isolates | | | Gram-positive isolates | | |
|---|---|---|---|---|---|---|
| **Antimicrobial** | **Susceptible** | **Intermediate** | **Resistant** | **Susceptible** | **Intermediate** | **Resistant** |
| Amikacin | 28 (82.4) | 1 (2.9) | 5 (14.7) | 12 (57.1) | 2 (9.5) | 7 (33.3) |
| Amoxicillin–clavulanic acid | 7 (58.3) | 1 (8.3) | 4 (33.3) | 8 (80.0) | 0 (0) | 2 (20.0) |
| Cefazolin | 19 (55.9) | 0 (0) | 15 (44.1) | 13 (61.9) | 3 (14.3) | 5 (23.8) |
| Cefotaxime | 11 (61.1) | 0 (0) | 7 (38.9) | 9 (64.3) | 0 (0) | 5 (35.7) |
| Cefoxitin | 5 (100) | 0 (0) | 0 (0) | 3 (60.0) | 0 (0) | 2 (40.0) |
| Cefpodoxime | 8 (61.5) | 1 (7.7) | 4 (30.8) | 7 (70.0) | 1 (10.0) | 2 (20.0) |
| Ceftazidime | 5 (71.4) | 0 (0) | 2 (28.6) | 1 (33.3) | 1 (33.3) | 1 (33.3) |
| Ceftiofur | 4 (57.1) | 0 (0) | 3 (42.9) | 3 (75.0) | 0 (0) | 1 (25.0) |
| Cephalothin | 25 (75.8) | 1 (3.0) | 7 (21.2) | 14 (66.7) | 0 (0) | 7 (33.3) |
| Ciprofloxacin | 16 (57.1) | 4 (14.3) | 8 (28.6) | 11 (64.7) | 1 (5.9) | 5 (29.4) |
| Clindamycin | 5 (71.4) | 0 (0) | 2 (28.6) | 7 (100.0) | 0 (0) | 0 (0) |
| Chloramphenicol | 0 (0) | 2 (7.1) | 26 (92.9) | 8 (47.1) | 3 (17.6) | 6 (35.3) |
| Doxycycline | 12 (63.2) | 2 (10.5) | 5 (26.3) | 13 (92.9) | 0 (0) | 1 (7.1) |
| Enrofloxacin | 3 (42.9) | 0 (0) | 4 (57.1) | 2 (50.0) | 1 (25.0) | 1 (25.0) |
| Erythromycin | 28 (93.3) | 0 (0) | 2 (6.7) | 16 (80.0) | 4 (20.0) | 0 (0) |
| Gentamicin | 4 (11.8) | 9 (26.5) | 21 (61.8) | 10 (47.6) | 6 (28.6) | 5 (23.8) |
| Imipenem | 26 (76.5) | 2 (5.9) | 6 (17.6) | 14 (66.7) | 2 (9.5) | 5 (23.8) |
| Marbofloxacin | 13 (92.9) | 0 (0) | 1 (7.1) | 7 (100.0) | 0 (0) | 0 (0) |
| Neomycin | 7 (100) | 0 (0) | 0 (0) | 2 (100.0) | 0 (0) | 0 (0) |
| Orbifloxacin | 9 (56.3) | 4 (25.0) | 3 (18.8) | 5 (71.4) | 0 (0) | 4 (28.6) |
| Ormetroprim-sulfadimethoxine | 7 (100) | 0 (0) | 0 (0) | — | — | — |
| Oracillin 2% NaCl | 3 (60.0) | 0 (0) | 2 (40.0) | 5 (71.4) | 2 (28.6) | 0 (0) |
| Penicillin | 5 (18.5) | 0 (0) | 22 (81.5) | 11 (64.7) | 0 (0) | 6 (35.3) |
| Rifampin | 2 (5.9) | 3 (8.8) | 29 (85.3) | 9 (42.9) | 1 (4.8) | 8 (38.1) |
| Sulfachloropyridazine | 10 (31.3) | 2 (6.3) | 20 (62.5) | 20 (95.2) | 1 (4.8) | 0 (0) |
| Tetracycline | 13 (81.3) | 0 (0) | 3 (18.8) | 4 (57.1) | 1 (14.3) | 2 (28.6) |
| Ticarcillin | 23 (69.7) | 1 (3.0) | 9 (27.3) | 11 (52.4) | 3 (14.3) | 7 (33.3) |
| Ticarcillin–clavulanic acid | 19 (57.6) | 1 (3.0) | 13 (39.4) | 15 (71.4) | 1 (4.8) | 5 (23.8) |
| Trimethoprim-sulfa | 18 (69.2) | 4 (15.4) | 4 (15.4) | 12 (85.7) | 0 (0) | 2 (14.3) |
| Vancomycin | 25 (73.5) | 0 (0) | 9 (26.5) | 17 (81.0) | 1 (4.8) | 3 (14.3) |

— = Not assessed.

