Journal of Veterinary Internal Medicine
Open Access
J Vet Intern Med 2015;29:673–677

Plasma C-Reactive Protein and Haptoglobin Concentrations in Critically Ill Neonatal Foals

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Background: Accurate diagnostic markers for sepsis in neonatal foals are needed. Plasma C-reactive protein concentration (p[CRP]) and haptoglobin concentration (p[Hp]) are well-established biomarkers of infection in humans, but studies are lacking in foals.

Hypotheses: p[CRP]) and p[Hp] are increased in septic foals compared to sick nonseptic and healthy control foals, and are predictive of survival.

Animals: Eighty critically ill foals (40 septic, 40 sick nonseptic) and 39 healthy control foals <1 week of age.

Methods: Multicenter, prospective observational clinical study. Venous blood was collected at admission from septic and sick nonseptic foals and from clinically healthy foals at 24 h of age. A diagnosis of sepsis was made based on positive blood culture or a sepsis score >11, and p[CRP] and p[Hp] were measured by using ELISA tests. Data were analyzed by using the Mann-Whitney *U*-test and forward stepwise multivariable linear regression. $P < .05$ was considered significant.

Results: Plasma [CRP] was positively associated with age, serum globulin, adrenomedullin, and bilirubin concentrations, aspartate aminotransferase activity, glutamyl-transferase activity, band neutrophil count, and rectal temperature, and was increased in foals with toxic neutrophils, enterocolitis, colic, rib fractures and septic arthritis. Surprisingly, p[Hp] was lower in septic foals than in sick nonseptic foals. Neither p[CRP] or p[Hp] was predictive of survival in critically ill foals.

Conclusions and Clinical Importance: Plasma [CRP] increases with inflammation in neonatal foals but is not indicative of sepsis. Single time point, admission sampling of p[CRP] and p[Hp] do not appear to be useful biomarkers for sepsis in foals.

Key words: C-reactive protein; Foal; Haptoglobin; Sepsis; Survival.

Bacterial sepsis remains a leading cause of morbidity and mortality in neonatal foals despite substantial advances in medical management.[1–4] Early and accurate diagnosis and treatment of neonatal sepsis are important for foal survival, but definitive diagnosis can be difficult. Confirmation of microbial infection in the presence of systemic inflammatory response syndrome (SIRS) is required for a diagnosis of sepsis, but microbial culture has poor sensitivity and specificity in foals.[5,6] A sepsis scoring system that utilizes historical and diagnostic variables is commonly used to diagnose sepsis in foals, but also is limited in sensitivity and specificity.[7–9] A simple, rapid and reliable test that provides an early and accurate diagnosis of sepsis and ideally predicts outcome therefore would serve to decrease morbidity, mortality, and associated treatment costs in affected foals.

Abbreviations:

CRP	C-reactive protein
p[CRP]	plasma C-reactive protein concentration
Hp	haptoglobin
p[Hp]	plasma haptoglobin concentration
LPS	lipopolysaccharide
RAO	recurrent airway obstruction
CBC	complete blood count

The acute phase response to sepsis involves release of proinflammatory cytokines that induce production of major and minor acute phase proteins (APPs) from hepatocytes. C-reactive protein (CRP) is a major APP in most species that is well-established as a biomarker of infection and inflammation in human infants.[10] During the acute phase of sepsis in humans, serum CRP concentration can increase up to 1,000-fold within hours.[10] Concentrations remain increased during persistent infection in humans and then decrease rapidly after resolution of infection, with a half-life of 19 h.[11] Moderate increases in plasma CRP concentration (p[CRP]) occur in human infants as a result of birth stress, but the increase is much lower than that observed in septic infants.[12] Studies in horses have determined that serum or plasma [CRP] is a minor APP that is moderately increased within 3–5 days of an inflammatory event. Serum [CRP] is increased with aseptic inflammation induced by IM turpentine injection,[13] and in horses with pneumonia, enteritis, arthritis,[14] and experimentally induced laminitis.[15] The

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This work was performed at Purdue University in West Lafayette, IN; at Hagyard Equine Medical Institute in Lexington, KY; at Washington State University in Pullman, WA; and at Gumz Farms in Morgantown, KY. The study was supported, in part, by the Purdue University College of Veterinary Medicine Summer Scholar's program. Results were presented, in part, at the 2013 Dorothy Havemeyer Neonatal Workshop in Saugerties, NY, USA.

