

# Analysis of factors influencing prognosis in foals with septic arthritis

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The purpose of this paper was to identify factors that would positively or negatively affect the short-term survival rate of foals with septic arthritis. Medical records of 81 foals ( $\leq$  seven months of age) with a clinical diagnosis of septic arthritis, referred to the equine hospital at Cornell University Hospital for Animals, between 1994 and 2003 were reviewed. Signalment, age at presentation, number of affected joints, joint fluid parameters, bacterial agents, treatment modalities and year of treatment were compared between survivors and non-survivors. Sixty-two of 81 foals (77%) were discharged from the hospital and classified as 'survivors'. Multiple joint involvement and detection of intra-articular Gram-negative, mixed bacterial infection and degenerate neutrophils were negatively associated with short-term survival. Initiation of treatment within 24hrs of onset of clinical signs and combination of treatment modalities were positively correlated with survival. Further investigation is needed to determine if these two factors have a similar influence on athletic performance.

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## Introduction

Septic arthritis is a potentially debilitating condition associated with significant morbidity and mortality in foals (Martens *et al.*, 1986). The source of infection may be haematogenous, extension from adjacent soft tissue or bony infection, or it may be caused by perforating trauma, either accidental or iatrogenic in origin (Martens *et al.*, 1986; Schneider *et al.*, 1992a; Schneider, 2006). Clinical signs of affected foals include moderate to severe lameness, joint distension and pain on flexion of the affected joint. Additional clinical abnormalities observed may be related to the infection's origin, which can be localised near the joint (adjacent infection, trauma, laceration), more remote (infection of umbilical structures, enteritis, lower airway infection), or systemic in nature (septicaemia) (Leitch, 1985; Martens *et al.*, 1986; Schneider *et al.*, 1992a; Meijer *et al.*, 2000). Final diagnostic confirmation is obtained by positively identifying bacterial agents on cytology or from cultures of synovial fluid or membrane (Bertone, 1996). Clinical case documentation shows that bacterial culture results from synovial fluids are negative in 33-60% of septic arthritis cases (Madison *et al.*, 1991; Honnas *et al.*, 1992; Schneider *et al.*, 1992b; Meijer *et al.*, 2000). A recent study demonstrated that both incubation of synovial fluid in a blood culture medium (BCM) and a polymerase chain reaction test (PCR) are more specific and sensitive methods of confirming synovial infection in horses. Therefore, diagnosing septic arthritis in clinical practice is based on the aforementioned

clinical signs combined with a synovial fluid cytology which shows a white blood cell count (predominantly neutrophils) greater than 5,000 cells/ $\mu$ l (Mahaffey, 2002) and total protein concentration above 2.5 g/dl (Steel *et al.*, 1999).

The principles of treatment of septic arthritis are early recognition, removal of infected tissue/fluids (thorough joint lavage, arthroscopy, arthrotomy, closed suction drainage) and appropriate antimicrobial therapy (Ross *et al.*, 1991; Bertone *et al.*, 1992; Honnas *et al.*, 1992; Schneider *et al.*, 1992a, 1992b; Baxter, 1996; Meijer *et al.*, 2000; Wright, 2003). The high mortality rate (22-58%) associated with septic arthritis despite treatment emphasises its clinical importance (Schneider *et al.*, 1992b; Steel *et al.*, 1999; Meijer *et al.*, 2000). Treatment survivors can have persistent osteoarthritis and lameness (Martens *et al.*, 1986; Goodrich and Nixon, 2004) with a reduced likelihood of ever starting in a race compared to controls (Smith *et al.*, 2004).

The authors of this paper hypothesised that there is a positive effect of the combination of treatment modalities such as arthroscopy, arthrotomy, regional deposition of antibiotics (intra-articular and regional perfusion) to improve chances for short-term survival as compared to treatment consisting of joint lavage and systemic antibiotics alone. In addition, the authors wished to identify factors negatively associated with short-term survival in a population of foals with septic arthritis diagnosed by practitioners and subsequently referred to a university hospital.

