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Factors associated with the risk of positive blood culture in neonatal foals presented to a referral center (2000-2014)

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Abstract

Background: Bloodstream infections (BSI) are common in sick foals and increase foal morbidity and mortality when they occur. Recognition of risk factors for BSI could be an important means to limit their occurrence, but studies on this topic are limited.

Objectives: Historical as well as maternal and foal physical examination findings will predict risk of BSI in neonatal foals.

Animals: Foals <14 days of age admitted to a referral equine hospital for care.

Methods: Retrospective case-control study with univariate and multivariable logistic regression analysis.

Results: Four hundred twenty-nine (143 cases and 286 controls) foals <14 days of age were studied. Risk of a foal having a BSI was increased in foals with umbilical disease (adjusted odds ratio [OR], 11.01; P = .02), hypoglycemia (adjusted OR, 13.51; P = .03), and the combined presence of umbilical disease and low hematocrit (adjusted OR, >999.99; P = .04). Factors not found to be risk factors for development of BSI included prematurity, hypothermia, abdominal disease, diarrhea, failure of passive transfer, and maternal uterine infection.

Conclusions and Clinical Importance: Several historical and physical examination findings increase the risk of foals being blood culture positive at presentation to the hospital. This knowledge may aid early identification of blood culture status, thus aiding in treatment decisions.

KEYWORDS
bacteremia, foal, neonate, septicemia

1 | INTRODUCTION

Neonatal septicemia is a major cause of death in foals <7 days of age[1] and is associated with substantial treatment expense and financial losses as a result of death. Bacteremia appears to be common in critically ill foals because 25% to 50% of foals requiring intensive care have been reported to be positive on blood culture.[2-6]

Various reports have found survival rates of 20% to 50% in foals with bacterial septicemia[7-9] but a more recent study reported improvement in outcomes.[10] Although a number of studies describe the bacterial isolates recovered, clinical signs associated with, and outcomes after bacteremia, very few studies have systematically evaluated factors associated with the risk of being found blood culture positive upon presentation to the hospital. Previously suggested risk

Abbreviations: AUC, area under the curve; BSI, bloodstream infection(s); CPAP, continuous positive airway pressure; EOS, early onset sepsis; FSS, foal sepsis score; ICU, intensive care unit; LOS, late onset sepsis; NEC, necrotizing enterocolitis; OR, odds ratio; RBC, red blood cell; RELR, random effects logistic regression.

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factors include failure of passive transfer (FPT), diarrhea, and umbilical contamination or disease.[6,11-13] A better understanding of the risk factors associated with bacteremia may mitigate complications by early intervention, as well as enhance client communications and prognostication. The purpose of our study was to determine the association of several historical, physical examination, and clinicopathologic findings on neonatal blood culture status. Secondary goals included summarizing the organisms recovered in this cohort of foals, determining their antimicrobial sensitivity patterns, and assessing the accuracy of the modified foal sepsis score (mSS).[14]

2 | MATERIALS AND METHODS

2.1 | Study design

A retrospective, case-control study of foals <14 days of age admitted to an equine intensive care unit (ICU; Marion duPont Scott Equine Medical Center) from 2000 to 2014 that had blood culture performed was carried out, and data were entered into an electronic spreadsheet. Cases were defined as any foal with a positive blood culture and controls as foals in which blood culture was performed and was negative. Foals were excluded from analysis if a blood culture was not performed at admission, final culture results were not available, or they were >14 days of age. Data recorded included historical (foal and maternal) and physical examination findings at presentation, and results of clinicopathologic testing performed within 2 hours of admission. Clinicopathologic findings recorded included CBC, differential nucleated cell count, and plasma fibrinogen concentration. Clinical biochemistry analyses included serum concentrations of electrolytes (sodium, potassium, chloride, magnesium, total calcium), serum activities of enzymes (γ-glutamyl transferase [GGT], alkaline phosphatase [AP], and creatine kinase [CK]), serum concentrations of small organic molecules (glucose, lactate, creatinine, urea nitrogen, total protein, albumin, and globulin, as well as total, direct and indirect reacting bilirubin), serum immunoglobulin G concentration, and venous blood gas results (pH, bicarbonate, and pCO_2). All diagnostic testing was at the clinicians' discretion, because of the retrospective nature of the study, and therefore not all information was collected on each foal. Demographic and historical information recorded included gestational age, postnatal age at presentation, time after foaling before standing and nursing, breed, presenting complaint, foaling history (normal, cesarean section, dystocia), gestational history (presence of maternal illness, vaginal discharge, or placental disease), and presence or absence of FPT (defined as serum IgG concentration <400 mg/dL determined from semiquantitative stall-side tests or immunoglobulin concentration from clinical chemistry analysis). Mean globulin concentration was calculated using definitive concentrations from clinical chemistry analysis only. Gestational age was determined from reported last breeding date and prematurity (present or absent) was defined as gestational age < 330 days,[15] as determined from reported breeding date if available or delivery >15 days before the owners' anticipated due date (if known). Physical examination findings recorded included rectal temperature, heart and respiratory rates, and the presence or absence of lameness, swollen joints, diarrhea, or abdominal distention. The presence of an umbilical abnormality of any type was documented (normal or abnormal), as well as the presence or absence of a patent urachus. The modified foal sepsis score (mSS) at presentation was determined as previously described, with a value ≥11 indicating bacteremia.[14] Clinical diagnosis, blood culture results, and short-term survival (ie, survival to discharge) were recorded.

For exposure variables, absence of a recorded physical examination finding in the medical record was not interpreted as absence of the finding in the foal, rather it was considered undocumented and excluded. Furthermore, if it could not be confirmed that data were recorded at or within 2 hours of admission that data were not included. Hence, not all variables of interest were recorded for every foal.

