J Vet Intern Med 2006;20:569–574

Prognostic Value of Clinicopathologic Variables Obtained at Admission and Effect of Antiendotoxin Plasma on Survival in Septic and Critically Ill Foals

Simon F. Peek, Sue Semrad, Sheila M. McGuirk, Ase Riseberg, Jo Ann Slack, Fernando Marques, Dane Coombs, Laura Lien, Nicholas Keuler, and Benjamin J. Darien

This prospective study compared survival rates of critically ill and septic foals receiving 1 of 2 different types of commercial equine plasma and analyzed admission variables as possible predictors of survival. Standardized clinical, hematologic, biochemical, and hemostatic admission data were collected and foals received either conventional commercially available hyperimmune equine plasma or equine plasma specifically rich in antiendotoxin antibodies in a double-blinded, coded fashion. Sepsis was defined as true bacteremia or sepsis score >11. Overall survival rate to discharge was 72% (49/68). Foals that were nonbacteremic and demonstrated a sepsis score of ≤11 at admission had a 95% (18/19) survival rate. The survival rate to discharge for septic foals was 28/49 (57%), with truly bacteremic foals having a survival rate of 58% (14/24), whereas that for nonbacteremic, septic foals was 56% (14/25). Sensitivity and specificity for sepsis score >11 as a predictor of bacteremia were 74 and 52%, respectively. For the entire study population, a higher survival rate to discharge was documented for those foals receiving hyperimmune plasma rich in antiendotoxin antibodies ($P = .012$, odds ratio [OR] 6.763, 95% confidence interval [CI]: 1.311, 34.903). Administration of plasma rich in antiendotoxin antibodies also was associated with greater survival in septic foals ($P = .019$, OR 6.267, 95% CI: 1.186, 33.109). Statistical analyses demonstrated that, among 53 clinical and clinicopathologic admission variables, high sepsis score ($P < .001$), low measured IgG concentration ($P = .01$), high fibrinogen concentration ($P = .018$), low segmented neutrophil count ($P = .028$), and low total red blood cell numbers ($P = .048$) were the most significant predictors of overall mortality.

Key words: Plasma; Sepsis; Systemic inflammatory response syndrome.

Neonatal septicemia is the most common cause of death in foals during the 1st week of life.[1–5] A strict consensus definition for sepsis in horses has not been established, but the terms sepsis, septic, and septicemia often are used in the literature interchangeably. In human medicine, sepsis, severe sepsis, systemic inflammatory response syndrome (SIRS), multiple-organ dysfunction (MODS), and septic shock are terms that have been developed to describe the sequentially worsening systemic pathology and impaired organ homeostasis that occurs as a consequence of an infectious process that causes the release of inflammatory mediators into the systemic circulation.[6,7] Similar criteria have been used to describe sepsis in adult horses and foals.[8] In the majority of cases, the inciting cause is a bacterial infection, but it can occur due to viral, fungal, or parasitic infections.[7,8] In foals, bacterial sepsis, commonly associated with failure of passive transfer, and primary gastrointestinal and pneumonic conditions are the most likely causes of sepsis and septic shock.[4,8] Although much of the available literature focuses on the role of gram-negative bacterial infections and endotoxin in the pathogenesis of sepsis, clinical signs of disease and multiple-organ dysfunction are seen with both gram-positive and gram-negative infections.[2,3,4,8] Previous studies examining survival rates in critically ill foals admitted to referral hospitals in the United States have documented survival rates that vary widely.[1–5] These studies have been predominantly retrospective in design and, in those instances in which prospective information was collected,[2,3] it was done to examine the prognostic value of specific clinicopathologic variables rather than approaches to treatment. Several referral practices and university hospitals throughout the world devote considerable resources, time, and effort to the treatment of neonatal foals at considerable financial cost to owners, but there is very little data from controlled studies to validate or confirm many of the commonly used components of therapy for critically ill foals. Although the use of equine plasma of varying types in the treatment and prevention of septicemia in foals is commonplace, only 1 prospective study compared the efficacy of different plasma types in hospitalized foals.[9] Consequently, we designed a double-blinded, prospective clinical study to examine the effect of 2 different plasma types in the treatment of neonatal septicemia in foals. One of the plasma types was a commonly used, commercially available hyperimmune equine plasma product,[a] and the 2nd was a product obtained from mares that had been hyperimmunized with a core mutant gram-negative *Escherichia coli* isolate and which contained much higher concentrations of antilipopolysaccharide (anti-LPS) antibody compared with the

