D-Dimer Improves the Prognostic Value of Combined Clinical and Laboratory Data in Equine Gastrointestinal Colic

By *M. Sandholm[1], A. Vidovic[2], A. Puotunen-Reinert[2], S. Sankari[1], K. Nyholm[1],* and *H. Rita[3]*

[1]Department of Clinical Sciences, College of Veterinary Medicine, Helsinki, Finland, [2]Hochmoor Tierklinik, Gescher-Hochmoor, Germany, and [3]Department of Forest Resource Management/Statistics, University of Helsinki.

Sandholm, M., A. Vidovic, A. Puotunen-Reinert, S. Sankari, and K. Nyholm: D-Dimer improves the prognostic value of combined clinical and laboratory data in equine gastrointestinal colic. Acta vet. scand. 1995, 36, 255-272. – The discriminating ability of 15 parameters alone or in combinations, including results from analysis of plasma endotoxin, the Nycomed plasma D-Dimer test and phospholipase A_2, were analyzed to predict morbidity and mortality in equine gastrointestinal colic. Endotoxaemia was a characteristic feature of the colic horses. The problem of adequately predicting nonsurvivors among colic horses required several parameters to be included in the logistic model: if the "classical parameters", (heart rate, respiratory rate, PCV, anion gap) were included in the model, addition of plasma D-dimer, phospholipase A_2, and Cl^- significantly improved the predictive value of the logistic model. Increasing heart rate and D-dimer together with decreasing chloride was a risk factor for nonsurvival. The sensitivity of this three-parameter logistic model to predict nonsurvival was 78% and specificity 77%. The Nycomed D-Dimer test is recommended as a horse-site test to predict disseminated intravascular coagulation and nonsurvival in equine colic.

horse; diagnosis; acute phase; mortality; inflammation; enzymes; sorbitol dehydrogenase; phospholipase; glutamate dehydrogenase; endotoxin; acid-base; thrombosis; fibrinolysis; DIC.

Introduction

Equine colic attributable to gastrointestinal tract disease is the leading cause of death in adult horses. Horses with acute abdominal crisis (colic) require immediate clinical decision-making as they often need surgery to open up mechanical obstructions, strangulations or displacements and to remove necrotic parts of the intestine. The operation requires skilful surgery, patient surveillance, and it is expensive. The mortality associated with such operations is high. Statistics from North American university clinics have shown that 40% of colic horses die in spite of surgery *(Morris* 1991). Therefore, it is highly desirable to have predictive clinical and laboratory tests to identify cases that need urgent surgical intervention and to judge whether irreversible damage already exists to indicate a hopeless prognosis.

When the intestinal wall is damaged, intestinal microflora-derived endotoxin is found in blood. The clinical features of gastrointestinal colic are very much the same as in gram-neg-

ative sepsis where the glycolipoid cell wall constituents (endotoxin, lipopolysaccharide, LPS) trigger the host to synthesize cytokines such as TNFα, IL-1 and IL-6. Cytokines in turn may induce the systemic inflammation response syndrome (SIRS) of the host and clinical features. Sepsis patients generally do not die of infection but of a hyperbolic inflammatory and an immune response that involves numerous biological pathways. The disease culminates in fluid- and acid-base disturbance, diffuse coagulopathy, multiple organ dysfunctions, and finally death. Survival largely depends on the degree of cardiovascular and metabolic derangement resulting from the lesion and host response.

Several studies have analyzed the diagnostic and prognostic value of predictor parameters and parameter combinations measured in routine examination of colic patients *(Parry et al.* 1983, *Puotunen-Reinert & Sandholm* 1985, *Puotunen-Reinert* 1986, *Orsini et al.* 1991, *Reevers et al.* 1992). High pulse rate associated with high packed cell volume, dull colour of mucous membranes, delayed oral mucous capillary refill time, disturbances in acid-base parameters (such as increased anion gap), and a hypercoagulative condition are currently considered valuable markers and can be used as predictors for poor prognosis in equine colic *(Darien et al.* 1991, *Gossett et al.* 1987, *Johnston & Crane* 1986, *Orsini et al.* 1988 & 1991, *Wirth* 1986). High blood lactate level has been taken as an estimator for the depth of shock *(Gossett et al.* 1987, *Waterman* 1977).