Bacterial culture was performed using routine clinical methods, and the technique used remained consistent throughout the study period. Blood for culture was collected using aseptic technique via an IV catheter coincident with placement of the catheter. The skin over the jugular vein was clipped and scrubbed using 2% chlorhexidine solution followed by swabbing with alcohol. Sterile surgical gloves were worn for placement of a sterile IV catheter, after which a sterile extension set and syringe were attached and 7-10 mL of blood were collected and the syringe capped with a sterile needle. Blood then was transferred, under a hood, to a commercial blood culture bottle containing tryptocase-soy broth and incubated aerobically at 35°C. The blood culture bottle was subcultured once per day for 7 days onto blood agar plates, which were incubated at 35°C. If there was a history of antimicrobial administration before admission, blood first was placed into an antibiotic removal device, then transferred to a blood culture bottle. Blood culture status (positive or negative) was determined based on the results of blood culture performed at the time of admission to the hospital; subsequent repeat cultures rarely were performed and if so those results were not included. Microbial sensitivity was determined using the disc diffusion method.

2.2 | Data analysis

After entry, data were analyzed using commercial statistical software (SAS 9.4, SAS Institute, Cary, North Carolina). Data were evaluated using descriptive and inferential methods; not all data were available for all foals. For descriptive purposes, continuous data were summarized by reporting the mean ± 1 SD; categorical data were reported as proportions or using contingency tables. Group means were compared using Student *t* test. For inferential analysis, the primary endpoint was the dichotomous outcome of positive bacterial culture (positive or negative).

2.2.1 | Model development

Continuous variables were re-coded as categorical variables assigned using published normal ranges.[16-19] Univariate odds ratios (OR) and

95% confidence intervals (CI) for the effects of each variable upon blood culture outcome were calculated by logistic regression using the EXACT statement for categories with expected N < 5. All variables with a univariate $P < .1$ then were included in a purposeful multivariable random effects logistic regression (RELR), including bivariate interaction terms.[20,21] Foal body weight was not included in multivariable equation development because body weights were not adjusted for breed or maternal weight; the mSS also was not included in the multivariable RELR because it is a derived factor using clinical and historical data that would have been duplicated in the model. The *a priori* significance level required for a variable to be retained in the final model was $P < .05$. Accuracy of the final multivariable model was expressed by calculation of the area under the curve (AUC). Some factors that did not achieve the predetermined *P* value to remain in the model ($P < .05$) and that were considered to be clinically relevant were forced into the model to maximize the AUC, and hence the accuracy of the predictive model. If a forced factor did not improve the AUC by >5%, it was not retained.

3 | RESULTS

The records of 562 foals were reviewed for inclusion in the study. Of these, 133 were excluded because of missing or incomplete primary outcome data (culture results), age > 14 days, or re-admits, resulting in a study population of 429 foals for analysis. The study population comprises 143 blood culture-positive cases (33%; 143/429) and 286 blood culture-negative controls (67%; 286/429). The short-term survival for foals with positive blood culture was 78% (110/141) and was 80% (219/275) for foals with negative blood culture ($\chi^2 = 0.14$; $P = .70$).

Foals of the study represented 30 different breeds and types, which for purposes of analysis were compressed into 1 of 5 categories: draft (2 cases and 6 controls), Quarter Horses (QH) and QH crosses and types (14 cases and 42 controls), Thoroughbred (TB) and TB crosses and types (98 cases and 188 controls), Warmbloods (WB) and WB crosses (18 cases and 24 controls), and “other” comprises miniatures, mules, and donkeys (8 cases and 8 controls). No difference in blood culture status was found between cases and controls based on breed type ($\chi^2 = 5.57$; $P = .23$).

Results of dichotomous physical examination and historical findings at presentation are summarized in Tables 1 and 2 including univariate ORs and 95% CIs for their association with blood culture. Additional physical examination findings are summarized in Table 3 and univariate effects of continuous findings examined as categorical variables are presented in Table 4. Results of the CBC at presentation are summarized in Table 5, and univariate analysis of CBC results analyzed as categorical variables are presented in Table 6. Clinical biochemistry results are summarized in Table 7 and reported as categorical values for their effects upon blood culture outcome in Table 8.

Blood culture identified 178 separate isolates among the 143 blood culture-positive foals; 31 foals had polymicrobic infections. Of these, 90 of 178 (51%) were Gram-positive organisms and 88/178 (49%) were Gram-negative. Of the Gram-negative organisms, Enterobacteriaceae predominated, representing 39% of the isolates (69/178), with *Escherichia coli* being the most common (31/178; 17%). Among the Gram-positive organisms recovered, *Staphylococcus* spp. and *Streptococcus* spp. were most common, representing 17% (31/178) and 13% (23/178), respectively. Summary data regarding the antimicrobial sensitivities of the bacterial isolates are presented in Table 9.

The mSS is reported in Tables 3 and 4; the calculated sensitivity and specificity of the mSS for predicting final blood culture status for this cohort of foals were 53.5% and 65.7%, respectively.

3.1 | Multivariable modeling

Multivariable model building resulted in a final model with an AUC of 0.94. Some factors were forced into the model to maximize the AUC. Factors in the final model included the presence of prematurity (adjusted OR, 0.49; 95% CI, 0.01-17.48; $P = .69$), presence or absence of umbilical disease (adjusted OR, 11.01; 95% CI, 1.43-85.55; $P = .02$), FPT (adjusted OR, 2.30; 95% CI, 0.42-120.51; $P = .34$), low rectal temperature (adjusted OR, 1.53; 95% CI, 0.21-11.36; $P = .68$), low blood glucose concentration (adjusted OR, 13.51; 95% CI, 1.36-124.07; $P = .02$), and low hematocrit (HCT) (adjusted OR, 3.32; 95% CI, 0.29-37.03; $P = .33$). The interaction of the presence of umbilical disease and low HCT was the only interaction term retained, with an adjusted OR of >999.99 (95% CI, 9.55-999.99; $P = .018$), indicating that the effect of umbilical disease was dependent on the value of the HCT. In this multivariable model, the OR for the effect of prematurity changed dramatically compared to that observed in the univariate analysis (OR, 1.88; 95% CI, 1.03-3.4; $P = .03$), suggesting its effects are poorly described by this model. Recalculation of the model with prematurity removed had minimal effect on model accuracy, decreasing the AUC to 0.88.