The antimicrobials included in the susceptibility test varied among bacterial isolates; therefore, the number of isolates classified within each antimicrobial varies. The percentage of isolates within each classification represents the percentage for gram-negative or gram-positive isolates. Isolates classified as susceptible were those that are inhibited by the usually achievable concentration of the antimicrobial under consideration when it is administered at the recommended dose for the site of infection. Isolates for which the minimum inhibitory concentration of the antimicrobial under consideration approached usually attainable concentrations in the target tissue following administration of the recommended dose, but for which the response rate might be lower than that for susceptible isolates were classified as intermediate. Isolates classified as resistant were those that were not inhibited by the usually achievable concentration of the antimicrobial under consideration when it is administered at the recommended dose for the target tissue.

*See* Table 1 for remainder of key.

Table 5—Median (range) values for various variables of the foals of Table 1 that did (n = 47) and did not (36) survive to hospital discharge.

| **Variable** | **Foals that survived to discharge** | **Foals that did not survive** | ***P* value** |
|---|---|---|---|
| Age (d) | 12 (0–180) | 7 (0–90) | 0.33 |
| WBC count (cells/µL) | 12,735 (2,540–281,100) | 10,915 (636–35,900) | 0.26 |
| Segmented neutrophil count (cells/µL) | 9,332 (430–38,760) | 8,780 (90–33,750) | 0.18 |
| Band neutrophil count (cells/µL) | 0 (0–3410) | 80 (0–5,360) | 0.42 |
| Fibrinogen (mg/dL) | 600 (200–1200) | 465 (149–1200) | 0.01 |
| Synovial fluid TNCC (cells/µL) | 49,250 (560–343,000) | 19,200 (1,500–114,000) | 0.17 |
| Synovial fluid protein (g/dL) | 3.7 (2.2–6.4) | 3.7 (2.4–7.5) | 0.95 |
| No. of joints affected | 1 (1–8) | 3 (1–10) | < 0.001 |

*See* Table 1 for key.

**Survival analysis**—Forty-seven of 83 (56.6%) foals survived to discharge, and the proportion of foals that survived to discharge did not differ significantly among the 3 age groups (Table 1). The medians of various variables for foals that did and did not survive to discharge were summarized (**Table 5**). Survival to discharge was not associated with the WBC count, segmented or band neutrophil count, synovial fluid TNCC or protein concentration, or type of infection (gram negative vs gram positive). Survival to discharge was positively associated with plasma fibrinogen concentration ($P = 0.014$) and negatively associated with the number of joints affected ($P < 0.001$). When the model was adjusted for the effect of age, the positive association between survival to discharge and plasma fibrinogen concentration remained significant ($P = 0.05$). The probability that a foal survived to hospital discharge increased 25% (OR, 1.25; 95% confidence interval, 1.03 to 1.55) for every 100 mg/dL increase in plasma fibrinogen concentration. Conversely, the probability that a foal survived to

hospital discharge decreased by 50% (OR, 0.50; 95% confidence interval, 0.33 to 0.71) for every additional joint that was affected. The probability of survival to discharge did not differ between foals that were treated at Iowa State University and those treated at Purdue University, nor did it differ by year during the study period.



## Discussion

Similar to human infants, foals are more susceptible to hematogenous infection of synovial structures than are adult horses because they have transphyseal vessels that can transport bacteria into joints, whereas adult horses and humans have separate blood supplies to the metaphysis and epiphysis.[1,19] Foals with septic arthritis are frequently encountered in clinical settings and the disease can have devastating consequences on the future athletic performance of affected horses. Thus, the presence and severity of septic arthritis have a substantial impact on decisions regarding the treatment or euthanasia of affected foals. Musculoskeletal disease, including septic arthritis, was the most common cause of death in a survey[20] of 2,468 foals from 167 farms, and results of another study[21] indicate a significant association between septic arthritis and death in bacteremic foals. In the present study, a number of important findings regarding septic arthritis were identified that might facilitate its diagnosis and treatment and aid in determining the short-term prognoses for affected foals.