From the Departments of Medical Sciences, University of Wisconsin-Madison, School of Veterinary Medicine, 2015 Linden Drive, Madison, WI (Peek, Semrad, McGuirk, Riseberg, Slack, Marques, Coombs, Lien, Darien); and the Department of Computing and Biometry, University of Wisconsin-Madison, College of Agriculture and Life Sciences, 1210 West Dayton Street, Madison, WI (Keuler). *Results from this study were presented in part at the 22nd Annual Forum of The American College of Veterinary Internal Medicine, in Minneapolis, MN, June 2004, and the 50th Annual Convention of The American Association of Equine Practitioners in Denver, CO, December 2004.*

Reprint requests: Simon F. Peek, BVSc, MRCVS, Diplomate ACVIM (Internal Medicine), PhD, Department of Medical Sciences, School of Veterinary Medicine, University of Wisconsin, Madison, WI 53706; e-mail: peeks@svm.vetmed.wisc.edu.

Submitted March 4, 2005; Revised July 6, August 24, October 7, 2005; Accepted October 7, 2005.

0891-6640/06/2003-0015/$3.00/0

conventional product.[b] The hypothesis was that survival of critically ill and septic foals would be enhanced by the administration of plasma rich in anti-LPS antibodies. Furthermore, by obtaining a standardized clinicopathologic data set from each foal at admission, we were able to analyze 53 variables as possible predictors of survival for 96 hours after hospitalization as well as to discharge from the hospital.

Materials and Methods

Animals

Foals referred for treatment to the Veterinary Medical Teaching Hospital (VMTH) at the University of Wisconsin during the 2002, 2003, and 2004 foaling seasons provided the case material for this study. All foals <7 days of age admitted to the neonatal intensive care unit (ICU) were eligible for the study.

Sample Collection

Each foal underwent a standardized series of clinicopathologic tests at admission, including CBC, serum sodium, potassium, chloride, calcium, total protein, phosphorus, magnesium, aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (AP), glucose, total CO_2, anion gap, creatine kinase (CK), creatinine, blood urea nitrogen (BUN), antithrombin III (ATIII), fibrinogen degradation products (FDP), 1 stage prothrombin time (OSPT), activated prothrombin time (APTT), endotoxin concentration assay,[c] and selenium concentration. An individual sepsis score was calculated for each individual according to the modified system of Brewer and Koterba.[1] Passive transfer of humoral immunity was assessed at the time of admission by a foal-side semiquantitative assay[d] and specifically quantitated by radioimmunodiffusion of IgG using a simultaneously acquired serum sample. Both aerobic and anaerobic blood cultures[e] were obtained at admission. In cases in which antimicrobials had been administered before referral, antibiotic filtration resins[f] were used to maximize chances for a positive culture.

Each foal received 1 of 2 commercial equine hyperimmune plasma products[a,b] immediately after initial admission tests were performed regardless of passive immunity status. Foals >25 kg in body weight received 2 L administered consecutively over the 1st 6–24 hours of therapy, whereas foals <25 kg received 1 L. Plasma bags were heparinized with 2,000 IU/L of heparin[g] before administration. Plasma was stored frozen at 0°C and thawed in warm water (approximately 25°C) immediately before use. Plasma administration was performed in a double-blinded fashion under code, with the coding system preserved for the entire 3 years of the study.

Initial antimicrobial treatment was standardized as follows:

(a) If serum creatinine concentration was <5 mg/dL at admission: potassium penicillin at 22,000 IU/kg IV q6h, and amikacin at 20 mg/kg IV q24h.
(b) If serum creatinine concentration was >5 mg/dL or the foal was anuric at admission: potassium penicillin at 22,000 IU/kg IV q6h and cefazolin at 20 mg/kg IV q8h.

