J Vet Intern Med 1999;13:81–88

Model to Predict Septicemia in Diarrheic Calves

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The difficulty in distinguishing between septicemic and nonsepticemic diarrheic calves prompted a study of variables to predict septicemia in diarrheic calves <28 days old that were presented to a referral institution. The prevalence of septicemia in the study population was 31%. Variables whose values were significantly different ($P < .10$) between septicemic and nonsepticemic diarrheic calves were selected using stepwise, forward, and backward logistic regression. Variables identified as potentially useful predictors were used in the final model-building process. Two final models were selected: 1 based on all possible types of predictors (laboratory model) and 1 based only on demographic data and physical examination results (clinical model). In the laboratory model, 5 variables retained significance: serum creatinine > 5.66 mg/dL (>500 μmol/L) (odds ratio [OR] = 8.63, $P = .021$), toxic changes in neutrophils ≥ 2+ (OR = 2.88, $P = .026$), failure of passive transfer (OR = 2.72, $P = .023$), presence of focal infection (OR = 2.68, $P = .024$), and poor suckle reflex (OR = 4.10, $P = .019$). Four variables retained significance in the clinical model: age ≤ 5 days (OR = 2.58, $P = .006$), presence of focal infection (OR = 2.45, $P = .006$), recumbency (OR = 2.98, $P = .011$), and absence of a suckling reflex (OR = 3.03, $P = .031$). The Hosmer–Lemeshow goodness-of-fit chi-square statistics for the laboratory and clinical models had *P*-values of .72 and .37, respectively, indicating that the models fit the observed data reasonably well. The laboratory model outperformed the clinical model by a small margin at a predictabilty cutoff of 0.5, however, the predictive abilities of the 2 models were quite similar. The low sensitivities (39% and 40%) of both models at a predicted probability cutoff of 0.5 meant many septicemic calves were not being detected by the models. The specificity of both models at a predicted probability cutoff of 0.5 was >90%, indicating that >90% of nonsepticemic calves would be predicted to be nonsepticemic by the 2 models. The positive and negative predictive values of the models were 66–82%, which indicated the proportion of cases for which a predictive result would be correct in a population with a prevalence of septicemia of 31%.

Key words: Age; Behavior; Creatinine; Failure of passive transfer; Focal infection; Toxic neutrophils.

The mortality risk of live-born neonatal calves <1 month of age has been reported to range from 15 to 30%.[1–4] The majority of deaths are attributable to infectious diseases; diarrhea, pneumonia, and septicemia are the most common.[5–8] The predominant pathogen cultured from calves with septicemia is *Eschericia coli*, but other gram-negative, gram-positive, and mixed bacterial infections have been documented.[9–12]

Important risk factors for the development of septicemia in calves include decreased passive transfer of colostral immunoglobulins and exposure to invasive bacterial serotypes.[13] Neonatal diarrhea may also predispose calves to septicemia. In 2 separate studies conducted on a California veal operation, blood cultures revealed bacteremia in 31% and 19% of calves with signs of diarrhea, depression, and/or weakness.[10,14] Septicemia in these calves was attributed to intestinal mucosal damage caused by bacterial, viral, or parasitic gastrointestinal infections, which allowed opportunistic gut pathogens to enter the systemic circulation.[10]

The early signs of septicemia in neonatal foals and calves are vague and nonspecific and are often indistinguishable from signs of noninfectious diseases or those of focal infections such as diarrhea.[14,15] Positive blood cultures are required for a definitive antemortem diagnosis of septicemia, but results are not reported for 48–72 hours, and false-negative culture findings are common.[12,16] No single laboratory test has emerged as being completely reliable for the early diagnosis of septicemia in farm animal neonates,[12,17] therefore, various scoring systems and predictive models using easily obtainable historical, clinical, and clinicopathologic data have been developed for this purpose.[14,17–19] The goal of these mathematical models is to identify septicemic neonates early in the course of disease when appropriate therapeutic intervention would most likely result in a favorable outcome.