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Submitted October 30, 2014; Revised December 31, 2014; Accepted February 3, 2015.

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DOI: 10.1111/jvim.12568

accuracy of a single p[CRP] measurement for the diagnosis of sepsis varies widely in human medicine,[16] with the ideal time point for measurement being unknown in foals. Newborn foals that have not suckled colostrum have very low serum [CRP] (<1 mg/L), but serum [CRP] rapidly increases after birth to a mean of 6.6 mg/L at 3 days of age.[13]

Haptoglobin (Hp) is another major APP in most species that increases during the acute phase response to sepsis in humans. Haptoglobin regulates monocyte activation after lipopolysaccharide (LPS) stimulation and is higher in septic human infants than in sick, nonseptic infants.[17,18] Studies in horses have determined that serum or plasma [Hp] is a minor APP that is moderately increased within 4–6 days of an inflammatory event. Serum [Hp] is increased in horses with recurrent airway obstruction (heaves), aseptic inflammation induced by IM turpentine injection, laminitis, and surgery.[19–22] Newborn foals that have suckled colostrum have mean serum [Hp] that vary depending on the assay used.[19,23] Serum [Hp] does not change appreciably in healthy foals after the first 12 months of life.[19]

We are unaware of any reports of p[CRP] or p[Hp] in critically ill neonatal foals. We hypothesized that p[CRP] and p[Hp] would be increased in septic foals compared to sick nonseptic and healthy control foals, and that increased p[CRP] and p[Hp] would be predictive of survival. The objectives of the study therefore were to compare p[CRP] and p[Hp] among septic, sick nonseptic, and healthy neonatal foals and determine the value of p[CRP] and p[Hp] in predicting survival.

Materials and Methods

Animals

This study was approved by the Purdue University Institutional Animal Care and Use Committee. Sick foals <1 week of age (n = 90) that were hospitalized at Purdue University's Veterinary Teaching Hospital and at Hagyard Equine Medical Institute during the 2011 and 2012 foaling season were recruited for the study. Foals were categorized retrospectively, with septic foals (n = 42) demonstrating a positive sepsis score (>11)[9] or a positive blood culture, and sick nonseptic foals (n = 48) having a sepsis score ≤11 and negative blood culture results when available. Foals euthanized for financial reasons were excluded.

Healthy foals (n = 39) were obtained from Washington State University's equine teaching herd and a private farm in Kentucky. Foals were considered healthy if there was normal parturition and normal gestation duration, normal physical examination findings at 24 h of age, and adequate transfer of passive immunity (IgG concentration >800 mg/dL) at 24 h of age.

Information obtained from medical records of septic and sick nonseptic foals at admission included signalment, historical complaints, physical examination findings, hematologic data, plasma fibrinogen concentration, serum biochemical data, arterial or venous blood gas data, blood L-lactate concentration, blood IgG concentration at 24 h of age, blood culture results, treatments, and outcome. Survival was defined as discharge from the hospital.

Sample Collection and Analytical Methods

In sick foals, jugular venous blood (10 mL) was collected in an EDTA tube at admission by venipuncture or IV catheter. In healthy foals, blood was collected by jugular venipuncture (10 mL) into an EDTA tube at 24 h of age. Plasma was separated within 30 min of collection by centrifugation at 1,300 × *g* (3,000 rpm) for 15 min at 4°C. Plasma was stored at −20°C at Hagyard Equine Medical Institute until transport to Purdue University, where samples were stored at −80°C until analysis.