Flunixin meglumine also was administered at 0.25 mg/kg IV q8h for the 1st 24 hours of hospitalization. All other treatments (eg, fluids, pressor agents, anticonvulsants) varied during hospitalization on a case-by-case basis.

Survival was described in 2 ways: 1st as survival to 96 hours from hospitalization and 2nd to discharge from the hospital.

Statistical Analyses

Analysis of Sepsis Score. For each foal in the study, the sepsis score on admission was determined as previously described.[1] The sensitivity and specificity of a sepsis score >11 compared with a gold standard of positive blood culture was calculated.

Survival Data and Comparisons between Plasma Types. A total of 53 variables were examined for prognostic value between surviving and nonsurviving foals. The following clinical and clinicopathologic variables were examined using admission data from each foal: pulse rate, rectal temperature, respiratory rate, total white blood cell count, segmented neutrophil count, band neutrophil count, presence or absence of metamyelocytes, lymphocyte count, monocyte count, eosinophil count, basophil count, presence or absence of toxic changes in neutrophils, red blood cell count, hemoglobin concentration, hematocrit, platelet count, packed cell volume, presence or absence of abnormal erythrocyte morphology, anion gap, sodium, potassium, chloride, calcium, phosphorus, magnesium, carbon dioxide, glucose, BUN, creatinine, albumin, globulin, total bilirubin, total protein, fibrinogen, as well as serum enzyme activities for AP, CK, AST, and GGT. In addition, AT III, OSPT, APTT, FDP concentration, whole-blood selenium concentration, IgG quantitation (by radial immunodiffusion [RID]), and endotoxin concentration also were examined for prognostic value using admission samples. Additional variables included from admission data were volume of plasma administered, body weight, sepsis score, presence or absence of a positive blood culture, gram-positive or gram-negative organism, year of the study, and plasma type administered.

For each of the variables measured, the 68 study foals initially were tested to determine whether recipients of the 2 different plasma types were approximately identical in all measurable respects. Continuous and categorical variables were screened using *t*-tests and chi-squared tests, respectively. The treatment groups were found to be significantly different for 3 of the 53 variables screened (sodium higher by 3.33 mEq/L in the group receiving plasma rich in anti-LPS antibody, $P = .049$; temperature higher by 1.09°F in the group receiving conventional hyperimmune plasma, $P = .053$; and anion gap, higher by 2.98 mEq/L in the group receiving plasma rich in anti-LPS antibody, $P = .083$). Because of the existence of these possible confounding variables, the evaluation of differences in the 2 plasma treatment groups was corrected by fitting a logistic regression model on survival that included all 3 confounders in addition to the plasma effect. For comparison purposes, the uncorrected analyses were performed as well using Fisher's test. Survival rates to 96 hours of hospitalization and discharge from the hospital for foals receiving the 2 different plasma types were compared for the following groups:

(a) The entire study population (n = 68).
(b) Foals that were bacteremic at admission (n = 24).
(c) Foals that either were bacteremic or had sepsis scores >11 at admission (septic foals; n = 46).
(d) Foals that were not bacteremic and that had sepsis scores ≤11 at admission (n = 22).

Analysis of Admission Variables as Potential Predictors of Survival. This analysis was performed as a 2-step procedure:

(a) All 53 variables initially were screened by comparing the mean values for foals that survived versus foals that died. Each variable was examined independently using a *t*-test for continuous variables and a chi-squared test for categorical variables. The necessary *P*-value to progress to the next step was arbitrarily set at .4.
(b) The pool of variables with *P*-values <.4 from step (a) was analyzed by logistic regression in a forward-selection procedure. The 1st term added to the survival model was that which had the lowest associated *P*-value from step (a). The next term added was that which achieved the smallest *P*-value when added to the

Table 1. Survival data for foals receiving hyperimmune equine plasma rich in anti-lipopolysaccharide antibodies (plasma a) or conventional equine hyperimmune plasma (plasma b).