Our research objective was to develop a quantitative colic assessment method that would provide a reliable clinical tool to predict mortality before the horse undergoes surgery. Therefore, the applicability of the conventional markers (heart rate, breath rate, PCV, ionic composition of plasma, acid-base parameters) as well as plasma endotoxin, indica-

tors of thrombotic and fibrinolytic activities and the enzymes phospolipase A_2 (PLA_2), sorbitol dehydrogenase (SDH) and glutamic dehydrogenase (GLDH) were compared. The study design was to collect a similar number (about 50) of surviving colic horses, nonsurviving colic horses and controls, and to analyze retrospectively, which physiological and laboratory analyses would be most valuable alone or in combinations to allocate the horses correctly.

Materials and methods

The material consisted of 105 horses with severe gastrointestinal colic, delivered for operation between March 1992 and November 1992 to the Hochmoor Animal Hospital, Gescher-Hochmoor, Germany. Eighty patients were operated and 25 were treated conservatively; 42 colic horses died or had to be euthanized within 3 days. Another 52 healthy horses served as controls. Table 1 summarizes the classification of the patients.

After the clinical examination, venous and arterial blood samples were drawn for acid-base studies and laboratory analyses. Blood samples were collected again at 10h intervals irrespective of the stage of surgery. The total number of blood samples from colic horses was 229.

Table 1. Classification of horses included in the study.

Diagnosis	No
Colic attributable to gastrointestinal disease	105
Involvement of small intestine	41
Involvement of large intestine	51
Combined problem (small & large intestine)	5
Ruptured intestine	4
Peritonitis	2
Other gastrointestinal problems	2
Healthy control horses	52

Laboratory analyses

Packed cell volume (PCV) was analyzed by the capillary microcentrifuge method using heparinized blood samples.

Acid-base parameters, pH, pO_2, pCO_2, bicarbonate and base excess were studied from arterial blood samples using the ABL 300 Acid-Base Laboratory (Radiometer, Copenhagen, Denmark).

Serum electrolytes. Sodium, potassium and chloride were analyzed using ion-selective electrodes (Microlyte 3 + 2 Ion-selective Analyzer, Kone Oy Espoo, Finland). The anionic gap was calculated of the difference $(Na^+ + K^+) - (HCO_3^- + Cl^-)$.

Endotoxin concentration in blood plasma. The analysis was carried out by the Limulus amoebocyte lysate test (LAL) using the chromogenic COATEST® kit (Chromogenix AB, S-431 53 Mölndahl, Sweden) as the endpoint assay. The measurements were carried out at 37°C using the Labsystems FP-901 analysing system (Labsystems, Pulttitie 8, P.O.B. 8, 00881 Helsinki, Finland). The heparinized venous blood samples were diluted 1:10 with pyrogen-free distilled water and heat-treated in a water bath at 75°C for 5 min. The pretreated plasma samples were mixed with an equal volume (50 μl) of LAL reagent and standards and incubated for 30 min; 100 μl of the chromogenic protease substrate was added and incubated further for 10 min. The substrate conversion was stopped by adding 100 μl of 20% acetic acid and the released para-nitroaniline was measured photometrically at 405 nm. Plasma blanks were used throughout the procedure because plasma samples from colic horses were often haemolytic or lipemic. Least-square linear fitting was used to produce the regression line to be used for interpolation of the endotoxin contents.

Fibrinogen concentration of plasma. Venous blood was drawn in citrated Vacutainer® tubes (Becton Dickinson No 12697, North Canaan, CT / Broken Bow, NE, U.S.A). Plasma was separated by centrifugation, 3000 g/10 min. The plasma was transferred in siliconized glass tubes and stored at –20°C until analyzed. The plasma samples were diluted 1:8 with barbital buffer, 0.02 M, pH 8.6. An equal volume of thrombin (300 μl containing 9 N.I.H units thrombin (Topostasine®, Roche, F. Hoffmann-La Roche & Co. AG, Basel, Switzerland) in the barbital buffer was mixed at 37°C with diluted plasma samples in 9-well microcuvettes. The Labsystems FP-901 Chemistry Analyzer was used. The increase in turbidity, as measured between 2 and 60 sec, showed linear relationship with the fibrinogen contents. Fibrinogen standards were prepared from plasma from a control horse with known fibrinogen level (which had been analyzed with the fibrin clot protein method) by diluting it 1:8, 1:16 and 1:32 in 0.9% saline.