For a period of time, routine blood cultures were performed on all diarrheic calves presented to the Atlantic Veterinary College Teaching Hospital regardless of whether the clinical or clinicopathologic findings indicated a diagnosis of septicemia. Results of this exercise indicated that septicemia was more common in diarrheic neonatal calves than we had anticipated and that it increased the cost of treatment while decreasing the prognosis for survival. A model capable of predicting sepsis in diarrheic neonatal calves presented to the hospital for treatment would assist the clinicians in distinguishing between calves with undifferentiated diarrhea and calves with diarrhea complicated by sepsis. In the case of a relatively low-value calf with diarrhea and predicted sepsis, the farmer may be advised not to initiate treatment because of the expense involved and the poor prognosis. In contrast, the owner of a valuable diarrheic calf that was predicted to be septic could be informed that early initiation of costly but appropriate antimicrobial and supportive therapy may result in an improved outcome.

Models to predict septicemia in calves have been published.[14,19] Study populations in these reports consisted of veal calves, 1 day to 4 months of age, with signs of serious illness (diarrhea, depression, and/or weakness)[14] and calves <30 days of age that were presented to a veterinary teach-

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Received June 26, 1996; Revised August 5, 1998; Accepted August 14, 1998.

0891-6640/99/1302-0001/$3.00/0

ing hospital for clinical evaluation and therapy.[19] The objective of this study was to develop a model that would predict septicemia in diarrheic calves <28 days of age presented for treatment to a veterinary teaching hospital.

Materials and Methods

Independent Variables

Medical records of calves <28 days of age presented to the Atlantic Veterinary College Teaching Hospital between the years 1989 and 1993 with a primary complaint of diarrhea were retrieved. Pretreatment data were extracted from the medical records of these calves. Independent variables included demographic information and physical examination findings and clinicopathologic values for hematology, venous blood gases, serum chemistry, and immunoglobulins (Table 1). Immunoglobulin concentration in serum was determined quantitatively or qualitatively using a variety of procedures, including the quantitative zinc sulfate turbidity test (69 calves),[20] sodium sulfite precipitation test (17 calves), gluteraldehyde coagulation test (62 calves), and radial immunodiffusion test (5 calves). Failure of passive transfer of immunoglobulins was defined as an IgG concentration of ≤800 mg/dL by any of the above mentioned tests, a globulin concentration of ≤2 g/dL (≤20 g/L), or total serum protein of ≤5 g/dL (≤50 g/L) (Table 1). Other information extracted from the medical records of the calves in the study population were fecal culture, fecal electron microscopic examination, and fecal floatation results.

Logistic regression assumes that the relationship between any independent variable recorded on a continuous scale (eg, respiratory rate) has a linear relationship with the logit of the probability of sepsis. For each such independent variable, this assumption was assessed by evaluating the distribution of the independent variable, categorizing the independent variable in 2 or more groups and cross-tabulating the new variable with sepsis, or running unconditional logistic regressions with the variable in question and evaluating the Hosmer–Lemeshow goodness-of-fit statistics. The most appropriate form for each independent variable was then chosen (Table 1). Categorical variables were all entered into the predictive models as a series of dummy variables.

Dependent Variables

The dependent variable of interest was a diagnosis of septicemia. A diagnosis of septicemia in diarrheic calves was based on the following antemortem criteria: (1) positive blood culture, (2) culture of the same bacterial agent from ≥2 body fluids, or (3) culture of a bacterial agent from a single joint in a calf with joint effusion involving multiple joints. Blood for culture was collected aseptically from the jugular vein and inoculated into the Oxoid Signal blood culturing system (Oxoid Canada, Inc, Nepean, ON, Canada). A number of criteria contributed to a postmortem diagnosis of septicemia, including (1) morphologic changes such as multiple disseminated abscesses of similar size, purulent vasculitis and intravascular identification of bacteria, or fibrin in multiple body cavities; (2) bacterial isolation from heart blood; or (3) recovery of the same bacterial organism from ≥2 body tissues (excluding intestine). Other outcome variables recorded were days hospitalized and calf survival.

Model-Building Procedure

Means for continuous variables were compared between septicemic and nonsepticemic calves using Student's *t*-test.[21] Categorical variables were analyzed using contingency table chi-square analysis.[21] Variables that were significantly different ($P < .10$) between septicemic and nonsepticemic calves were grouped into 1 of 3 categories: physical variables, hematological variables, and chemistry variables, which included measures of passive transfer. Variables in each group were selected for logistic regression models using stepwise, forward, and backward selection procedures.[22] Variables identified as possibly useful

Table 1. Demographic, physical examination, and laboratory variables extracted from the records of diarrheic calves in a retrospective study of risk factors for septicemia.