	Overall Survival						
	Lived			Died			
	Plasma a	Plasma b	Total Lived (%)	Plasma a	Plasma b	Total Died	Grand Total
Septic foals	17	11	28 (61%)	8	10	18	46
Not septic foals	10	11	21 (95%)	1	0	1	22
All foals	27	22	49 (72%)	9	10	19	68
Bacteremic foals	8	6	14 (58%)	5	5	10	24
Gram-negative foals	4	4	8 (57%)	2	4	6	14
	Survival to 96 hours						
	Lived			Died			
	Plasma a	Plasma b	Total Lived (%)	Plasma a	Plasma b	Total Died	Grand Total
Septic foals	18	12	30 (65%)	7	9	16	46
Not septic foals	11	11	22 (100%)	0	0	0	22
All foals	29	23	52 (76%)	7	9	16	68
Bacteremic foals	8	6	14 (58%)	5	5	10	24
Gram-negative foals	4	4	8 (57%)	2	4	6	14

model already containing the previously added term. This process was continued until no addition resulted in a *P*-value <.05. *P*-values for addition to the survival model were calculated using the likelihood ratio test.

Results

Sixty-eight foals were enrolled in the study. Forty-six foals were defined as septicemic on the basis of positive blood culture or sepsis score >11 using clinicopathologic data and samples obtained at admission. There were 24 blood culture-positive foals, 14 of which had single gram-negative infections. There were 39 foals with sepsis score >11, 17 of which also had positive blood cultures. Seven foals with sepsis score of ≤11 had positive blood cultures. Sensitivity and specificity for sepsis score (>11) as a predictor of true bacteremia were 74 and 52%, respectively.

Data describing survival to 96 hours of hospitalization as well as to discharge from the hospital are summarized in Table 1. Of the 19 foals that did not survive to discharge, 8 died, 7 were euthanized primarily for financial concerns, and 4 were euthanized primarily based on a hopeless prognosis. Only 3 foals were alive at 96 hours of hospitalization that did not survive to discharge, all of which were euthanized due to financial concerns. Survival rates to 96 hours of hospitalization and discharge from the hospital did not differ significantly for each category of foal analyzed.

Statistical analyses demonstrated significant differences in survival for foals that received plasma that was rich in anti-LPS antibodies (Table 2). Twenty-seven of the 36 foals that received plasma that was rich in antiendotoxin antibodies survived (75% survival) to discharge, compared with 22/32 (68% survival) of the foals that received the other plasma type. For the entire study population, a significant

Table 2. Determination of differences in survival due to plasma type.

	Overall Survival							
	n	Deviance	df	OR a/b[a]	95% Lower	95% Upper	LR *P*-Value[b]	Fisher's *P*-Value
All foals	68	6.305	1	6.763	1.311	34.903	.012	.599
Septic foals	46	5.535	1	6.267	1.186	33.109	.019	.367
Bacteremic foals	24	0.990	1	3.382	0.279	40.972	.320	1.000
Gram-negative foals	14	3.693	1	59.597	0.137	25,867.9	.055	.627
	Survival to 96 hours							
	n	Deviance	df	OR a/b	95% Lower	95% Upper	LR *P*-Value	Fisher's *P*-Value
All foals	68	4.119	1	4.119	0.963	20.806	.042	.568
Septic foals	46	3.559	1	4.137	0.875	19.566	.059	.360
Bacteremic foals	24	0.990	1	3.382	0.279	40.972	.320	1.000
Gram-negative foals	14	3.693	1	59.597	0.137	25,867.9	.055	.627

[a] Odds ratio for probability of survival for foals receiving hyperimmune equine plasma rich in antilipopolysaccharide antibodies (plasma a) compared with foals receiving conventional equine hyperimmune plasma (plasma b).