In the foals of the present study, gram-negative bacteria were isolated from affected joints more frequently than were gram-positive bacteria, a finding that was similar to the results of most other studies in the literature, although in 1 study,[2] gram-positive bacteria were isolated more frequently than were gram-negative bacteria from the joints of foals with septic arthritis. *Staphylococcus* spp are the bacteria most frequently isolated from the joints of children with septic arthritis[22,23] and adult horses with septic arthritis secondary to intra-articular injections, penetrating wounds, idiopathic infections, and surgical procedures.[5] The different routes by which joints generally become infected in foals (hematogenous) versus adult horses (direct inoculation) likely contribute to the difference in the types of bacteria (gram negative vs gram positive) isolated from those joints. In the present study, age was not significantly associated with the isolation of either gram-negative or gram-positive organisms from the infected joint; however, results of another study[20] indicate that gram-negative bacteremia and sepsis were more prevalent in younger foals than in older foals. Enterobacteriaceae are commonly isolated from bacteriologic cultures of blood, and *E coli* is the most common cause of bacteremia in neonatal foals.[21,24] Given that the joints of foals are generally infected by the hematogenous route, it is not surprising that *E coli* was the most common gram-negative bacteria isolated from the septic joints of the foals in the present study as well as other studies.[2,3,7] Thirty-one of 45 (69%) gram-negative organisms isolated from the joints of the foals of the present study belonged to the family Enterobacteriaceae, which highlights the importance and frequency of involvement of this bacterial family in the development of septic arthritis. Therefore, clinicians should select antimicrobials that are effective against Enterobacteriaceae for the empirical treatment of foals with septic arthritis. Interestingly, 13 foals of the present study had bacteria cultured from a blood sample; however, in the majority (n = 7) of those foals, the bacteria isolated from the blood sample differed from that isolated from the synovial fluid sample. This finding suggested that it is important to perform bacteriologic culture of both blood and synovial fluid in overtly ill foals.

Definitive diagnosis of septic arthritis can be difficult because of the lack of established diagnostic criteria for synovial fluid variables, the low number of bacteria frequently cultured from infected synovial structures, and nonspecific changes in hematologic and biochemical analyses.[1–3,6,7,21] Consequently, a variety of diagnostic criteria have been used to diagnose septic arthritis in foals, which has inevitably led to discrepancies in the estimates of its true prevalence.[1–3,7] The cutoffs used as criteria to diagnose septic arthritis range from 5,000 to 30,000 cells/µL for synovial fluid TNCC and 2.5 to 4 g/dL for synovial fluid protein concentration.[1–3,7,25] In a study[26] in which synovial fluid changes were compared among healthy horses and horses with osteochondritis dissecans, traumatic noninfectious synovitis, and infectious synovitis, the highest mean synovial fluid neutrophil count ($380 \times 10^3$ neutrophils/µL) and protein concentration (6.2 g/dL) were observed for horses with infectious synovitis, although the ranges for those variables overlapped considerably with the ranges of the corresponding variables for horses with traumatic noninfectious synovitis. In another study,[5] the mean synovial WBC count was $76.49 \times 10^3$ WBCs/µL for 192 horses with septic arthritis or tenosynovitis. Although the clinical tendency may be to assume a positive association between severity of disease and synovial fluid TNCC or protein concentration, this assumption has yet to be validated.[2,5] Survival was not significantly associated with either synovial fluid TNCC or protein concentration in the present study or another study[2] of 81 foals with septic arthritis. In the study[5] of horses with septic arthritis or tenosynovitis, the proportion (30/66 [45%]) of foals < 6 months that survived was significantly lower than the proportion of adult horses that survived (107/126 [85%]); however, the synovial fluid TNCC did not differ significantly between foals and adult horses.