## Materials and methods

Medical records of 81 foals ( $\leq$  seven months old) with a recorded diagnosis of septic arthritis referred to the Cornell University Veterinary Hospital between January 1, 1994 and January 1, 2004 were retrieved and reviewed. Foals were included in this study if two or more of the following criteria were met: clinical signs of septic arthritis (e.g., joint distension, lameness); positive results for bacterial culture from synovial fluid; synovial fluid protein concentration  $>2.5$  g/dl;  $>5,000/\mu\text{l}$  nucleated cells in synovial fluid; and, radiographic evidence of osteomyelitis affecting the epiphysis or physis on initial radiographs. The following information was retrieved from the medical records: year of admission; age; gender; breed; duration of condition prior to admission; number of swollen joints and anatomical location; rectal temperature at admission; records documenting the presence of umbilical infection, pneumonia, and/or enteritis; cytological examination of synovial fluid (total protein concentration, nucleated cell count, percentage of macrophages and degenerate neutrophils and red blood cell count); and, results of bacterial culture (aerobic and anaerobic). In addition, type and frequency of treatments, as well as days of hospitalisation, were recorded. Treatments performed included through-and-through needle joint lavage, arthrotomy, arthroscopy, regional intravenous perfusion, local implantation of antibiotic-impregnated polymethylmethacrylate (AIPMMA) beads and intra-articular antimicrobial treatment. The presence of associated diseases following diagnosis of septic arthritis was recorded, for example septicaemia or an infectious process at a remote site (umbilical and urachal infection). Finally, an epiphyseal or physal infection was recorded as present if radiolucent areas were seen on initial radiographs. Survival was defined as discharged from the hospital alive. For statistical purposes, the foals were classified in two groups. Group one consisted of foals that were discharged from the hospital alive (survivors). Group two consisted of foals that, despite treatment in the hospital, did not survive (non-survivors). The data relating to the foals were compared by using the Chi Square test or Fisher's exact test, as appropriate, for qualitative (dichotomous) parameters (sex, breed, rectal temperature [fever or not], presence of osteomyelitis, treatment combinations performed per foal and duration of condition prior to admission [greater than

or equal to 24hrs or not]). The Mann Whitney U test and Student's t-test, as appropriate, were used for comparison of quantitative (continuous) parameters (number of survivors/non-survivors, age, year of admission, number of swollen joints per foal, number of hind limbs/front limb joints infected, number of single/multiple joints infected, number of pure Gram-positive/pure Gram-negative infections, number of multiple/single bacterial infections, number of invasive treatments such as needle-through-and-through joint lavages, arthroscopies and arthrotomies, and number of days of hospitalisation). The synovial fluid cytology results (total protein level, nucleated cell count, red blood cell count, percentage of degenerate neutrophils and percentage of macrophages) were compared between both groups, using the Wilcoxon rank sum test and Student's t-test. Statistical comparisons were performed using computer software (SPSS@12.0; SPSS Inc., Chicago, IL, USA). The level of significance was set at  $P \leq 0.05$ .

## Results

Sixty-two (77%) of the 81 foals were discharged from the hospital. The number of survivors was significantly larger ( $n=62$ ) than the non-survivors ( $n=19$ ) ( $P < 0.0001$ ). There were no sex or breed differences between the survivor and non-survivor groups. The median age of the survivors (24 days; range 1-207) was not significantly different from the non-survivors (15 days; range 3-127). Although the number of foals brought to the hospital increased significantly towards the end of the 1990s, there was not a significant effect on the overall survival rate in foals admitted in the first half of the study compared to the second half. The total number of infected joints in all 81 foals was 151. The group of survivors had significantly more single joint infections (43 out of 62 foals; 69%) compared with the non-survivor group (four out of 19 foals; 21%) ( $P < 0.0001$ ). Conversely, the mean number of infected joints per foal was significantly larger in the non-survivor group (2.84 joints; range 1-8) compared to the survivors (1.56 joints; range 1-6) ( $P < 0.05$ ). **Table 1** shows the number and anatomical location of the septic joints in the foal population. The location of the infected joints did not differ between survivors and non-survivors. Osteomyelitis was diagnosed more often in the non-survivor group (53%), when compared to the survivor group (13%) ( $P = 0.001$ ). The results of synovial fluid analysis are summarised in