[b] Likelihood ratio test *P*-value.

difference was seen in the survival to 96 hours ($P = .042$) as well as to discharge from the hospital ($P = .012$) for foals that received hyperimmune plasma that was rich in antiendotoxin antibodies compared with those that received the other plasma type. Statistical analyses demonstrated that these differences were independent of foal body weight and the volume of plasma administered. Administration of plasma rich in antiendotoxin antibodies also was associated with greater survival to discharge in the 46 septic foals ($P = .019$). No difference was seen in overall survival rate for those foals that were bacteremic at admission according to plasma type administered ($P = .320$). When considering only foals with gram-negative infection (n = 14), the survival rates were not statistically significantly different for the 2 different plasma types ($P = .055$).

For survival to discharge, statistical analyses demonstrated that of the 53 clinicopathologic admission variables examined, only 5 were retained in the final survival model. Specifically, sepsis score ($P < .001$) and fibrinogen concentration ($P = .018$) were negatively related to survival, whereas measured IgG concentration ($P = .01$), segmented neutrophil count ($P = .028$), and total red blood cell numbers ($P = .048$) were positively related to survival. When considering survival to 96 hours, the retained variables were sepsis score ($P < .001$) and fibrinogen concentration ($P = .007$), which again were negatively associated with survival, and segmented neutrophil count ($P = .055$) and blood glucose concentration ($P = .024$), which were positively associated with survival. The details of the model's fit are presented in Table 3. The logistic regression equations for survival to discharge and survival to 96 hours of hospitalization are given below:

logit (survival to discharge) = 0.019 + (−0.456)sepsis score + (0.519)segmented neutrophil count + (0.003)IgG + (−0.004)fibrinogen + 0.563(RBC).

Table 3. Details of logistic survival model.

Overall Survival			
Variable	Coefficient	SE	LR *P*-Value
Intercept	0.019	3.543	NA
Sepsis score	−0.456	0.185	<.001
SEGS	0.519	0.208	.028
RID	0.003	0.001	.010
FIB	−0.004	0.002	.018
RBC	0.563	0.309	.048
Survival to 96 hours			
Variable	Coefficient	SE	LR *P*-Value
Intercept	5.852	2.544	NA
Sepsis score	−0.346	0.151	<.001
SEGS	0.270	0.130	.055
FIB	−0.006	0.002	.007
Glucose	0.017	0.008	.024

[a] LR, likelihood ratio test *P*-value; SEGS, segmented neutrophil count; RID, radial immunodiffusion; RBC, red blood cell; FIB, fibrinogen concentration.

logit (survival to 96 hours) = 5.582 + (−0.346)sepsis score + (0.270)segmented neutrophil count + (−0.006)fibrinogen + 0.017(glucose).

Discussion

Our finding that the administration of plasma harvested from mares hyperimmunized with LPS was associated with greater survival in all foals admitted to our ICU as well as the septicemic foal subpopulation is a unique observation. It contrasts with findings in a prior study by Morris and Whitlock[9] that also prospectively looked at anti-LPS antibody-rich plasma in comparison with lower anti-LPS titer plasma. That study was a multicenter study that did not demonstrate any significant difference in survival for critically ill neonates receiving either plasma type. We were able to demonstrate enhanced survival for the entire study population as well as for foals that we defined as septic by virtue of positive blood culture or sepsis score >11 at admission. Although statistical significance was identified both for overall short-term survival (96 hours of hospitalization, $P = .042$) and survival to discharge ($P = .012$) for those foals receiving hyperimmune plasma that was rich in anti-LPS antibody, the clinical relevance was less compelling, with 75% survival to discharge versus 68% for the 2 different plasma types. Statistical significance does not necessarily imply clinical relevance. From a statistical standpoint, it can be seen from the higher values for Fisher's *P*-values in Table 2 that, if corrections had not been made in our data analysis for those factors that were not randomly distributed between foals receiving the 2 plasma types (sodium, temperature, and anion gap), we would not have identified a significant difference at all. There were no significant differences noted in survival between foals that were bacteremic and those that were not nor between those that had a gram-negative isolate obtained compared with a gram-positive isolate from samples obtained at admission. The overall difference in survival rate suggests that administration of plasma rich in anti-LPS conferred the greatest benefit on nonbacteremic foals. It is not clear from this study whether anti-LPS antibody-rich plasma may confer a therapeutic or survival benefit on foals with gram-negative sepsis.