Variable	Unit or Description
Demographic	
Age	0 = >5 days; 1 = ≤5 days
Breed	One of 10 possible breeds, coded 1–10
Sex	0 = female; 1 = male
Physical examination	
Attitude	0 = bright and alert; 1 = depressed; 2 = unresponsive or comatose.
Capillary refill time	Seconds
Dehydration	% body weight loss
Focal infection	Hypopyon/uveitis, joint effusion, omphalitis, or neurologic signs suggestive of meningitis; 0 = no; 1 = yes
Mucous membrane color	0 = pink; 1 = pale; 2 = hyperemic or cyanotic
Posture	0 = standing; 1 = sternal or lateral recumbency
Pulse rate	Beats/minute
Respiratory rate	Breaths/minute
Scleral injection	0 = no; 1 = yes
Suckling reflex	0= strong; 1 = weak or absent
Rectal temperature	°C
Hematologic	
Packed cell volume	%
White blood cells	$\times 10^3/\mu L$
Segmented neutrophils	$\times 10^3/\mu L$
Band neutrophils	$\times 10^3/\mu L$
Neutrophil toxic changes	0 = toxic changes scored ≤1+; 1 = toxic changes scored ≥2+
Total plasma protein	g/dL
Fibrinogen	mg/dL
Venous blood gas	
Blood pH	$[-\log(H^+)]$
Bicarbonate	mEq/L
Blood CO_2	mmHg
Base excess	mEq/L
Serum chemistry	
Albumin	g/dL
Chloride	mEq/L
Creatine kinase	IU/L
Creatinine	1 = ≤1.98 mg/dL (≤175 μmol/L) (normal); 2 = 1.99–5.66 mg/dL (176–500 μmol/L) (moderate increase); 3 = (>500 μmol/L) (marked increase)
Glucose	mg/dL
Glutamyl transferase	IU/L
Ionized calcium	mg/dL
Potassium	mEq/L
Sodium	mEq/L
Immunoglobulin	
Failure of passive transfer	IgG ≤800 mg/dl, globulin ≤2 g/dL (≤20 g/L), total serum protein ≤5g/dL (≤50 g/L); 0 = no; 1 = yes

predictors by the various selection procedures were used in the final model building process. This process involved comparing a number of possible models and selecting those that maximized the area under the receiver operating characteristic (ROC) curve[23] but that did not include any variables whose coefficients were not significant ($P < .05$). Two final models were selected: one based on all possible types of predictors (the laboratory model) and one based only on demographic data and physical examination results (the clinical model).

Odds ratios (OR) derived from the models were interpreted as measures of increased risk of disease. Because septicemia was not a rare condition, the OR were not precise measures of increased risk, but the approximation was reasonable and was utilized to clarify the presentation of results.

Once final models were selected, their sensitivity and specificity were determined at predictive probability cutoff points of 0.5 and 0.3 (the points that roughly balanced the sensitivity and the specificity). The goodness of fit of the models was evaluated using the Hosmer–Lemeshow goodness-of-fit chi-square statistic[22] with the data divided into 5 groups. For each model, the Pearson residuals, the standardized Pearson residuals, and the $\Delta\beta$ values were computed for all covariate patterns to determine if any specific covariate pattern had an undue influence on the model.

Because evaluating the fit of a model using the same data that were used to build the model is likely to overestimate the predictive ability of the model, a split sample goodness-of-fit evaluation was also carried out. The data were randomly (using a computer based random number generator) divided into 2 separate databases with 60% and 40% of the observations in each. The 2 models were refit using the database containing 60% of the observations by forcing in all of the independent variables included in the 2 final models described above. The predictive ability of the resulting models was assessed using the database containing 40% of the observations.

Analyses were performed on a personal computer using the statistical software package STATA (Stata Corp, College Station, TX).

Results

Calves

Two hundred fifty-four calves met the criteria for inclusion in the study. However, 2 calves were excluded from analysis because they could not be classified as either septicemic or nonsepticemic based on criteria established for the study; *Campylobacter*-like organisms were seen on Gram stains of their blood, but the organisms were not recovered from blood culture.