Plasma D-dimer. The fibrin(ogen) degradation product D-dimer was analyzed by the Nycomed NycoCard D-Dimer test (Nycomed Pharma Oslo, Norway). The test is based on immunofiltration through a membrane with attached monoclonal antibody and secondary staining with colloidal gold-labelled monoclonal antibody (Fig. 1) *(Gogstad et al.* 1993). In pilot studies we observed a cross reactivity between human and equine D-dimer using the test antibody.

Sorbitol dehydrogenase (SDH, EC 1.1.1.14) activity of plasma was analyzed by the method of *Gerlach & Hiby* (1974).

Glutamate dehydrogenase (GLDH, EC 1.4.1.3) activity of plasma was analyzed according to the recommendations of the German Society for Clinical Chemistry.

Phospholipase A_2 (PLA_2, EC 3.1.1.4) activity of plasma was analyzed by radial enzyme diffusion in lecithin-agar gels essentially

4) Buffer

3) Labeled antibody (colloid-gold)

2) Citrated plasma sample ⟻ D-Dimer

1) Buffer

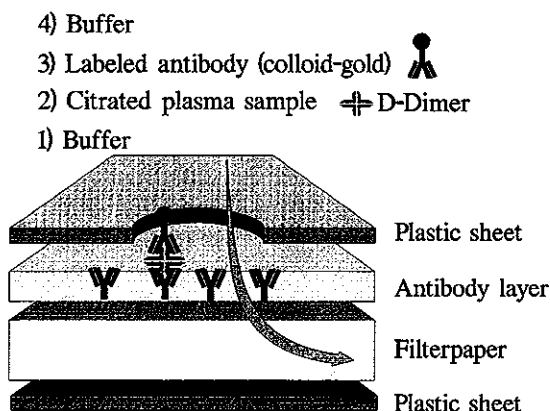
Plastic sheet

Antibody layer

Filterpaper

Plastic sheet

Figure 1. Principle of the NycoCard D-Dimer test. A filter paper layer is used to suck the plasma sample (50 μl) through the membrane with fixed antibody (both antibodies against D-Dimer). The trapped D-dimer is detected by the colloid-gold labelled second antibody. A purple colour (colloid-gold) indicates presence of D-Dimer in the plasma sample. The intensity of the colour is measured from the top by a reflectance meter or interpolated visually using a colour scale as reference. The result is obtained within 2 min. Elevated D-dimer indicates ongoing thrombosis and fibrinolytic process (disseminated intravascular coagulation DIC).

as described by *Puotunen-Reinert & Sandholm* (1985), but replacing the soybean lecithin with egg yolk. Thereby, the sensitivity of the assay increased. The turbid 2 mm thick agar plate contained 0.11% micellar egg yolk and 1% agar in 0.125 M TRIS-buffer, pH 8.0 containing 4 mM $CaCl_2$, and 0.1% NaN_3 as preservative. The 4 mm diameter wells were filled with 20 μl of plasma samples. The diameters of the cleared zones were measured after 24h of diffusion at 37°C. For interpolation, a standard dilution series of phospholipase A_2 (2, 0.2 and 0.02 U/ml, Sigma P-6534, Sigma Chemical Company St. Louis, MO, U.S.A.) was run in parallel. The interpolation was carried out using a log-linear least-squares fitting (log of PLA activity versus diameter of the cleared zone).

Statistical analysis

Two major problems in equine colic are A)

which parameters and combinations separate healthy and colic horses, and B) which parameters or combinations predict nonsurvival within the colic horses. The dynamic nature of the condition has to be considered, so we also looked at changes which occurred within the first 10h at the clinic.