Another important fact to consider is that, although 1 of our plasma types was obtained from donors that were hyperimmunized with the J5 vaccine[h] product, it would be incorrect to assume that the other plasma type used in our study was devoid of anti-LPS antibody. Precise anti-LPS antibody titrations were not performed on every bag or batch of plasma used in this study. All of the donors for the anti-LPS antibody-rich plasma had titers of >1 : 12,000, but approximately 10% of the donors for the other plasma type also had titers this high.[i] However, 50% of donors of the other plasma type had negative anti-LPS antibody titers at a dilution of 1 : 1,600. Therefore, our data actually may underestimate the potential beneficial effect of anti-LPS antibody in treating sick foals.

Another relevant difference between our study and that of Morris and Whitlock[9] was the fact that all plasma was heparinized before administration to the

foals in our study. Some hemostatic variables differ between newborn and 1-month-old foals[10] as well as between newborn foals and adults,[11,12] but clinically relevant disorders of hemostasis only become apparent during acquired conditions, such as septicemia.[13,14] Hemostatic abnormalities in association with neonatal septicemia are well established in foals,[5,15] but our findings are in accordance with those of Barton et al,[5] who observed that survival did not significantly correlate with coagulopathy. The heparin used in our study was of porcine origin[8] and of mixed molecular weight and may have conferred a beneficial effect on the treatment of sepsis when combined with plasma by virtue of both its anticoagulant and antithrombotic properties.[13] Heparinization of plasma alone, however, could not have been the only factor involved in enhancing survival rates compared with previous studies because both plasma types were treated with 2,000 IU/L of sodium heparin, and statistically significant differences were seen between the 2 plasma types administered. All foals in this study received flunixin meglumine in addition to heparinized plasma and antibiotics on the 1st day of hospitalization, even those for which the sepsis score was ≤11 on admission. Arguably, the use of this drug was not justifiable in all study foals, but in designing a prospective study, we sought to provide a standardized initial therapeutic regimen for comparative reasons and to ensure that the quality of care for the sickest client-owned foals was not compromised. Because of concerns regarding ulcerogenesis and renal toxicity associated with the use of nonsteroidal anti-inflammatory medications, especially in compromised neonates, other clinicians may reasonably elect not to use flunixin meglumine in all cases.

Of the 53 admission variables measured on every foal in this study, 4 were significantly associated with survival to discharge from the hospital. In terms of *P*-value, sepsis score was the most significant ($P < .001$), with higher sepsis score foals having a poorer chance of survival. No metabolic variables were retained as being significantly associated with survival to discharge from the hospital. This finding is in contrast with previous studies that have demonstrated high anion gap and low venous oxygen tension,[2] or low glucose, low albumin, and low pH,[4] to be associated with poorer survival rates for foals admitted to ICUs at different institutions. Interestingly, low blood-glucose concentration at admission was associated with poorer survival to 96 hours of discharge in our study but was not retained in the model examining survival to discharge. Other admission variables that were significantly associated with survival to discharge were IgG concentration (as measured by RID), fibrinogen concentration, total neutrophil count, and total red blood cell (RBC) count. Low IgG concentration, as a consequence of failure of passive transfer, potentially compounded by antibody consumption in the early stages of infection, was not a surprising risk factor for failure to survive in critically ill neonates. Three studies comparable with ours examined factors potentially associated with survival in septicemic[4] foals or foals admitted to referral hospitals for intensive care,[2,3] and in 2 of those,[3,4] low neutrophil count was documented as a variable that was significantly different between survivors and nonsurvivors. Although low neutrophil count was significantly associated with failure to survive in our study ($P = .028$) it was not as statistically significant as sepsis score, IgG concentration, and fibrinogen concentration. The finding that a high fibrinogen concentration was significantly associated with failure to survive ($P = .018$) is a novel finding, and one that suggests that foals with evidence of acute-phase inflammation, in conjunction with failure of passive transfer and neutrophil sequestration, are the poorest survival candidates. The admission variable with significance ($P = .048$) as a predictor of survival that potentially is the hardest to explain is the total RBC count. Although it demonstrated the lowest *P*-value in the final set of retained variables, its persistence in our analyses indicates that low RBC numbers are somehow related to survival. Whether this observation reflects anemia, low-grade hemolysis, or both granulocytic and erythropoetic precursor suppression is an area worthy of further study.