Demographic Information and Fecal Culture Results

The mean age of diarrheic calves at presentation was 9.4 days. Crossbred beef calves (32.9%) and Holstein calves (22.2%) constituted the majority of admissions. There were 119 female and 131 male calves; the sex of 2 calves was not recorded. Fecal cultures were positive for enterotoxigenic strains of *E. coli* in 68 of 177 (38.4%) calves in which fecal cultures were performed. Electron microscopy was used to evaluate fecal samples from 181 calves and was positive for rotavirus in 22 calves (12.2%), positive for coronavirus in 70 calves (38.7%), and positive for both viruses in 15 calves (8.3%). Cryptosporidia were demonstrated on fecal floatation in 59 of 178 calves (33.1%).

Septicemic Calves and Bacterial Pathogens Recovered

Seventy-eight (31%) of the calves met the study criteria for a diagnosis of septicemia. Positive blood cultures were used to diagnose 50 cases (40.7% of all blood cultures were positive). A single organism was cultured from most calves but 3 of the blood cultures yielded 2 isolates each. *E coli* accounted for 29 (55%) of the isolates from blood. An additional 10 bacterial agents were cultured from the blood, including *Campylobacter* spp. (8), *Staphylococcus* spp. (5), *Streptococcus* spp. (3), *Pseudomonas aeruginosa* (2), *Actinomyces pyogenes* (1), *Pasteurella haemolytica* (1), *Enterococcus* spp. (1), *Acinetobacter* spp. (1), *Bacillus* spp. (1), and *Clostridium* spp. (1). Culture of the same pathogen from $\geq$2 body fluids antemortem were used to diagnose 6 cases, and a positive antemortem joint culture from a calf with multiple enlarged joints was used to diagnose 1 case. The same bacterial agent was cultured from $\geq$2 tissues at necropsy in 33 calves, postmortem heart blood culture was positive in 1 calf, and morphologic lesions such as multiple abcessation, purulent vasculitis, intravascular identification of bacteria, and fibrin exudation in multiple body cavities, were present in 18 calves. *E coli* was also the most frequent isolate in antemortem body fluid and postmortem tissue samples, accounting for 7/11 (64%) and 93/154 (60%) isolates, respectively. Because individual calves often satisfied multiple criteria for a diagnosis of septicemia, the totals for all the above criteria are greater than the total number of septicemic calves.

Outcomes for Septicemic and Nonsepticemic Calves

One hundred forty-one of the 174 nonsepticemic calves (81%) were discharged from the hospital (survived) compared with only 23 of 78 septicemic calves (29.5%). The mean hospital stay for nonsepticemic calves that lived was 4.1 days compared with 5.0 days for septicemic calves that survived.

Variables Identified as Potentially Useful Predictors

Variables identified as potentially useful predictors ($P < .1$) are described in Table 2. Septicemic calves had significantly higher ($P < .05$) values for respiratory rate, packed cell volume, band neutrophil count, and venous P_{CO_2} than did nonsepticemic calves. Mean values for rectal temperature and total plasma and serum protein, globulin, calcium, and glucose concentrations were significantly lower ($P < .05$) in septicemic than in nonsepticemic calves. A significantly larger ($P < .05$) proportion of septicemic calves was $\leq$5 days of age, unresponsive or comatose, and in sternal or lateral recumbency at presentation when compared with nonsepticemic calves. The proportion of septicemic calves exhibiting a weak or absent suckling reflex, scleral injection, and hyperemic or cyanotic oral mucous membranes was also significantly greater ($P < .05$). Elevated serum creatinine concentration, toxic changes in neutrophils $\geq$2+, and failure of passive transfer of colostral immunoglobulins were present more frequently in septicemic than in nonsepticemic calves ($P < .05$).

Selection of Models and Evaluating Goodness of Fit and Predictive Abilities

Two final models, the laboratory model and the clinical model, were selected based on the maximal area under the

Table 2. Means of continuous independent variables and frequency distributions (%) and odds ratios (OR) of categorical independent variables identified as potentially useful predictors ($p < 0.1$) of septicemia in diarrheic calves.