4 | DISCUSSION

We systematically examined factors associated with foals that were blood culture-positive on hospital admission. Our study was performed by examination of numerous clinical, historical, and clinicopathologic variables that are commonly collected during the examination of a critically ill neonate. Continuous data were examined as categorical values to determine if there were important threshold values (rather than a monotonic increase in magnitude of a variable) that impacted blood culture outcome.

Our findings reinforce and extend previous studies on this topic in foals, adding increased precision because of higher numbers, as well as considering some factors, such as maternal health and foaling circumstances, that have not been reported previously. The strength of the data collected was the fact that during the time period of the study the same historical and physical examination forms were used, and the faculty clinicians and laboratory personnel conducting the assays remained the same throughout this time period.

TABLE 1 Summary proportions and univariable logistic regression ORs for maternal and foaling history variables of sick foals with or without a positive blood culture presented to an equine hospital

Variable	Blood culture negative, N/total (%)	Blood culture positive, N/total (%)	OR (95% CI)	*P*
Dystocia				
Absent	224/272 (82%)	116/140 (83%)	1	
Present	48/272 (18%)	24/140 (17%)	0.99 (0.57-1.69)	.97
Uterine infection				
Absent	56/60 (93%)	29/30 (97%)	1	
Present	4/60 (7%)	1/30 (3%)	0.48 (0.02-3.45)	.52
Premature				
Absent	244/272 (90%)	115/140 (82%)	1	
Present	28/272 (10%)	25/140 (18%)	1.89 (1.03-3.39)	.037
Cesarean section				
Absent	262/272 (96%)	138/140 (99%)	1	
Present	10/272 (4%)	2/140 (1%)	0.42 (0.06-1.67)	.27
Maternal illness				
Absent	51/60 (85%)	30/31 (97%)	1	
Present	9/60 (15%)	1/31 (3%)	0.18 (0.01-1.06)	.18
Vaginal discharge				
Absent	54/58 (93%)	30/30 (100%)	1	
Present	4/58 (7%)	0/30 (0%)	0.001 (– - 1.68)	.98
Placental abnormalities				
Normal	221/266 (83%)	112/138 (81%)	1	
Abnormal	45/266 (17%)	26/138 (19%)	1.14 (0.66-1.93)	.63
Enema given				
No	16/50 (32%)	10/24 (42%)	1	
Yes	34/50 (68%)	14/24 (58%)	0.66 (0.24-1.82)	.42

Maternal health during late pregnancy and factors associated with parturition have been determined to have an effect upon neonatal foal survival,[7] and are considered risk factors for the development of sepsis in neonatal foals,[22] but these effects have not been well described in previous studies. Our study found that late-gestation maternal illness, uterine infection during pregnancy, late-term vaginal discharge, and a history of dystocia or cesarean section did not increase the risk of a foal being blood culture-positive during the first 14 days of life in this population of foals. However, there were very small numbers of foals in these categories, and the statistical power was very low. Further investigation with larger sample sizes is needed to verify or refute these findings.

A significant factor in the univariate assessment contributing to the risk of blood culture-positive status in the foals of the study was prematurity (gestational age < 330 days). Prematurity is commonly viewed as a risk factor for sepsis, but has not been studied extensively in the equine veterinary literature.[15,23] In a study of human infants, birth at a gestational age of <26 weeks was associated with increased risk of BSI of 1.58 to 2.67.[24] The presence or absence of prematurity (gestational age < 330 days) is a factor in the neonatal foal mSS, but specific mathematical characterization of ORs for blood culture status associated with prematurity was not performed in the description of the foal mSS.[15] In a smaller study of septic foals (blood culture positive or foal body fluid culture positive), the presence of prematurity was significantly associated with sepsis with an OR of 0.994 to 0.998.[23] Although this result was statistically significant, the effect was minimal, and the data may have been skewed because of the small study size. In a recent study assessing the performance of the foal Sepsis Score, gestational age was not retained in the final model and the authors suggested that physical indicators of maturity may be of greater utility than numerical gestational duration.[25] This observation has not been confirmed, and hence we chose to use a standard and conventional definition of prematurity (gestational age < 330 days). Evaluation of the association of other signs of physical immaturity and blood culture status would be warranted. In our study, premature foals (gestational age < 330 days) were 1.89 times more likely to be blood culture-positive than were foals born at normal gestational age based on univariate analysis. In the multivariable equation however the adjusted OR for prematurity changed to 0.49, and removal of prematurity (gestational age < 330 days) as a factor had only a modest effect on model accuracy. These findings suggest that the factor of prematurity (gestational age < 330 days) is confounded by other factors in the model, reflecting the complexity of the model and the condition under investigation.

TABLE 2 Summary proportions and univariable logistic regression ORs for categorical physical examination findings of sick foals with or without a positive blood culture presented to an equine hospital

Variable	Blood culture negative, N/total (%)	Blood culture positive, N/total (%)	OR (95% CI)	*P*
Umbilical hernia				
Absent	70/80 (87%)	37/38 (97%)	1	
Present	10/80 (13%)	1/38 (3%)	0.19 (0.01-1.04)	.12
Patent urachus				
Absent	76/79 (96%)	35/38 (92%)	1	
Present	3/79 (4%)	3/38 (8%)	2.17 (0.38-12.25)	.36
Lameness				
Absent	71/80 (89%)	37/40 (93%)	1	
Present	9/80 (11%)	3/40 (7%)	0.64 (0.14-2.29)	.52
Swollen joints				
Absent	75/79 (95%)	37/40 (93%)	1	
Present	4/79 (5%)	3/40 (7%)	1.52 (0.28-7.23)	.59
Abdominal distention				
Absent	68/80 (85%)	32/39 (82%)	1	
Present	12/80 (15%)	7/39 (18%)	1.24 (0.43-3.39)	.68
Diarrhea				
Absent	51/80 (64%)	29/39 (74%)	1	
Present	29/80 (36%)	10/39 (26%)	0.60 (0.25-1.39)	.25
Failure of passive transfer				
Absent	198/271 (73%)	88/139 (63%)	1	
Present	73/271 (27%)	51/139 (37%)	1.57 (1.01-2.43)	.042
Umbilical disease				
Absent	205/275 (75%)	87/142 (61%)	1	
Present	70/275 (25%)	55/142 (39%)	1.85 (1.20-2.86)	.005