Our final survival models included both sepsis score and several of its components (ie, segmented neutrophil count, fibrinogen, and IgG for overall survival and segmented neutrophil count, fibrinogen, and glucose for survival to 96 hours). This finding is evidence that a component measure may provide information on survival that is not captured by that component's contribution to the sepsis score. This result may occur because of the inherent loss of information that occurs when a continuous predictor is categorized, as is the case for most of the other components of the sepsis score. It therefore seems reasonable and desirable to allow some predictors to be included twice, once as a component of the sepsis score and once as a separate predictor. When performing multiple logistic regression, correlation between the potential predictor variables (also known as multicolinearity) is always a major concern. Multicolinearity can lead to misleading or inaccurate estimates, standard errors, or *P*-values. In most cases, highly correlated predictors will not appear together in a model formed through a forward-selection procedure such as the one used in this study. This is because correlated predictors explain roughly the same portion of the response and generally will not both show as significantly predictive when included together, even if they may be predictive when included alone. Because forward selection implicitly protects against multicolinearity, correlations among all 53 potential predictors were not calculated. However, because it was known that sepsis score is composed of several of the other measured variables, it seemed prudent to explicitly check for correlations between sepsis score and those variables. Correlations were quite small for all such variables and thus should not have caused problems in the model fitting.

Although the precision of sepsis scoring with respect to accurately identifying truly septic foals has been the subject of recent debate,[16] our data suggest sepsis scoring can be useful prognostically in a referral population. When defining the sensitivity and specificity of sepsis

score in our hospital, we used a gold standard of true bacteremia, which is more stringent and arguably too narrow by comparison with the definition originally used by Brewer and Koterba.[1] Consequently, our calculated values for sensitivity and specificity are low (74% and 52% compared with 93% and 86%, respectively). Undoubtedly, there are many non-bacteremic foals that could reasonably be described as septic and there is variation in acceptance of sepsis score among institutions and individual clinicians. However, our findings suggest that the calculation of sepsis score using the system and criteria described by Brewer and Koterba[1] gave the most prognostically useful index of survival for neonatal foals in our hospital.

The overall survival rate for foals admitted to our ICU was 72%, with the septicemic population and truly bacteremic foals having lower survival rates of 58 and 57%, respectively. The survival rate for all ICU admissions in our study was comparable with those documented by Hoffman et al[2] (66%) and Furr et al[3] (74%), but our survival rate for septicemic foals was higher than those previously published for comparably defined populations by Gayle et al[4] (45%) and Morris and Whitlock[9] (52.5%). Comparisons among referral hospitals are obviously of limited value when criteria for admission to neonatal intensive care units likely vary among institutions. In our hospital, not all foals <7 days of age are admitted to the ICU, several categories of foals (eg, angular limb deformities and other neonatal orthopedic problems in which foals can still nurse, mild enteric and respiratory disease cases) seen by the surgery and medicine services remain in the main hospital population. Although all foals that require IV fluid support and close monitoring are admitted to our ICU, the ultimate decision is clinician dependent and empirical, such that we may have different criteria compared with other studies and therefore a slightly different population base for comparative purposes. Our observation that approximately equal proportions of truly bacteremic and septicemic foals survived to discharge from the hospital was somewhat surprising; however, the fact that we performed blood cultures routinely, using antimicrobial retrieval systems for those foals that had been pretreated with antibiotics, may have increased the numbers of foals from which positive cultures were obtained. Survival rates for septicemic and bacteremic foals likely have increased over the last decade given improvements in critical care, therapeutics, and intensive nursing care available at university and private referral practices.