Although culture of bacteria from synovial fluid provides a definitive diagnosis of septic arthritis, the proportion of synovial fluid samples from foals with septic arthritis that yielded bacterial growth ranged from 45% to 78% in other studies.[1–3,7,27] Bacteria were isolated from 60 of the 70 (86%) synovial fluid samples that were submitted for bacteriologic culture in the present study. It is possible that the strict inclusion criteria used for the foals in this study contributed to the higher proportion of culture-positive synovial fluid samples, compared with that of other studies.[1–3,7,27] Interestingly, bacteriologic culture of a synovial biopsy specimen is even less rewarding than bacterio-

logic culture of a synovial fluid sample. In a study[27] of 64 horses with suspected infectious arthritis, bacteria were isolated from 52% of synovial fluid samples and only 36% of synovial membrane biopsy specimens. Of the 17 horses that had bacteriologic culture performed on both a synovial fluid sample and synovial membrane biopsy specimen in that study,[27] 16 had positive results for the synovial fluid sample, whereas only 1 had positive results for the synovial membrane biopsy specimen. In a study[28] that involved dogs with experimentally induced septic arthritis, bacteria were cultured from 8 of 9 synovial fluid samples but only 6 of 9 synovial membrane specimens, although this difference was not significant. Additionally in that study,[28] incubation of synovial fluid samples in blood culture medium for 24 hours before initiation of culture resulted in bacterial growth from all samples.

The number of joints affected per foal (mean ± SD, 2.4 ± 2 joints) in this study was similar to that of another study.[2] Results of other studies[2,9] indicate that the joints most commonly affected in foals with septic arthritis are the tarsocrural and femorotibial joints. In the foals of the present study, the tarsal and stifle joints comprised 76 (39%) and 41 (21%), respectively, of the 196 affected joints. In children with septic arthritis, the hip joint is the joint most commonly affected because of the shared metaphyseal and epiphyseal blood supply and the intracapsular nature of the femoral metaphysis.[19] In the present study, only 3 of the 196 (1.5%) affected joints were hip joints, a finding that was similar to the results of other studies[2,7] of foals with septic arthritis in which the hip joint represented only 2.3% and 2.6% of the affected joints. Differences in the anatomy and skeletal maturation may explain the apparent differences in predilection sites for septic arthritis between foals and children. In neonatal foals, blood vessels connect the metaphyseal and epiphyseal blood supplies together. However, those vessels generally close when foals are between 7 and 10 days old, which may explain why the foals in the oldest age group (31 to 180 days old) of the present study had fewer affected joints than did the foals in the other 2 age groups (≤ 7 and 8 to 30 days old). The close proximity of the physis and metaphysis to the capsule in the femorotibial and tarsocrural joints may contribute to the frequency with which those joints are infected in both foals and human patients. Additionally, the large size of these joints, compared with the size of the proximal and distal interphalangeal joints, may account for the higher frequency of diagnosis because joint effusion is more easily detected.

Unlike adult horses with septic arthritis, foals with septic arthritis frequently have evidence of substantial systemic inflammation.[5] In foals, plasma fibrinogen concentrations between 500 and 800 mg/dL are often associated with septic arthritis and nonrhodococcal pneumonia.[29] For the foals of the present study, the probability of survival to hospital discharge was positively associated with plasma fibrinogen concentration but was not significantly associated with peripheral WBC count. Results of multiple studies[15,30,31] have failed to indicate a significant association between the likelihood of survival and plasma fibrinogen concentration. In studies that involved foals with neonatal sepsis[32] and acute colitis,[33] the mean plasma fibrinogen concentration was higher for foals that survived, compared with that for foals that did not survive, although that difference was not significant. Conversely, in another study of critically ill foals,[34] a fibrinogen concentration increased from the basal level was identified as a predictor of death. However, in a study[35] of human neonates with sepsis, mean fibrinogen concentration was higher in survivors than that in nonsurvivors. In the present study, mean WBC count, segmented neutrophil count, and plasma fibrinogen concentration were significantly lower for foals ≤ 7 days old, compared with those for the foals in the other 2 age groups, which suggested that concurrent systemic disease (ie, sepsis) may be more common at younger ages.