TABLE 3 Summary descriptive physical examination findings of sick foals with or without a positive blood culture presented to an equine hospital

	Blood culture negative		Blood culture positive		
	N	Mean (SD)	N	Mean (SD)	*P*
Age at presentation (days)	274	2.7 (3.3)	140	2.7 (2.9)	.95
Sepsis score	210	9.4 (6.0)	114	12.5 (5.7)	<.001
Gestational age (days)	17	338 (16.4)	8	364.7 (56.4)	.28
Temperature (°C)	73	38.1 (32.2)	38	37.7 (18.3)	.079
Pulse (bpm)	78	103.8 (26.0)	40	111.2 (67.9)	.61
Respiration (bpm)	72	36.6 (17.7)	35	45.7 (80.1)	.28
Time to stand (h)	37	1.6 (2.1)	14	4.1 (14.8)	.54
Time to nurse (h)	34	1.7 (2.2)	10	3.5 (10.3)	.59

Low birthweight is commonly cited as a risk factor for development of BSI in humans,[26,27] but it is not universally found. In a previous study, birth weight was not a factor that increased the frequency of BSI when controlled for gestational age.[24] We were unable to determine the effects of birth weight because of the wide range of expected normal weights associated with the range of maternal size and breed, as well as the relatively small number of foals in which weight was reliably recorded at the time of admission and before treatment. Although it is logical to conclude that low birth weight would be a risk factor for foals because of the finding of prematurity (gestational age < 330 days), results of the multivariable modeling suggest that it would be inappropriate to draw such a conclusion with currently available information.

TABLE 4 Summary proportions and univariable logistic regression ORs for physical examination findings of sick foals with or without a positive blood culture presented to an equine hospital, examined as categorical values

	Blood culture negative N (%)	Blood culture positive N (%)	OR (95% CI)	*P*
Age at presentation (days)				
0-2.9	208/273 (76%)	95/139 (68%)	1	
3.0-5.9	25/273 (9%)	30/139 (22%)	2.63 (1.47-4.74)	.001
6.0-9.9	22/273 (8%)	8/139 (6%)	0.79 (0.32-1.79)	.60
10-14	18/273 (7%)	6/139 (4%)	0.73 (0.26-1.80)	.52
Sepsis score				
0-10	138/210 (66%)	53/114 (47%)	1	
≥11	72/210 (34%)	61/114 (53%)	2.21 (1.39-3.52)	<.001
Temperature (°C)				
<37.2	9/73 (12%)	11/36 (31%)	3.33 (1.22-9.35)	.019
Normal (37.2-39.3)	60/73 (82%)	22/36 (61%)	1	
>39.3	4/73 (6%)	3/36 (8%)	2.04 (0.38-10.01)	.37
Pulse (bpm)				
<70	6/78 (8%)	1/38 (3%)	0.22 (0.012-1.42)	.18
Normal (70-100)	35/78 (45%)	26/38 (68%)	1	
>100	37/78 (47%)	11/38 (29%)	0.40 (0.17-0.91)	.033
Respiration (bpm)				
<19	3/72 (4%)	0/33 (0%)	...	...
Normal (20-40)	54/72 (75%)	29/33 (88%)	1	
>41	15/72 (21%)	4/33 (12%)	0.89 (0.13-1.52)	.25

TABLE 5 Mean values for hematology and blood gas analysis results for sick foals with or without a positive blood culture presented to an equine hospital

	Blood culture negative		Blood culture positive		
	N	Mean (SD)	N	Mean (SD)	*P*
White blood cells (/μL)	81	7348.4 (4045.1)	43	6129.7 (4106.1)	.11
Segmented neutrophils (/μL)	71	5450.3 (3744.4)	43	4378.7 (3932.4)	.15
Band neutrophils (/μL)	71	273.4 (587.4)	43	429.4 (708.5)	.21
Lymphocytes (/μL)	71	1435.9 (1411.7)	43	1066.7 (674.1)	.067
Monocytes (/μL)	71	255.3 (252.3)	43	341.6 (375.5)	.19
Eosinophils (/μL)	71	10.2 (39.2)	43	133.5 (771.5)	.31
Platelets ($\times 10^3$/μL)	16	315.2 (151.0)	7	360.3 (192.0)	.55
Fibrinogen (mg/dL)	75	302.7 (142.3)	40	357.5 (173.8)	.072
Red blood cells ($\times 10^6$/μL)	77	9.3 (1.4)	40	8.4 (1.7)	.003
Hematocrit (%)	80	36.5 (5.8)	44	33.3 (6.2)	.007
Hemoglobin (g/dL)	79	13.1 (2.0)	42	12.5 (3.5)	.18
pH (venous)	72	7.38 (.13)	41	7.36 (.12)	.64
Bicarbonate (venous) mEq/L	72	26.5 (8.9)	41	27.7 (10.7)	.18
pCO_2 (venous) mmHg	72	43.5 (12.7)	41	46.3 (16.87)	.034

Hypoglycemia has been determined to be an independent risk factor for mortality in severe illness,[28,29] and its presence increases the incidence of complications including bacteremia in humans.[30] Hypoglycemia also increased the risk of antibiotic failure in human neonates, with an OR of 4.28 (1.45-12.60) on the first day of life and 3.72 (1.55-8.97) on day 2 or 3 of life.[31] The association of hypoglycemia with bacterial sepsis is well documented, and 1 study of children found that bacteremia was increased by 68% in neonates with