Stored plasma samples were selected at random (by pulling case numbers from a hat) from 42 septic, 48 sick nonseptic, and 61 healthy control foals. Samples had been previously thawed once to determine plasma adrenomedullin concentrations and then refrozen, results of which are included in a separate study.[24] Human plasma CRP is stable for at least 20 years at −70°C[25] and for at least 7 freeze-thaw cycles.[26] Human plasma Hp is stable for at least 1 year at −70°C.[27] Plasma [CRP] and p[Hp] were measured using previously validated, commercially available equine-specific ELISAs for CRP[a] and Hp,[b] respectively. For [CRP] and [Hp], the company's reported intra-assay and interassay coefficients of variation (CV) are <10%. Samples and standards were tested in duplicate and concentrations were determined using a standard curve.

Statistical Analysis

Continuous data were expressed as median and range for each of the 3 groups of foals because of nonnormally distributed data based on the Shapiro-Wilk test for normality. Significance was set at $P < .05$. Clinicopathologic findings in septic and nonseptic sick foals, and associated clinical diagnoses, have been reported elsewhere.[24] Associations between clinicopathologic factors and p[CRP] or p[Hp] for septic and nonseptic sick foals were examined by using Spearman's rho (r_s). The Mann-Whitney *U*-test was used to evaluate comparisons of interest between categorical variables and p[CRP] or p[Hp]. Forward stepwise multivariable linear regression was used to determine the association of various clinicopathologic factors and clinical diagnoses with p[CRP] and p[Hp] using variables with $P < .20$ based on application of Spearman's rho (continuous variables) or the Mann-Whitney *U*-test (categorical variables). To minimize the effects of collinearity, when 2 evaluated variables were closely correlated with each other ($r_s > 0.75$), only the variable that had the highest r_s was entered into the model. The relative importance of the included variables was assessed by the order of entry as well as by the change in the model R^2 value (ΔR^2). Residual plots of each model were examined to confirm an approximately normal distribution of residuals. A statistical software program[c] was used for all analyses.

Results

Study Population

The 39 healthy foals were 24 h of age. The healthy control group breeds were Arabians (24) and Quarter Horses (15). Healthy foals were comprised of 59% (23/39) colts and 41% (16/39) fillies.

A total of 40 septic, 40 sick nonseptic and 39 healthy foals <1 week of age were enrolled in the study. The median age (range) of septic and sick nonseptic foals were 10 (1–192) and 6 (1–72) h, respectively. Representative breeds in the 40 septic foals were Thoroughbreds (28), Quarter Horses (7), Standardbreds (2), Clydesdales (1), and Warmbloods (1) and in the 40 sick nonseptic foals were Thoroughbreds (34), Quarter Horses (2), Standardbreds (2), Clydesdales (1), and Arabians (1). In the septic group, there were 58% (23/40) colts and 42% (17/40) fillies. In the sick nonseptic group, there were 73% (29/40) colts and 27% (11/40) fillies. Of the septic

foals, microbial blood culture submitted at the time of admission was positive in 21 (53%) cases. The survival rates for septic and sick nonseptic foals were 70% (28/40) and 80% (32/40), respectively.

Plasma [CRP]

There was no difference in p[CRP] between critically ill foals and healthy foals ($P = .14$) or between septic and sick nonseptic foals ($P = .26$, Table 1). Plasma [CRP] was not predictive of survival in critically ill foals (n = 60, $P = .64$).