Table 1: Location of affected joints in 81 foals with septic arthritis

Joint affected	Number of infected joints in survivor group	Number of infected joints in non-survivor group	Total number of infected joints
Tarsus	37	15	52
Femoropatellar/femorotibial	24	13	37
Metacarpo/metatarso-phalangeal	13	8	21
Distal interphalangeal	2	1	3
Carpus	17	13	30
Scapulohumeral	1	0	1
Coxofemoral	2	2	4
Cubital	1	2	3
Total	97	54	151

**Table 2.** A significantly greater percentage of degenerate neutrophils were seen in the joints of non-survivor foals (70%), as compared to survivors (50%) ( $P=0.028$ ). The mean red blood cell count in the infected joints of survivors ( $243.87 \times 10^3$  cells/ $\mu\text{l}$ ) was greater than in the non-survivors ( $94.90 \times 10^3$  cells/ $\mu\text{l}$ ) ( $P=0.018$ ). However, the nucleated cell count, percentage of macrophages and total protein concentration were not significantly different between the two groups.

Overall, more pure Gram-positive bacterial infections (26) were confirmed than Gram-negative infections (8) ( $P=0.043$ ). Pure Gram-positive cultures were seen more often in the survivor group (22 out of 46; 48%) than in the non-survivor group (four out of 13; 31%) ( $P=0.045$ ). In contrast, pure Gram-negative cultures were seen more often in the non-survivor group (six out of 13; 46%) compared to the survivor group (two out of 46; 4%) ( $P<0.0001$ ). Multiple bacterial species cultures were more numerous in the non-survivor group (three out of 13 submitted synovial fluid samples; 23%) compared with the survival group (three out of 46 submitted synovial fluid samples; 7%) ( $P=0.05$ ). Only one was positive on anaerobic culture, a *Clostridium perfringens* infection within the non-survivor group of foals. Within the group of survivors, *Streptococcus zooepidemicus* and *Staphylococcus aureus* were more commonly isolated (10 out of the 46 submitted samples). Within the non-survivor group, *Enterobacteriaceae* (especially *Escherichia coli*) were most commonly isolated (4 out of 13 submitted samples). Time of initiation of treatment in relation to onset of clinical signs was documented in 50 of the foals. All but one of the 15 foals (93%) that were treated at the hospital within 24hrs of recognition of clinical signs survived, while 23 (66%) of the 35 foals whose treatment was delayed (range 24hrs to 10 days) survived. After 24 hours, the time of initiation of treatment after onset of clinical signs was not significantly different between survivors (mean 6.6 days; range 1-42 days) and non-survivors (mean 4.5 days; range 2-10 days).

All the foals were treated with systemic antibiotics upon arrival. In general, a combination of sodium penicillin G (22,000 IU/kg IV, every 6hrs) and amikacin sulphate (21 mg/kg IV, every 24hrs) or gentamicin sulphate (6.6 mg/kg IV, every 24hrs) was initiated as a broad-spectrum

**Table 2:** Results of 174 joint synovial fluid analyses obtained from 81 foals with a clinical diagnosis of septic arthritis stratified within hospital survivor and non-survivor foal groups.