TABLE 6 Summary proportions and univariable logistic regression ORs for complete blood cell results for sick foals with or without a positive blood culture presented to an equine hospital

	Blood culture negative, N/total (%)	Blood culture positive, N/total (%)	OR (95% CI)	*P*
White blood cells (/μL)				
<8000	19/81 (23%)	15/44 (34%)	1.30 (0.52-3.23)	.57
Normal (8-11 000)	29/81 (36%)	19/44 (43%)	1	
>11 000	33/81 (41%)	10/44 (23%)	0.53 (0.21-1.31)	.17
Red blood cell (×10^6/μL)				
<8	11/77 (14%)	17/40 (42%)	3.83 (1.58-9.66)	.003
Normal (8-11)	57/77 (74%)	23/40 (58%)	1	
>11	9/77 (12%)	0/40 (0%)	0 (0-0.62)	.97
Hemoglobin (g/dL)				
<14	54/79 (68%)	30/41 (74%)	1.28 (0.55-3.14)	.91
Normal (14-17)	23/79 (29%)	10/41 (24%)	1	
>17	2/79 (3%)	1/41 (2%)	1.15 (0.05-13.41)	.58
Hematocrit (%)				
<32	13/80 (16%)	18/44 (41%)	3.43 (1.48-8.19)	.004
Normal (32-45)	62/80 (78%)	25/44 (57%)	1	
>45	5/80 (6%)	1/44 (2%)	0.49 (0.02-3.28)	.53
Neutrophils (/μL)				
<5000	14/71 (20%)	14/42 (33%)	1.5 (0.51-4.5)	.47
Normal (5-8500)	16/71 (22%)	10/42 (24%)	1	
>8500	41/71 (58%)	18/42 (43%)	0.64 (0.24-1.75)	.37
Bands (/mcL)				
Normal (0-100)	41/71 (58%)	14/42 (33%)	1	
High (> 100/mcL)	30/71 (42%)	28/42 (67%)	2.73 (1.25-6.18)	.010
Lymphocytes (/μL)				
<1000	10/69 (14%)	15/41 (37%)	3.13 (1.24-8.19)	.010
Normal (1-1800)	50/69 (72%)	24/41 (56%)	1	
>1800	9/69 (13%)	2/41 (5%)	0.46 (0.067-1.97)	.35
Monocytes (/μL)				
<100	12/71 (17%)	9/42 (22%)	1.70 (0.60-4.71)	.31
Normal (100-300)	43/71 (60%)	19/42 (45%)	1	
>300	16/71 (23%)	14/42 (33%)	1.98 (0.81-4.89)	.14
Eosinophils (/μL)				
Normal (0-20)	63/69 (91%)	37/42 (88%)	1	
>20	6/69 (9%)	5/42 (12%)	1.42 (0.385-5.03	.58
Fibrinogen (mg/dL)				
<300	26/75 (35%)	14/40 (35%)	1.57 (0.64-3.93)	.33
Normal (300-499)	38/75 (50%)	13/40 (32%)	1	
>499	11/75 (15%)	13/40 (33%)	3.45 (1.26-9.82)	.017
Platelets (×10^3/μL)				
<200	3/16 (19%)	1/7 (14%)	0.67 (0.026-8.43)	.76
Normal (200-340)	6/16 (37%)	3/7 (43%)	1	
>340	7/16 (44%)	3/7 (43%)	0.86 (0.12-6.25)	.88
IgG (mg/dl)				.78
<400 mg/dL	12/40 (30%)	5/19 (26%)	0.83 (0.23-2.75)	
Normal (≥ 400 mg/dL)	28/40 (70%)	14/19 (74%)	1	

TABLE 6 (Continued)

	Blood culture negative, N/total (%)	Blood culture positive, N/total (%)	OR (95% CI)	*P*
pH (venous)				
<7.38	23/72 (32%)	17/40 (42%)	1.97 (0.48-10.02)	.36
Normal (7.38-7.40)	8/72 (11%)	3/40 (7%)	1	
>7.4	41/72 (57%)	20/40 (50%)	1.30 (0.33-6.42)	.72
pCO_2 (venous)(mmHg)				
<44	43/74 (58%)	24/40 (60%)	1.488 (0.39-7.78)	.58
Normal (44-47)	8/74 (11%)	3/40 (11%)	1	
>47	13/74 (31%)	13/40 (32%)	1.51 (0.36-7.79)	.59
Bicarbonate (venous)(mEq/L)				
<25	23/71 (32%)	15/40 (37%)	1.96 (0.56-8.03)	.31
Normal (25-27)	12/71 (17%)	4/40 (10%)	1	
>27	36/71 (51%)	21/40 (53%)	1.75 (0.53-6.91)	.38

TABLE 7 Summary descriptive clinical chemistry results for sick foals with or without a positive blood culture presented to an equine hospital