In septic and nonseptic sick foals, p[CRP] was positively associated with age ($r_s = 0.64$; $P < .0001$; Fig 1), serum globulin concentration ($r_s = 0.64$; $P < .0001$), adrenomedullin concentration ($r_s = 0.56$; $P < .0001$), aspartate aminotransferase activity ($r_s = 0.53$; $P < .0001$), serum total bilirubin concentration ($r_s = 0.46$; $P < .0001$), band neutrophil count ($r_s = 0.45$; $P < .0001$), rectal temperature ($r_s = 0.44$; $P < .0001$), and serum glutamyl-transferase activity ($r_s = 0.39$; $P = .0004$), and negatively associated with serum alkaline phosphatase activity ($r_s = -0.33$; $P = .0027$), serum calcium concentration ($r_s = -0.33$; $P = .0033$), serum albumin concentration ($r_s = -0.27$; $P = .015$), and platelet count ($r_s = -0.25$; $P = .031$). Plasma [CRP] was not associated with p[Hp] ($P = .56$).

Plasma [CRP] was increased in foals with toxic changes in neutrophils (n = 35, $P < .0001$), enterocolitis (n = 14, $P = .0034$), colic (n = 8, $P = .0048$), rib fractures (n = 10, $P = .033$), and septic arthritis (n = 2, $P = .036$). Plasma [CRP] was decreased in foals that were born by cesarean section (n = 10, $P = .0043$), born in dystocia (n = 38, $P = .0080$), or that were premature (n = 16, $P = .018$).

Plasma [Hp]

There was no difference in p[Hp] between critically ill foals and healthy foals ($P = .34$), but p[Hp] was decreased in septic foals compared to sick nonseptic foals ($P = .047$; Table 1). Plasma [Hp] was not predictive of survival in critically ill foals (n = 60, $P = .49$).

In septic and nonseptic sick foals, p[Hp] was positively associated with plasma fibrinogen concentration ($r_s = 0.51$; $P < .0001$; Fig 2), lymphocyte count ($r_s = 0.37$; $P = .0013$), hemoglobin concentration ($r_s = 0.33$; $P = .0028$), and platelet count ($r_s = 0.32$; $P = .0041$). Plasma [Hp] was negatively associated with serum creatine kinase activity ($r_s = -0.40$; $P = .0003$) and serum total bilirubin concentration ($r_s = -0.40$; $P = .0003$).

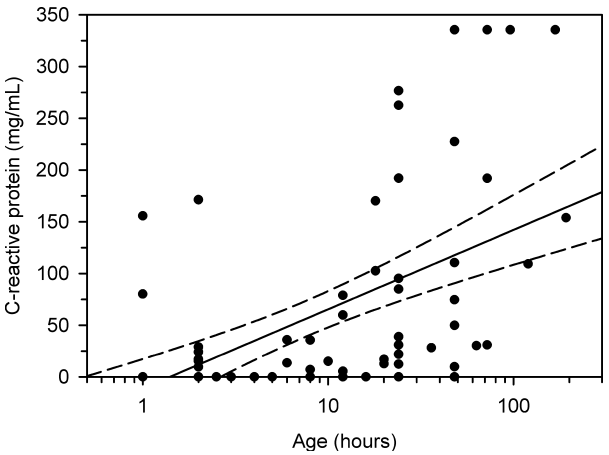

Fig 1. Scatterplot of the association ($r_s = 0.64$, $P < .0001$) between plasma C-reactive protein concentration and age (log scale) for 80 critically ill foals with sepsis or nonseptic illness. A linear regression line (solid line) and 95% confidence interval for the line (dashed lines) are presented as a visual guide.

Multivariable Regression

Forward stepwise multivariable regression indicated that the most important predictor of p[CRP] was age at admission, which explained 38% of the variability in p[CRP] (Table 2). Other independent predictors were the serum total bilirubin concentration, rectal temperature, and the presence of toxic neutrophils in the blood smear. The final model explained 57% of the variability in p[CRP].

Forward stepwise multivariable regression indicated that the most important predictor of p[Hp] was plasma fibrinogen concentration, which explained 52% of the variability in p[Hp] (Table 2). Other independent predictors were serum creatine kinase activity and hemoglobin concentration. The final model explained 88% of the variability in p[CRP].