For ethical reasons, it is unlikely that a controlled, prospective study establishing whether plasma administration to critically ill foals confers a survival advantage over antibiotics and intensive supportive therapy alone will be conducted. However, we have been able to demonstrate that, within our referral population, the administration of anti-LPS-rich antibody plasma is associated with higher survival rates. Furthermore, the combination of failure of passive transfer, neutropenia, high fibrinogen concentration, and low RBC counts as measured at admission, warrants a graver prognosis.

Footnotes

[a] Polymune, Veterinary Dynamics, Templeton, CA
[b] Polymune Plus antiendotoxin Ab, Veterinary Dynamics, Templeton, CA
[c] Limulus Amebocyte Assay, BioWhittaker Co, Wlakersville, MD
[d] Snap IgG Test, Idexx Laboratories, Westbrook, ME
[e] BBL Septi-Chek Columbia Broth, Becton Dickinson and Company, Sparks, MD
[f] BBL Septi-Chek TSD With Resins, Becton Dickinson and Company, Sparks, MD
[g] Heparin sodium injection USP, Elkins Sinn Inc, Cherry Hill, NJ
[h] J5 Hygeica Biological Corporation, Woodland, CA
[i] Personal communication, Dennis Brook, Veterinary Dynamics, Templeton, CA

Acknowledgment

This study was supported by a Companion Animal Grant from the University of Wisconsin-Madison, Madison, WI.

References

1. Brewer BD, Koterba AM. Development of a scoring system for the early diagnosis of equine neonatal sepsis. Equine Vet J 1988;20(1):18–22.
2. Hoffman AM, Staempfli HR, Willan A. Prognostic variables for survival of neonatal foals under intensive care. J Vet Intern Med 1992;6:89–95.
3. Furr M, Tinker MK, Edens L. Prognosis for neonatal foals in an intensive care unit. J Vet Intern Med 1997;11:183–188.
4. Gayle JM, Cohen ND, Chaffin MK. Factors associated with survival in septicemic foals: 65 cases (1988–1995). J Vet Intern Med 1998;12:140–146.
5. Barton MH, Morris DD, Norton N, Prasse KW. Hemostatic and fibrinolytic indices in neonatal foals with presumed septicemia. J Vet Intern Med 1998;12:26–35.
6. Hothekiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med 2003;348:138–150.
7. Bone RC. Sir Isaac Newton, sepsis, SIRS and CARS. Crit Care Med 1996;24:1125–1128.
8. Roy MF. Sepsis in adults and foals. Vet Clin North Am Equine Prac 2004;20:41–61.
9. Morris DD, Whitlock RH. Therapy of suspected septicemia in neonatal foals using plasma-containing antibodies to core lipopolysaccharide (LPS). J Vet Intern Med 1987;1:175–182.
10. Barton MH, Morris DD, Crowe N, et al. Hemostatic indices in healthy foals from birth to one month of age. J Vet Diag Invest 1995;7:380–385.
11. Darien BJ, Carleton C, Kurdowska A, et al. Haemostasis and antithrombin III in the full term newborn foal. Comp Haematol Inter 1991;1:161–165.
12. Clemmons RM, Dorsey Lee MR, Gorman NT, et al. Haemostatic mechanisms of the new born foal; reduced platelet responsiveness. Equine Vet J 1984;16:353–356.
13. Darien BJ. Heparin therapy: Rationale and clinical implications. Comp Cont Educ Pract Vet 1993;15:1273–1276.
14. Weiss DJ, Rashid J. The sepsis-coagulant axis: A review. J Vet Intern Med 1998;12:317–324.
15. Darien BJ, Williams MA. Possible hypercoagulation in 3 foals with septicemia. Equine Vet Educ 1993;5:19–22.
16. Corley KT, Furr MO. Evaluation of a score designed to predict sepsis in foals. J Vet Emerg Crit Care 2003;13:149–155.