	Septicemic Calves		Nonsepticemic Calves			
Variable	n (%)	Mean	n (%)	Mean	OR[a] (95% CI)	*P*
Continuous						
Dehydration, %	72	7.7	166	6.7		0.079
Respiratory rate, breaths/minute	74	44	159	37		0.011
Rectal temperature, °F (°C)	76	99.7 (37.6)	169	100.8 (38.2)		0.009
Band neutrophils, $\times 10^3/\mu L$ ($\times 10^9/L$)	54	2.4 (2.4)	146	1.3 (1.3)		0.005
Packed cell volume, % (L/L)	72	40 (0.40)	160	36 (0.36)		0.001
Total plasma protein, g/dL	65	6.14 (61.4)	147	6.72 (67.2)		0.002
Serum albumin, g/dL	59	2.82 (28.2)	133	2.94 (29.4)		0.053
Ionized calcium, mg/dL (mmol/L)	68	4.72 (1.18)	152	4.92 (1.23)		0.046
Serum globulin, g/dL	59	2.59 (25.9)	133	3.05 (30.5)		0.02
Serum glucose, mg/dL (mmol/L)	54	60 (3.3)	123	89.09 (4.9)		0
Total serum protein, g/dL	59	5.40 (54.0)	133	5.94 (59.4)		0.012
Blood CO_2, mmHg	68	54.5	153	48.5		0.004
Categorical						
Age						
>5 days	45	(57.7)	134	(77.5)		0.001
≤5 days	33	(42.3)	39	(22.5)	2.5 (1.42–4.46)	
Creatinine						
<1.98 mg/dL (≤175 mmol/L)	29	(49.2)	93	(68.9)		0.001
1.99–5.66 mg/dL (176–500 mmol/L)	22	(37.3)	40	(29.6)	1.8 (0.91–3.42)	
>5.66 mg/dL (>500 mmol/L)	8	(13.6)	2	(1.5)	12.8 (2.88–nd) (2.57–63.83)[b]	
Neutrophil toxic changes						
No (≤1+)	30	(56.6)	125	(85.6)		0.000
Yes (≤2+)	23	(43.4)	21	(14.4)	4.6 (2.25–9.26)	
Failure of passive transfer[c]						
No	21	(30.9)	95	(62.9)		0.000
Yes	47	(69.1)	56	(37.1)	3.8 (2.07–6.97)	
Attitude						
Bright, alert	1	(1.3)	27	(13)		0.000
Depressed	53	(68.8)	120	(71)	11.9 (1.99–nd) (1.58–90.07)[b]	
Unresponsive or comatose	23	(29.9)	57	(16)	23.0 (3.63–nd) (2.90–182.6)[b]	
Mucous membrane color						
Pink	21	(28)	93	(68.9)		0.002
Pale	33	(44)	40	(29.6)	3.7 (1.89–7.04)	
Hyperemic or cyanotic	21	(28)	2	(1.5)	46.5 (11.1–nd) (10.1–218.8)[b]	
Posture						
Standing	12	(15.4)	81	(48.2)		0.000
Sternal or lateral recumbency	66	(84.6)	87	(51.8)	5.1 (2.6–10.1)	
Scleral injection						
No	53	(74.6)	135	(88.8)		0.007
Yes	18	(25.4)	17	(11.2)	2.7 (1.3–5.58)	
Suckling reflex						
Strong	6	(8.2)	64	(39.8)		0.000
Weak or absent	67	(91.8)	97	(60.2)	7.4 (3.08–17.55)	

[a] Odds ratios for categorical variables with >2 categories were computed by comparing each level to the baseline level. CI, confidence interval.
[b] Woolf's approximation for CI was used when the upper limit of the Cornfield's approximation was not defined (nd).
[c] Failure of passive transfer defined as IgG ≤ 800 mg/dL, serum globulin ≤ 2.0 g/dL, or serum total protein ≤ 5.0 g/dL.

Table 3. Logistic regression models for septicemia in diarrheic calves. One model (laboratory) was based on all possible predictors, including physical examination and laboratory data. The other model (clinical) was based solely on findings from the physical examination and history of the calf.