Discussion

The main finding of the study reported here was that p[CRP] does not indicate the presence of septic or nonseptic illness in neonatal foals. However, p[CRP] was positively associated with band neutrophil count and rectal temperature, and negatively associated with serum albumin concentration and platelet count, and increased in foals with toxic neutrophils, enterocolitis, colic, rib fractures, and septic arthritis, suggesting that p[CRP] might increase with inflammation. Plasma [CRP] previously has been shown to increase in horses

Table 1. Plasma concentrations of C-reactive protein and haptoglobin in septic foals, sick nonseptic foals, and healthy foals. Concentrations are median and range in parentheses.

Factor	Septic Foals (n = 40)	Sick Nonseptic Foals (n = 40)	Healthy Foals (n = 39)
C-reactive protein (mg/mL)	15 (0–336)	6 (0–260)	39 (0–240)
Haptoglobin (mg/mL)	1,190 (238–3,200)	1,619 (392–3,200)	1,627 (601–3,224)

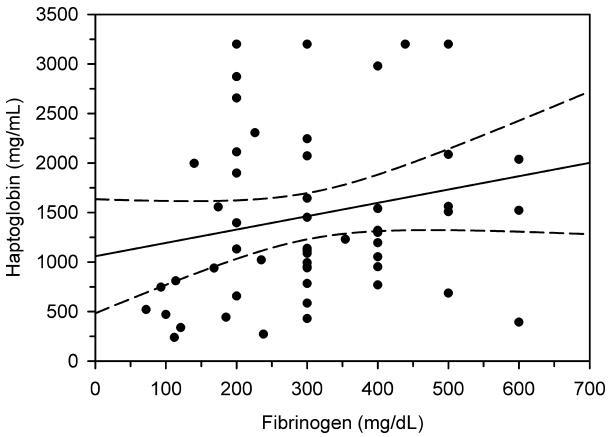

Fig 2. Scatterplot of the association ($r_s = 0.51$, $P < .0001$) between plasma haptoglobin concentration and plasma fibrinogen concentration for 80 critically ill foals with sepsis or nonseptic illness. A linear regression line (solid line) and 95% confidence interval for the line (dashed lines) are presented as a visual guide.

with pneumonia, enteritis, arthritis, laminitis, and turpentine-induced muscle injury.[14,15] Taken together, these data suggest that p[CRP] increases with nonspecific inflammation in horses but is not associated specifically with sepsis.

Plasma [CRP] was positively associated with age and was lower in foals that were premature, had experienced dystocia, or had been delivered by cesarean section. Given that the median age of foals presented with prematurity, dystocia, or cesarean section was 2 h (range, 1–48 h), our findings are consistent with those of a previous study that found that foals have very low serum [CRP] at birth, and that serum [CRP] increases rapidly after birth.[13] It remains to be determined whether suckling colostrum influences the increase in p[CRP] after birth. Birth stress increases p[CRP] in human infants, with peak concentrations observed at 48 h of age.[10,12,25] Serial measurements of p[CRP] in healthy neonatal foals therefore are required to assess whether or not birth stress affects p[CRP], and if so, when the maximal response to birth stress is expected to occur. Healthy control foals in this study were 24 h of age, and peak p[CRP] related to birth stress may not yet have peaked in this population. Given that 69% of critically ill foals were <24 h of age, birth stress increases may not have been appreciated in the majority of these foals. In septic human patients, p[CRP] reaches peak levels 36–50 h after the onset of sepsis.[26] Among septic foals, p[CRP] may not have been different compared to sick nonseptic or healthy control foals because concentrations had not yet increased appreciably or peaked after the onset of sepsis in this population. Finally, p[CRP] may be a poor indicator of inflammation in neonatal foals. Serial measurements of p[CRP] in septic and sick nonseptic foals are necessary to determine the diagnostic utility of this APP in neonatal foals.