Parameters	Survivors	Non-survivors
	Mean ( $\pm$ s.d.) n=number of samples	
Total protein (g/dl)	3.74 (5.9) (n=172)	3.55 (4.1) (n=40)
Nucleated cells count ( $10^3$ cells/ $\mu\text{l}$ )	42.83 (313) (n=170)	45.57 (165) (n=34)
Degenerate Neutrophils* (%)	50.4 (50) (n=49)	69.7 (55) (n=7)
% Macrophages	16.7 (31) (n=23)	13.8% (44) (n=6)
Red blood cell count * ( $10^3$ cells/ $\mu\text{l}$ )	243.87 (3271) (n=169)	94.90 (410) (n=40)

\*Significantly different at  $P<0.05$ .

antibiotic treatment before identification of the causative agent was established. Multiple other treatment modalities were often used in combination: through-and-through needle joint lavage (n=66), arthroscopy (n=12), arthrotomy (n=16), regional intravenous perfusion (n=6), intra-articular antibiotic administration (n=34) and implantation of an antimicrobial carrier beads (AIPMMA) (n=6). The number of joint lavage treatments (4.71; range 1-18) and joint lavages per joint (2.99; range 1-8) was greater in the survivor group and lower in the non-survivor group (7.45, range 1-36; and 4.05, range 1-15, respectively) ( $P<0.05$ ). Significantly more survivors (15 out of 62; 24%) were treated with arthrotomy than non-survivors (one out of 19; 5%) ( $P=0.048$ ). Twelve out of 62 (19%) survivors were treated with arthroscopy but none of the 19 non-survivors were ( $P=0.038$ ). Within the survivor group, 52 foals (84%) received a combination of invasive procedures, for example a joint lavage and an arthrotomy or an arthroscopy and local perfusion techniques, whereas only one combination (joint lavage and arthrotomy) was carried out in the non-survivor group ( $P<0.001$ ). The median hospitalisation time for survivors was 10 days compared to three days for the non-survivors ( $P=0.01$ ).

## Discussion

Interpretation of the results of this study must be informed by the certainty of diagnosis, because joint infections are difficult to confirm through bacterial culture. Many reports have established a range of 0 to 60% for the false negative rate from bacterial culture of synovial fluid (Madison *et al.*, 1991; Honnas *et al.*, 1992; Schneider *et al.*, 1992b; Meijer *et al.*, 2000). Therefore, the diagnosis was made based on a combination of clinical signs and cytological examination of the synovial fluid. It is therefore possible that some joints were inflamed and not septic or no longer infected at the time of presentation. Retrospective studies, such as this one, allow assessment of the usefulness of diagnostic procedures developed over time. Relatively new diagnostic techniques, such as PCR, show a far better sensitivity than previously available methods (Pille *et al.*, 2007). However, as Pille *et al.* (2007) reported, even these new diagnostics do have shortcomings in sensitivity, specificity, costs and the sheer complexity of the techniques described. In addition, interpretation of the present study's findings should be made in the knowledge that treatments were not randomly assigned and other factors, such as perceived value of the animal or financial limits of the owner and surgeon's individual treatment preference, might have influenced treatment selection and/or survival rate. Finally failure, or partial failure, of passive transfer of immunity is a major risk for septicaemia, multi-systemic disease and septic arthritis and responses to treatment (Becht and Semrad 1992; Raidal 1996). In this study, the failure of passive transfer was not documented reliably in the medical records. The mortality rate of 23% and survival rate of 77% in this study compared favourably with previous reports (22-58%) (Schneider *et al.*, 1992a, 1992b; Meijer *et al.*, 2000) and was very similar to the report of Steel *et al.* (1999) with a 78%

survival rate in a 93-foal population. As previously reported, the age at admission to the hospital, gender, and breed were not statistically significant in relation to prognosis (Martens *et al.*, 1986; Schneider *et al.*, 1992a; Meijer *et al.*, 2000; Smith *et al.*, 2004).

The authors did, however, identify several factors that were associated with survival rate. As others have reported, the number of infected joints was important, as foals with only one joint affected were more likely to survive (Schneider *et al.*, 1992a, 1992b; Steel *et al.*, 1999; Meijer *et al.*, 2000). This may reflect the animal's systemic condition (e.g., septicæmia, immune status), rather than the difficulties associated with the successful local treatment of more than one infected joint. Furthermore, the decreased activity associated with multiple joint infections may lead to formation of decubital sores, decreased appetite and, hence, sub-optimal nutritional support.