Variable	Coefficient	Probability	Odds Ratio	95% confidence interval		
Laboratory model (n = 148 calves)						
Intercept	−2.741	0				
Serum creatinine (moderate increase)	0.727	0.116	2.069	0.836	–	5.119
Serum creatinine (marked increase)	2.155	0.021	8.629	1.383	–	53.827
Neutrophil toxic changes	1.057	0.026	2.878	1.131	–	7.318
Passive transfer failure	1.003	0.023	2.72	1.150	–	6.490
Focal infection	0.985	0.024	2.678	1.135	–	6.317
Suckling reflex	1.142	0.019	4.102	1.257	–	13.383
Hosmer–Lemeshow goodness-of-fit $\chi^2 = 1.32$, df = 3, $P = .72$						
Clinical model (n = 220 calves)						
Intercept	−2.199	0				
Age	0.948	0.006	2.58	1.310	–	5.080
Focal infection	0.895	0.006	2.448	1.286	–	4.662
Posture	1.092	0.011	2.979	1.289	–	6.889
Suckling reflex	1.109	0.031	3.03	1.107	–	8.293
Hosmer–Lemeshow goodness-of-fit $\chi^2 = 3.11$, df = 3, $P = .37$						

ROC curve (Table 3). Variables included in the laboratory model were serum creatinine concentration, toxic changes in neutrophils ≥2+, failure of passive transfer, focal infection, and a poor suckle reflex. The clinical model identified age of ≤5 days, focal infection, recumbency, and a poor suckle reflex as predictors of septicemia. The laboratory model indicated that calves with moderately increased serum creatinine concentration were twice as likely to be septicemic (OR = 2.07; 95% CI = 0.836–5.119), whereas those with creatinine concentration of >5.66 mg/dL (>500 μmol/L) were 8 times more likely to be septicemic (OR = 8.63; 95% CI = 1.383–53.827). Similarly, evidence of toxic changes in their neutrophils (≥2+), failure of passive transfer, or evidence of focal infections all increased the risk of septicemia by 2.68–2.88 times. Calves with a poor suckle reflex were 4 times as likely to be septic. The clinical model (ie, model containing only data from the physical examination and history) showed that each of the following was a factor that increased the risk of being septicemic by approximately 2.5–3-fold: <5 days of age, signs of focal infection, recumbent on admission, and poor suckle reflex.

The Hosmer-Lemeshow goodness-of-fit chi-square statistics for the laboratory and clinical models had *P*-values of 0.72 and 0.37, respectively, indicating that the models fit the observed data reasonably well. Evaluation of residual patterns did not identify any outlining observations, and no specific group of calves (ie, calves with a common covariate pattern) exerted a large influence on the model. We concluded that the models fit the data reasonably well.

Table 4. Predictive ability of logistic regression models based on full data set (full) and 60% of data set (split) at 2 different cutoff values for considering a calf to be septic.

Model	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ROC[3]
Cutoff 0.5					
Laboratory model					
Full	40	95.4	76.2	81.1	0.817
Split	23.5	94.1	66.7	71.1	0.813
Clinical model					
Full	39.4	90.6	66.7	75.8	0.78
Split	26.5	96.2	81.8	66.7	0.761
Cutoff 0.3					
Laboratory model					
Full	75	75	52.6	89	0.817
Split	70.6	76.5	60	83.9	0.813
Clinical model					
Full	69	74.5	56.3	83.5	0.78
Split	76.5	76.9	68.4	83.3	0.761

PPV, positive predictive value; NPV, negative predictive value; ROC, area under the ROC curve.

The predictive abilities of the models are presented in Table 4. When evaluated at a cutoff value of 0.5 (ie, a calf was predicted to be septicemic if the predicted probability was ≥0.5), all models had quite low sensitivity and very high specificity. A cutoff of 0.3 roughly balanced the sensitivity and specificity and has been presented for comparison purposes. The laboratory models outperformed the clinical models, but only by a small margin. Similarly, the models based on the full data set outperformed those in which the model was constructed on 60% of the data and its predictive ability was evaluated in the other 40%. However, the differences were small.

Overall, using a probability cutoff of 0.5 to define predicted sepsis, the model sensitivities ranged from 25 to 40% and the specificities ranged from 90 to 95%. The low sensitivities mean that many septicemic calves would not be detected by the model. However, the positive and negative predictive values ranged from 66 to 82%, which indicates the proportion of cases in which the predicted result was correct (for a population with a prevalence of septicemia of 31%).

At a cutoff of 0.3, the models had sensitivities and specificities in the 70–75% range, which means that a much

higher proportion of septicemic calves would have been detected by the model. However, a positive prediction was only associated with a 52–68% probability (positive predictive value) that the calf was truly septic. However, a negative prediction was associated with an 83–89% probability (negative predictive value) that the calf was not septic.