Treatment of septic arthritis in neonatal foals involves lavage and surgical debridement of the affected synovial structure and systemic and localized antimicrobial administration. Selection of an antimicrobial for the treatment of foals with septic arthritis should take into account the antimicrobial susceptibility profile of the causative pathogen as well as the potential adverse effects of the drug. Results of the antimicrobial susceptibility testing for the isolates of the present study suggested that aminoglycosides (eg, amikacin and gentamicin) and various cephalosporins would be reasonable options for the empirical treatment of foals with septic arthritis presumed to be caused by gram-negative organisms. Gram-positive organisms had variable susceptibility to commonly administered antimicrobials; 17 of 21 (81%) gram-positive isolates tested were susceptible to trimethoprim-sulfamethoxazole combinations, whereas only 14 (67%) were susceptible to ceftiofur. Many of the isolates of the present study appeared to be susceptible to fluoroquinolones in vitro, including ciprofloxacin, enrofloxacin, marbofloxacin, and orbifloxacin; however, the detrimental effects of fluoroquinolones on developing cartilage should preclude their use in foals unless absolutely warranted.[36,37] Susceptibility to cephalosporins varied between gram-negative and gram-positive bacteria. Because the later (third or later) generations of cephalosporins have an increased gram-negative spectrum, compared with that of the first and second generations of cephalosporins, ceftiofur, cefpodoxime, and ceftazidime may be more appropriate choices for the empirical treatment of septic arthritis in foals.[38] The limited number of isolates tested for susceptibility against some of the antimicrobials assessed in the present study might have skewed the data; thus, selection of an antimicrobial for the empirical treatment of foals with septic arthritis solely on the basis of these findings is not recommended.

Septic arthritis is the most common cause of lameness in foals and can have devastating consequences, which can include death and decreased future athletic performance.[1,3,5] The survival rate (56.6% [47/83]) for the foals of the present study was consistent with those (45% to 78%) reported by investigators of other stud-

ies[5,7,21] of foals with septic arthritis. Foals with septic arthritis that are treated and survive frequently do not achieve their full performance potential, which may explain why many foals with septic arthritis are euthanized without attempting aggressive treatment.[6] In a study[6] examining future performance of foals treated for septic arthritis, although 58 of 69 (84%) foals with septic arthritis survived, only 23 of those foals went on to start ≥ 1 race during their lifeline, and foals that survived septic arthritis were significantly ($P = 0.008$) less likely to start a race than were their unaffected siblings (OR, 0.36).

The major limitation of the present study was its retrospective nature, which has inherent biases. Some medical records were incomplete, which resulted in data sets that did not have entries for all study subjects. Foals that did not survive to hospital discharge were analyzed together, regardless of the role that financial constraints may have had on the decision to euthanize versus treat. It is likely that patients with a poor prognosis and high estimated treatment costs were more likely to be euthanized, thus skewing the proportion of foals that survived to discharge. The inclusion criteria may have been excessively stringent and limited the number of cases included in the study, which could have potentially skewed the data. The specific cell populations identified in the synovial fluid samples were not analyzed because of inconsistencies in the performance of cytologic analyses. For example, foals that had synovial fluid samples with a low TNCC, of which a high percentage of cells were neutrophils, may have been excluded from the study population, despite being considered septic by other standards. Because the study population included foals treated at 2 facilities, the variables measured and culture methodologies varied, which made comparisons for some variables difficult. It is possible that additional associations might have been identified had a larger population been assessed. The number of subjects in this study limited the power to detect significant differences between rates of infection with gram-positive and gram-negative bacteria; a larger study is necessary to better elucidate those frequencies.

In the present study, differences and similarities in multiple variables were identified among age groups for foals with septic arthritis. Although age group (≤ 7, 8 to 30, and 31 to 180 days old) was not significantly associated with the type of bacteria (gram negative or gram positive) cultured from the affected joints, gram-negative bacteria were cultured from the synovial fluid of affected joints more frequently than were gram-positive bacteria, and *E coli* was the organism most commonly isolated from all age groups. The probability of survival to discharge did not differ significantly among the 3 age groups; however, it was negatively associated with the number of joints affected. The mean number of joints affected per foal was significantly lower for foals in the 31 to 180 days old group, compared with that for foals in the other 2 groups. Interestingly, the probability of survival to discharge from the hospital was positively associated with plasma fibrinogen concentration but not with the other hematologic variables and synovial fluid characteristics assessed. To our knowledge, this study is the first to indicate a significant positive association between the probability of short-term survival and plasma fibrinogen concentration in foals with septic arthritis and that provided a description of the antimicrobial susceptibility results for bacterial isolates commonly cultured from the septic joints of foals. This information may be helpful during the initial assessment and empirical treatment of foals with septic arthritis.

a. TREK Sensititre, Thermo Scientific, Westlake, Ohio.
b. SAS, version 9.3, SAS Institute Inc, Cary, NC.

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