	Blood culture negative		Blood culture positive		
	N	Mean (SD)	N	Mean (SD)	*P*
Sodium (mEq/L)	81	135.4 (6.1)	43	135.5 (5.3)	.94
Potassium (mEq/L)	81	3.84 (0.61)	43	4.01 (0.72)	.19
Chloride (mEq/L)	77	101.1 (6.2)	41	101.7 (4.7)	.53
Magnesium (mg/dL)	61	1.66 (0.51)	36	1.63 (0.51)	.69
Calcium (total) (mg/dL)	51	10.5 (1.7)	27	10.4 (1.2)	.72
Glucose (mg/dL)	76	139.8 (58.5)	39	105.82 (58.4)	.005
Creatinine (mg/dL)	79	2.66 (2.29)	40	2.64 (1.99)	.95
Urea nitrogen (mg/dL)	77	21.4 (17.6)	38	23.9 (21.7)	.52
Total protein (g/dL)	71	5.1 (1.0)	36	5.3 (1.4)	.49
Albumin (g/dL)	55	2.9 (0.4)	26	2.8 (0.4)	.36
Globulin (g/dL)	51	2.1 (1.0)	26	1.8 (1.2)	.43
Total bilirubin (mg/dL)	54	3.8 (1.4)	26	5.1 (2.3)	.012
Indirect bilirubin (mg/dL)	51	3.1 (1.3)	25	4.2 (2.1)	.018
Direct bilirubin (mg/dL)	52	0.7 (0.4)	25	0.8 (0.2)	.22
Triglyceride (mg/dL)	48	48 (43)	25	1366 (1133)	.042
Lactate (mmol/L)	48	3.8 (2.7)	25	3.9 (2.4)	.91
Alkaline phosphatase (IU/L)	44	1567 (841)	24	1671 (725)	.61
Asparate aminotransferase (IU/L)	50	191 (151)	25	192 (73)	.97
Creatine kinase (IU/L)	51	1966 (9211)	25	1081 (1725)	.66
γ-Glutamyl transferase (IU/L)	51	22 (14)	26	32 (32)	.096

hypoglycemia.[32] Hypoglycemia has been shown to be a risk factor for sepsis in equine neonates as well.[33,34] Our results reinforce this increase in risk for bacteremia in foals with hypoglycemia. The hypoglycemia associated with bacteremia is a multifactorial process and although the pathophysiology is not clear, it may be both a cause and result of bacterial infection. Hypoglycemia has been shown to induce a proinflammatory state, including upregulation of endothelial cell adhesion factors, altered responses of inflammatory cells, and high circulating concentrations of cytokines such as tumor necrosis factor and interleukin-6, which may predispose to altered immune clearance of bacterial organisms.[32,35] The weakness and impaired mentation associated with infection contribute to poor nursing, exacerbating the hypoglycemia and perhaps compromising adoptive transfer of immunoglobulins, although this interaction (hypoglycemia

TABLE 8 Summary proportions and univariate logistic regression ORs for clinical chemistry results for sick foals with or without a positive blood culture presented to an equine hospital, presented as categorical values

	Blood culture negative, N/total (%)	Blood culture positive, N/total (%)	OR (95% CI)	*P*
Sodium (mEq/L)				
<125	5/81 (6%)	2/42 (5%)	0.76 (0.11-3.70)	.75
Normal (125-159)	76/81 (94%)	40/42 (95%)	1	
>159	0/81 (0%)	0/42 (0%)	…	…
Potassium (mEq/L)				
<3.6	29/81 (36%)	15/42 (36%)	1.03 (0.47-2.25)	.93
Normal (3.6-5.6)	52/81 (64%)	26/42 (62%)	1	
>5.6	0/81 (0%)	1/42 (2%)	…	…
Chloride (mEq/L)				
<91	4/77 (5%)	1/40 (3%)	0.462 (0.023-3.25)	.49
Normal (91-113)	72/77 (94%)	39/40 (98%)	1	
>113	1/77 (1%)	0/40 (0%)	…	…
Magnesium (mg/dL)				
<0.7	1/61 (2%)	0/36 (0%)	…	…
Normal (0.7-4.2)	60/61 (98%)	36/36 (100%)	1	
>4.2	0/61(0%)	0/36 (0%)	…	…
Calcium (total) (mg/dL)				
<9.8	17/51 (33%)	5/27 (19%)	0.43 (0.13-1.26)	.14
Normal (9.8-13.7)	32/51 (63%)	22/27 (81%)	1	
>13.7	2/51 (4%)	0/27 (0%)	…	-
Creatinine (mg/dL)				
<1.1	12/79 (15%)	6/39 (15%)	1.018 (0.326-2.916)	.97
Normal (1.2-4.3)	57/79 (72%)	28/39 (72%)	1	
>4.4	10/79 (13%)	5/39 (13%)	1.018 (0.294-3.159)	.98
Glucose (mg/dl)				
<100	13/76 (17%)	17/39 (43%)	3.53 (1.47-8.73)	.005
Normal (100-200)	54/76 (71%)	20/39 (51%)	1	
>200	9/76 (12%)	2/39 (5%)	0.60 (0.08-2.58)	.54
Urea nitrogen (mg/dl)				
<8	7/77 (9%)	4/37 (11%)	1.3 (0.32-4.66)	.69
Normal (9-40)	66/77 (86%)	29/37 (78%)	1	
>41	4/77 (5%)	4/37 (11%)	2.28 (0.51-10.23)	.27
Albumin(g/dl)				
<2.4	6/55 (11%)	4/26 (15%)	1.39 (0.33-5.39)	.63
Normal (2.5-3.6)	46/55 (84%)	22/26 (85%)	1	
>3.7	3/55 (5%)	0/26 (0%)	…	…
Globulin (g/dL)				
<1.4	19/51 (37%)	12/26 (46%)	1.63 (0.61-4.41)	.33
Normal (1.5-4.6)	31/51 (61%)	12/26 (46%)	1	
>4.7	1/51 (2%)	2/26 (8%)	5.167 (0.45-117.23)	.19
Total bilirubin (mg/dL)				
<1.2	0/54 (0%)	0/26 (0%)	…	-
Normal (1.3-4.5)	41/54 (76%)	11/26 (42%)	1	
>4.6	13/54 (24%)	15/26 (58%)	4.301 (1.61-12.0)	.004

TABLE 8 (Continued)