Discussion

Thirty-one percent of the diarrheic calves in this study were diagnosed with septicemia based on results of blood cultures, antemortem or postmortem tissue or fluid cultures, and morphologic changes at postmortem. The prevalence of septicemia in this study was identical to that reported for calves with diarrhea, depression, and/or weakness on a veal raising facility,[14] which suggests that the predictive values of the models developed herein may be relevant to other calf populations. The risk of contamination of the blood sample for culturing probably was low, so it is unlikely that many truly nonsepticemic calves were misclassified as septicemic. However, because of the low sensitivity of blood cultures[24,25] and the fact that blood was not cultured for some surviving calves, some truly septicemic calves may have been misclassified as nonsepticemic if they survived and were not subjected to postmortem examination. However, this misclassification probably was not common because (1) the calves survived, and the probability of survival was low if the calf was truly septicemic; and (2) the effect of misclassification of truly septicemic calves on the model would likely been a reduction in specificity, but low specificity was not a problem with either model.

E coli was the bacterial agent cultured with greatest frequency from septicemic calves in this study, a finding that agrees with results of previous investigations[10,12] and may be attributed to the fact that certain strains of *E coli* possess virulence factors that promote systemic invasion.[26] In addition to *E coli,* a variety of noncoliform bacteria were isolated. Of particular interest was the recovery of *Campylobacter fetus* subsp. *fetus* from blood of 8 diarrheic calves (15% of the isolates from blood); there is only 1 previous report of this agent being cultured from a septicemic calf.[10] Possible explanations for the frequent isolation of *Campylobacter* spp. in this study were that the Oxoid Signal® blood culture system was more effective than other blood culture systems for growing this agent or that there were unique predisposing factors leading to *Campylobacter* bacteremia in calves in our geographic location.

Two models, the laboratory model and the clinical model, were ultimately selected to predict septicemia in diarrheic neonatal calves presented for treatment. The laboratory model, which included all possible variables, was intended for use in a hospital setting where the clinician would have access to laboratory facilities. The clinical model, which contained only demographic and physical examination variables, was developed for use in the field.

Clinicopathologic parameters identified by the laboratory model as being associated with an increased risk of septicemia were moderate (1.99–5.66 mg/dL) (176–500 μmol/L) and marked (>5.66 mg/dL) (>500 μmol/L) increases in serum creatinine concentration, moderate to marked toxic changes in neutrophils (≥2+), and failure of passive transfer (IgG concentration ≤ 800 mg/dL, globulin ≤ 2 g/dL [≤20 g/L]), and total serum protein ≤ 5 g/dL (≤50 g/L). Because Azotemia secondary to shock and dehydration was anticipated in both septicemic and nonsepticemic diarrheic calves presented for treatment, it was interesting to note that moderate and marked increases in serum creatinine concentration in this study increased the risk of a calf being septicemic by 2- and 8-fold, respectively. Moderate to severe azotemia in septicemic calves was attributed to endotoxin induced tubular necrosis and embolic nephritis, in addition to decreased renal perfusion associated with dehydration. Toxic changes in neutrophils, which are induced by inflammatory mediators and endotoxins, are frequently encountered in septicemic calves[12]; therefore, inclusion of this variable in the laboratory model was not unexpected. Because the relationship between septicemia and failure of colostral antibody transfer has been documented in previous studies,[12,14] the increased risk of septicemia in calves with failure of passive transfer was also anticipated.

Both the laboratory model and the clinical model indicated that the risk of septicemia in calves with identified sites of focal infection (omphalitis, arthritis, meningitis, uveitis) was more than double that of calves without evidence of focal infection. This association was biologically plausible because one of the initial sites of bacterial invasion in septicemic calves is the umbilicus,[13] and hematogenous spread of infection to the meninges, synovial lining, and uveal tract are known to occur.[12] Inclusion of poor suckling reflex by both models and recumbency by the clinical model as predictors of septicemia in a population of diarrheic calves presented for treatment was unforseen. The fluid, blood gas, and electrolyte derrangements associated with the diarrhea could have caused recumbency and disinterest in suckling in the majority of calves in the study. However, multiple organ invasion by bacterial pathogens and the cascade of inflammatory reactions initiated by these infecting agents were more likely responsible for the increased frequency of recumbency and poor suckling reflex in septicemic calves. The clinical model indicated that being <5 days of age increased the risk of septicemia by 2.5-fold. This contrasts with results of a study conducted in veal calves where age >7 days significantly increased the risk of being blood culture positive.[14] The reason for this discrepancy between the 2 studies is unclear. Because most calves in the present study were presented for treatment in the winter months when all calves presented to the hospital would be born inside and there is increased stocking density in maternity pens, they could have been heavily exposed to pathogens early in life. The theory that enteritis predisposes calves >1 week of age to septicemia[10] was not supported by results of this study.