Septic arthritis has been termed a medical emergency (Koch, 1979; Madison *et al.*, 1991; Bertone *et al.*, 1992). The present study revealed an increased chance of survival when treatment was initiated within 24hrs. As far as the authors are aware, no other data have been reported that relate to the timing of treatment. It is thought that other factors came into play when the time lapse before initiation of treatment was extended beyond 24hrs, as the survival rate decreased (from 93% to 66%) after that period. Perhaps this is because appropriate treatments were only initiated in some foals after 24hrs. One should also consider that the more valuable the foals were, the more likely they were to be admitted to the hospital within 24hrs of recognition of clinical signs and perhaps had environmental conditions superior to foals presented after 24hrs.

The results of synovial fluid (Table 2) show a range with regards to the mean values. The range clearly shows a large overlap in individual parameters between the two groups and points out that synovial fluid parameters ideally should be used in combination with each other in order to have any predictable value. The percentage of degenerate neutrophils in relation to nucleated cells was higher in non-survivors than survivors, making it a negative indicator for survival. An increase in nucleated cells (> 5,000 cells/ $\mu$ l (Mahaffey, 2002) is clearly a hallmark of septic arthritis in any species, but especially in horses. The toxic effects of bacteria on neutrophils make degenerate neutrophils typical in septic exudates. Indeed, degenerate neutrophils are more numerous surrounding a microcolony in a septic joint (Bertone *et al.*, 1992; Mahaffey, 2002). The elevated percentage of degenerate neutrophils in non-survivors likely indicates a more advanced or virulent infection, which is consistent with the negative association finding for survival in this study (Mahaffey, 2002).

The finding that Gram-positive infections were more frequent in this study differs from previous reports (Bertone *et al.*, 1992; Schneider *et al.*, 1992a; Steel *et al.*, 1999). The reason for this difference is unknown but might reflect regional geographic differences. This study agreed with previous reports that Gram-negative infections were more prevalent in non-survivors and are associated with a

poor prognosis (Wright and Scott, 1989; Schneider *et al.*, 1992a, 1992b; Meijer *et al.*, 2000). Additionally, infection with multiple bacterial-type species in the synovial fluid worsens the prognosis for foals with septic arthritis (Madison *et al.*, 1991; Bertone *et al.*, 1992; Schneider *et al.*, 1992a). Finally, osteomyelitis is often seen in foals with septic arthritis (Trotter, 1996). This study suggests that the presence of osteomyelitis worsens the prognosis, since the incidence of osteomyelitis was significantly higher in the non-survivor group.

It is difficult to assess which treatment has more value in managing septic arthritis since randomisation was not performed in this study. However, supplemental treatments beyond joint lavage and systemic antibiotics, such as arthrotomy, arthroscopy and regional intravenous perfusion, were performed more frequently in survivors, suggesting an added value. The study also suggests that higher morbidity was not associated with more aggressive therapies. This is consistent with other authors who have advocated the use of arthrotomy (Bertone *et al.*, 1992), arthroscopy (McIlwraith and Fessler, 1978; Wright and Scott, 1989; Wright, 2003), regional perfusion (Whitehair *et al.*, 1992; Santschi *et al.*, 1998; Schneider, 2006) and antibiotic-impregnated beads (Calhoun and Malder 1989; Farnsworth *et al.*, 2001; Ducharme and Mitchell, 2004) to facilitate in the treatment of septic arthritis in horses.

## Conclusion

In conclusion, initiation of prompt treatment within 24hrs is of particular significance in foals with signs of septic arthritis. Lack of response to joint lavage and systemic antibiotics should lead to consideration of additional treatment modalities such as regional delivery of antibiotics, arthroscopy and/or arthrotomy, since these treatment modalities significantly improved chances for survival.

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