	Blood culture negative, N/total (%)	Blood culture positive, N/total (%)	OR (95% CI)	*P*
Direct bilirubin (mg/dL)				
<0.2	2/52 (4%)	0/25 (0%)	-	-
Normal (0.3-0.7)	39/52 (75%)	8/25 (32%)	1	
>0.8	11/52 (21%)	17/25 (68%)	7.53 (2.66-23.20)	<.001
Indirect bilirubin (mg/dL				
<0.9	1/51 (2%)	0/25 (0%)	…	…
Normal (1.0-3.8)	39/51 (76%)	13/25 (52%)	1	
>3.9	11/51 (21%)	12/25 (48%)	3.27 (1.18-9.39)	.02
Triglyceride (mg/dL)				
<29	13/48 (27%)	1/24 (4%)	0.13 (0.007-0.073)	.06
Normal (30-193)	34/48 (71%)	20/24 (80%)	1	
>194	1/48 (2%)	3/24 (13%)	5.10 (.61-106.97)	.17
Lactate (mmol/L)				
<0.5	0/41 (0%)	0/23 (0%)	…	…
Normal (.6-1.9)	10/41 (24%)	3/23 (13%)	1	
>2.0	31/41 (76%)	20/23 (87%)	2.15 (0.57-10.46)	.29
Alkaline phosphatase (IU/L)				
<860	8/44 (18%)	3/24 (13%)	0.59 (0.12-2.39)	.48
Normal (861-2671)	30/44 (68%)	19/24 (79%)	1	
>2672	6/44 (14%)	2/24 (8%)	0.53 (0.07-2.56)	.46
Aspartate aminotransferase(IU/L)				
<145	22/50 (44%)	7/25 (28%)	0.468 (0.16-1.30)	.16
Normal (146-340)	25/50 (50%)	17/25 (68%)	1	
>341	3/50 (6%)	1/25 (4%)	0.490 (0.023-4.20)	.55
Creatine kinase (IU/L)				
<39	1/50 (2%)	2/23 (9%)	4.87 (0.44-109.26)	.21
Normal (40-909)	39/50 (78%)	16/23 (70%)	1	
>910	10/50 (20%)	5/23 (21%)	1.22 (0.34-4.03)	.75
γ-Glutamyl transferase (IU/L)				
<18	21/51 (41%)	11/24 (42%)	1.29 (0.45-3.57)	.16
Normal (18-43)	27/51 (53%)	11/24 (42%)	1	
>44	3/51 (6%)	4/24 (16%)	3.27 (0.63-19.03)	.63

and FPT) was not found to be a statistically significant risk factor in our study.

We reconfirmed that an abnormal mSS (≥11) was significantly associated with an increased risk of the foal being blood culture-positive. This finding was not unexpected because the purpose of the foal mSS is to predict the occurrence of bacteremia.[15] Even so, the OR for this effect was modest, indicating the association was weak at best, and the calculated sensitivity and specificity of the foal mSS on this data set were poor (54 and 66%, respectively). Poor sensitivity and specificity (67% and 76%, respectively) have been documented previously[23] from the same institution as our study, although our findings indicate even poorer performance when applying the mSS outside of the original institution in which it was developed. Using the original cut-off point of ≥11 for the mSS, a previous study reported sensitivity of 62% and specificity of 64%,[34] whereas another study reported sensitivity of 56.4% and specificity of 73.4%.[25] Although a useful tool for the management of sick neonates, these findings further underscore the poor reliability of the foal mSS in its current form and suggest that overdependence on this tool should be avoided.

Previous research has suggested an increased incidence of bacteremia in foals with diarrhea, in that a higher proportion of foals with diarrhea had positive blood cultures (50%) compared to a historical population of all presenting foals to the same hospital.[6] Our findings did not support such a conclusion in that there was no increased risk for blood culture-positive status associated with the presence of diarrhea at presentation. There are substantial differences in study design and population that may explain the different findings, however. In the previous study, foals up to 30 days of age were included,[6]

TABLE 9 Microbial sensitivity results for organisms recovered from blood culture of neonatal foals (<14 days of age) presented to an equine neonatal ICU

Category	Antimicrobial Amik Ns/N (%)	Amp Ns/N (%)	Ceft Ns/N (%)	CHPC Ns/N (%)	Enro Ns/N (%)	Gent Ns/N (%)	Imipen Ns/N (%)	Pen Ns/N (%)	Tet Ns/N (%)	TMS Ns/N (%)
All bacteria	97/149 (65)	84/137 (61)	98/148 (66)	94/146 (64)	100/128 (78)	86/118 (73)	101/116 (87)	57/133 (43)	75/104 (72)	81/148 (55)
All Gram positive	42/80 (53)	55/78 (71)	49/79 (62)	44/78 (56)	45/71 (63)	43/64 (67)	55/60 (92)	42/77 (55)	43/58 (74)	37/79 (47)
Group C *Streptococcus* spp.[a]	2/5 ([a])	4/4 ([a])	5/5 ([a])	2/5 ([a])	2/4 ([a])	3/4 ([a])	4/4 ([a])	4/5 ([a])	2/3 ([a])	1/5 ([a])
Enterococcus spp. and group D *Streptococcus* spp.	2/14 (14)	11/14 (79)	7/14 (50)	7/14 (50)	6/13 (46)	6/13 (46)	11/12 (92)	6/14 (43)	8/12 (66)	3/14 (21)
All Gram negative	55/69 (80)	29/59 (49)	49/69 (71)	50/68 (74)	55/57 (97)	43/54 (80)	46/56 (82)	15/56 (27)	32/46 (70)	44/69 (64)
Escherichia coli	21/24 (88)	14/24 (58)	19/24 (79)	19/24 (79)	17/19 (89)	14/18 (78)	17/20 (85)	1/20 (5)	10/19 (53)	15/24 (63)

Note: Data are presented as the number of organisms classified as sensitive (Ns) and the total number of organisms (N). Amik refers to amikacin, Amp (ampicillin), Ceft (ceftiofur), CHPC (chloramphenicol), Enro (enrofloxacin), Gent (gentamicin), Imipen (imepenim), Pen (penicillin), tet (tetracycline), and TMS (trimethoprim-sulfadiazine).