Although the laboratory model outperformed the clinical model by a small margin at a probability cutoff of 0.5, the predictive abilities of the 2 models were remarkably similar (Table 4). Thus, the practitioner in the field, without immediate access to a laboratory, could use the clinical model to predict septicemia in a diarrheic calf with almost the same accuracy as that of the clinician at a referral institution, who would be using the laboratory model for the same purpose. The low sensitivities (39% and 40%) of both mod-

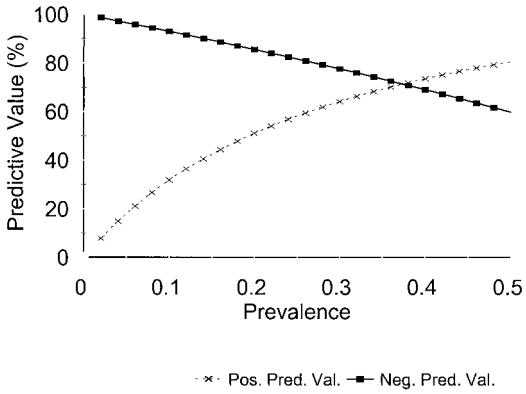

Fig 1. Relationship between the positive and negative predictive values of the clinical model for predicting septicemia in calves (sensitivity = 39.4%, specificity = 90.6%) and the prevalence of septicemia in the calf population examined.

els at a probability cutoff of 0.5 meant that many septicemic calves were not being detected by the models. One explanation is that other useful predictors of septicemia were not included in the models. However, with the exception of historical data pertaining to calving and management practices, most variables previously identified as risk factors in calves and foals were evaluated.[14,17,18] There may be no group of variables unique to the septicemic calf, partly because septicemia is a dynamic process and laboratory and clinical parameters can vary widely depending on when in the disease course the calf is evaluated. The specificity of both models at a cutoff of 0.5 was >90%, indicating that >90% of nonsepticemic calves would be predicted to be nonsepticemic by the 2 models.

When the predictive probability cutoff value was set to 0.5, the laboratory model had a positive predictive value of 76%. This cutoff could be used when the clinician wants to be relatively certain that a calf predicted to be septicemic would, in fact, be septicemic. For example, when dealing with a relatively low-value calf, a decision to euthanize the calf may be made given the poor prognosis for septicemic calves. In this situation, a high positive predictive value would be desirable.

When the predictive probability cutoff was set to 0.3, the positive predictive value decreased but the negative predictive value rose to 89%. Consequently, a clinician could be relatively certain that a calf that tested negative was, in fact, nonsepticemic. This would be a desirable situation when treating a valuable calf with diarrhea in which ancillary treatments for septicemia (broad spectrum antimicrobials and plasma) would only be omitted from the treatment plan if the clinician was relatively confident that the calf was nonsepticemic.

The predictive values for any test depend on the sensitivity and the specificity of the test and the prevalence of the disease. All of the predictive values discussed above are based on the assumption that the prevalence of septicemia was 31%. If the prevalence of septicemia in a population of calves presented for treatment were <31%, the negative predictive value of the test would rise but the positive predictive value would drop off dramatically (Fig 1).

The relatively small reduction in the predictive ability of the models when they were evaluated using a split sample approach was encouraging and suggests that the models may perform reasonably well in predicting future observations. However, there may still be a slight upward bias in the assessment of the performance of these models because the variables chosen for inclusion in the split sample assessment were those obtained from the analysis of the whole data set.

In conclusion, the predictive models fit the observed data reasonably well and had moderate predictive ability. The main limitation in the models seemed to be a low sensitivity. Many of the septicemic calves may have been early in the course of the disease and may not have had any distinguishing features that could be used to identify them as septicemic. Reassessment of these calves as the disease progresses may clarify their septicemia status but would not help in making initial decisions about therapy.

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