Decreased p[Hp] in critically ill foals was associated with sepsis in our study. This result might be because of hemolysis, because p[Hp] was negatively associated with serum total bilirubin concentration, and because hemolysis can lead to Hp-hemoglobin binding and thereby decrease p[Hp].[27] However, septic foals did not have clinical or hematologic evidence of hemolysis, and hematology results from healthy control foals were not available for comparison. Interestingly, serum [Hp] is decreased in newborn foals with anemia and babesiois because of transplacental infection with *Babesia equi*.[28] The strong association between p[Hp] and plasma fibrinogen concentration observed in our study suggests that measurement of p[Hp] has minimal clinical utility because analytical methods for fibrinogen determination are faster and more widely available at lower cost than analytical methods for p[Hp].

The inclusion criteria for sepsis in this study were positive microbial blood culture or a positive sepsis score. False-positive blood culture results may have resulted from bacterial contamination of needles or skin, or culture of transient bacteria that can be found in healthy foals early in the postnatal period.[5] False-negative blood culture results could result from low numbers of circulating bacteria or a relatively low volume of blood used for culture. Taken together, more rigorous criteria for sepsis, such as a positive microbial blood culture in combination with a positive sepsis score or isolation of the same bacteria from at least 2 different sites may provide a more accurate assessment of sick neonatal foals.

Table 2. Results of stepwise multiple linear regression for the prediction of plasma C-reactive protein concentration or plasma haptoglobin concentration in 80 critically ill foals. These models explained 56% of the variation of plasma C-reactive protein concentration and 52% of the variation of plasma haptoglobin concentration.

Order of entry	Variable	ΔR^2	Model R^2	Coefficient	±SE	*P*-value
C-reactive protein (mg/mL)						
	Intercept	–	–	−842	320	0.010
1	Age (h)	0.384	0.384	0.92	0.24	0.0003
2	Total bilirubin (mg/dL)	0.099	0.483	9.3	2.2	<0.0001
3	Rectal temperature (°F)	0.043	0.525	8.3	3.2	0.012
4	Neutrophil toxic changes	0.037	0.563	38.1	15.5	0.016
Haptoglobin (mg/mL)						
1	Fibrinogen (mg/dL)	0.301	0.301	3.39	0.66	<0.0001
2	Creatine kinase (U/L)	0.168	0.469	−0.34	0.09	0.0007
3	Hemoglobin (g/dL)	0.051	0.519	100	45	0.032

NS, not significant.

A major limitation of this study was the lack of age-matched control foals, particularly in light of the positive association between p[CRP] and age. In a clinical setting, it is impossible to determine the exact time of sepsis onset, making it difficult to assess single concentrations of APPs in septic foals. Although not observed in this study, increases in p[CRP] or p[Hp] might occur several hours after admission. Taken together, serial measurements of APPs in healthy neonatal foals are necessary to evaluate the potentially dynamic nature of these proteins in the postnatal period. Similarly, serial measurements of APPs in critically ill neonatal foals would allow more complete assessment of their diagnostic and prognostic utility in sepsis.

Footnotes

[a] Horse CRP ELISA Cat. No. KT-487, Kamiya Biomedical Company, Seattle, WA
[b] Horse Haptoglobin ELISA Cat. No. KT-488, Kamiya Biomedical Company, Seattle, WA
[c] SAS 9.3, SAS Inc, Cary, NC

Acknowledgments

The authors thank Dr. Katherine MacGillivray, Dr. Michele Frazer, and Dr. Kim Sprayberry for sample collection and evaluation of critically ill foals that presented to Hagyard Equine Medical Institute, Dr. Robert Mealey at Washington State University and Megan Lundquist at Gumz Farms for providing control foal samples, and Anisa Dunham and Tina Elam for technical assistance.

Conflict of Interest Declaration: Peter Constable is a Consulting Editor for Experimental Design and Statistics at the Journal of Veterinary Internal Medicine.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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