[a]Percentages for this group not presented due to low numbers of observations.

compared to our study population which included foals <14 days of age, as well as differences in primary diagnoses, co-morbidities, and geographic region. Furthermore, most foals in our study were <72 hours of age at the time of presentation, a period during which the integrity of the mucosal barrier is not well developed. This conclusion is supported by the observation in another study of bacteremia in 4/7 of clinically normal, healthy foals in the first 3 days of life.[36] The blood culture-positive results of 33% in our study are similar to other reports, in which the blood culture-positive rate ranged from 26%[2] to 63%.[4,10,25,34,37]

The nature of the organisms recovered in our study also was similar to other studies, but differed somewhat in the proportions observed.[2,10,37] Our study documented a higher proportion of Gram-positive organisms than did previous studies, in which Gram-negative bacteria typically predominated. This finding is consistent with a documented trend toward an increase in Gram-positive isolates over the last 20 years.[2,5,37,38]

The findings in our study regarding the antimicrobial susceptibilities of the isolates identified are similar to other recent reports.[5,38] Of concern was the apparent efficacy of amikacin and gentamicin, at only 80% against all Gram-negative isolates, whereas amikacin had a higher efficacy against *E coli* (88%) as compared to gentamicin (78%). Other recent reports have indicated that >90% of Gram-negative isolates were sensitive to amikacin.[5,38] Given the widespread use of ceftiofur as a first-line drug in equine neonates in the United States, additional concern was noted because of the relatively low sensitivity of organisms to ceftiofur in our study as compared to other studies, with only 66% of all isolates being susceptible (62% of Gram-positive organisms and 71% of Gram-negative organisms).[38] Tetracyclines had a relatively high in vitro sensitivity for organisms in our study, with 72% of all isolates susceptible, whereas only 55% of isolates were susceptible to trimethoprim/sulfonamide combinations.

Clinicians must carefully evaluate antimicrobial selection and make treatment choices based on the specific needs of the patient. Direct extrapolation from in vitro sensitivity to in vivo efficacy is not always appropriate; it is necessary to consider factors such as co-morbidities, bioavailability, site of infection, and the presence of purulent material, which might influence effectiveness. For example, a drug with good in vitro sensitivity may have poor PO bioavailability, limiting its effectiveness if given by that route. In addition, elaboration of extended spectrum beta-lactamase enzyme (ESBL) by *E coli* organisms can dramatically alter in vivo effectiveness compared to in vitro testing. The *E coli* organisms reported in our study were not routinely tested for the presence of ESBLs. Proper antimicrobial stewardship requires careful evaluation of all pertinent patient factors and should be based on more than just the in vitro sensitivity results, although such results are crucial to proper selection of antimicrobials.

Our study had some limitations, most of which reflect issues inherent to retrospective analyses. Incomplete recorded data as well as an inconsistent method of assigning diagnoses are possible factors. We attempted to compensate for these factors by careful examination of all data points to ensure they were taken within the defined 2-hour time limit after admission, because of the potential effects of rehydration and initial treatment. Furthermore, absence of notation in the records regarding a clinical observation was not interpreted as being absence of the factor, rather it was considered missing data and was instead removed. These actions resulted in the loss of some data; however, this approach was considered important for the validity of

the conclusions. For example, for numerous foals, a value for lactate concentration was present but we often were unable to confirm the precise time at which the sample was taken relative to admission. These results then were eliminated to avoid bias potentially caused by the effects of therapeutic intervention. Given the frequency with which this variable is evaluated in clinical patients, it would be of interest to examine this analyte further in additional studies. Similar challenges existed for several other variables.

An additional potential complicating factor is the blood culture technique, which could lead to failure to identify a truly positive blood culture or recovery of contaminants. For foals in our study, the samples were taken using strict aseptic technique, but only 1 sample was collected. Numerous factors can impact the sensitivity of microbial recovery from blood culture in humans including the blood volume, multiple vs single collection, the sampling site, preparation of the venipuncture site, use of sterile gloves, catheter dwell time, nature of antisepsis, and use of a catheter vs direct collection.[39] None of these factors have been evaluated in foals to our knowledge, and it is impossible to know what effects the sampling technique might have had on the culture results. A second concern is the potential for contamination and false positives.[39] Studies of false-positive blood culture results in human patients have been reported and range as high as 56% in studies from the 1990s[40,41] to much lower rates (2.4-8.2%) in more recent reports.[424344] A false-positive rate of 1.6% has been reported in humans using a newly inserted catheter and sterile technique, as was done in our study.[45] Although it is possible that false-positive results may have occurred in our study, we believe they are unlikely to have been a common occurrence because of the consistent use of an aseptic sampling protocol, which has been determined in humans to result in a low incidence rate. We believe, however, that the technique used for blood collection in our study was robust and of a high standard. Because the same technique was used for all foals, potential systematic bias should have been minimal and group comparisons remain valid. Furthermore, the results obtained in terms of overall recovery are similar to other widely reported studies of blood culture in foals. Therefore, we feel that false-positive and false-negative results had limited effects on our study conclusions.

Proper interpretation of the data also requires an understanding of the meaning of risk factors in the context of epidemiological investigations. A risk factor is defined as "an attribute or exposure (sometimes called determinant) that is associated with an increased probability of a specific outcome" (in this case, blood culture-positive status).[46] In the context of our investigation, the term risk factor is not intended to imply causation and should not be construed as such. Finally, our conclusions apply only to sick neonatal foals in a hospital setting; it would be inappropriate to extrapolate these findings to normal, healthy foals in a nonhospital setting.

Our results identify several factors that increase the probability of a foal having a positive blood culture. The presence of an umbilical abnormality, hypoglycemia, and anemia is highly predictive of bacteremia. Other clinical findings that have been reported to be associated with increased risk of bacteremia, such as diarrhea and FPT, were not found to significantly increase the risk for a foal to be found to be bacteremic in our study. Furthermore, our results support the findings of other investigators that the mSS has moderate to poor accuracy in prediction of bacteremia. Knowledge of these risk factors and their limitations potentially can aid clinicians in making clinical decisions about the care of neonatal foals as well as guiding owners and animal caretakers.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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