Univariate analysis. As the distributions of several parameters did not appear normal, Spearman's rank-order correlation matrices (Tables 3 and 4) were used for exploratory data analysis. Transformations (ln transformation or squaring) were used to normalize the distribution of each parameter. When calculating diagnostic sensitivity and specificity, the threshold value of each parameter was set manually at the point where the vertical distance of the sigmoidal cumulative distribution of each pair (Fig. 2) was at its widest (maximum number of correct answers when the number of samples in both groups is identi-

Table 2. A. Comparison of samples from colic horses and control horses collected at admission. B. Comparison of survivors and nonsurvivors within the colic horses. Means, medians and significance of differences are given. The significance of the difference is based on nonparametric comparison (Mann-Whitney U-test).

| | A. | | | | | B. | | | | |
| | Controls (n = 52) | | Colic (n = 105) | | | Colic survivors (n = 63) | | Colic nonsurvivors (n = 42) | | |
Parameter	Mean	Median	Mean	Median	(p)	Mean	Median	Mean	Median	(p)
Heart rate/min	44.5	44.0	70.7	70.0	0.000	65.5	60.0	79.1	80.0	0.000
Breath rate/min	12.7	12.0	28.9	24.0	0.000	27.9	24.0	30.7	28.0	0.173
PCV %	39.0	39.0	46.4	45.0	0.000	44.1	43.0	49.8	49.5	0.005
K^+ mEq/l	4.3	4.3	3.4	3.4	0.000	3.4	3.3	3.5	3.5	0.730
Na^+ mEq/l	138.5	139.0	139.3	139.0	0.084	139.6	139.0	138.9	139.5	0.529
Cl^- mEq/l	100.9	101.0	98.3	99.0	0.000	99.2	99.0	96.9	97.5	0.013
HCO_3^- mEq/l	27.5	28.0	26.5	26.4	0.134	27.0	26.9	25.7	26.0	0.124
Anion gap mEq/l	14.4	14.3	18.0	16.9	0.000	16.7	16.6	19.8	18.5	0.007
Endotoxin ng/l	5.9	5.1	66.0	76.0	0.000	66.7	79.3	64.7	65.8	0.917
Tot.plasma prot. g/l	63.2	62.0	67.7	67.0	0.009	67.3	66.0	68.5	70.0	0.473
Fibronogen g/l	4.0	3.8	3.5	3.3	0.000	3.3	3.3	3.7	3.1	0.631
D-dimer mg/l	0.2	0.2	0.8	0.5	0.000	0.5	0.5	1.2	0.6	0.004
Phospholipase U/ml	297.0	265.1	507.5	370.8	0.000	394.5	313.5	677.1	457.4	0.005
SDH U/l	3.2	2.3	9.8	4.7	0.000	8.3	3.7	12.0	6.5	0.000
GLDH U/l	2.2	1.1	36.4	3.4	0.000	28.5	2.2	48.5	4.3	0.033

cal). The same variable sets were analyzed by logistic regression. In this case, the threshold was placed at 0.5 probability level; π (p) = ½. The aim was to use an objective threshold criterion and to avoid specific features of this data to influence the estimation discriminating potential (diagnostic specificity and sensitivity) of each predictor. The sensitivity ("true positives") and specificity ("true negatives") percentages derived from comparison of observed and predicted probabilities (Table 5). In colic horses for which there was more than 1 sample (the second sampling at 10h from admission), the 10h value and the 0-10h change of each parameter were used as additional predictors. This would indicate the trend showing which parameters become more important towards death. The Statgraphics 6 plus statistical graphics package was used (Manugistics, Rockville, MD, U.S.A.). The Statistix 4.1 package was used for logistic pro-

cedures (Analytical Software, Tallahassee, FL, U.S.A.)

Multivariate statistics. Multiple logistic regression, was used as the means for selecting predictor variables to differentiate A) between healthy and colic, and B) between survivors and nonsurvivors. We first studied whether the "new" variables (endotoxin, D-dimer, PLA_2, SDH, GLDH and Cl^-) would improve the model when added to the "classical" set of predictors (heart rate, breath rate, PCV and anion gap). The "new" variables were added one by one to the model including the "classical" variables. The observed proportion of deaths (or disease, in problem A) was compared with the expected proportion (i.e. predicted by logistic regression models) for each increment. Their significance was based on the improvement of G^2 statistic. The other method was to avoid assumptions and to find out which set of parameters would re-
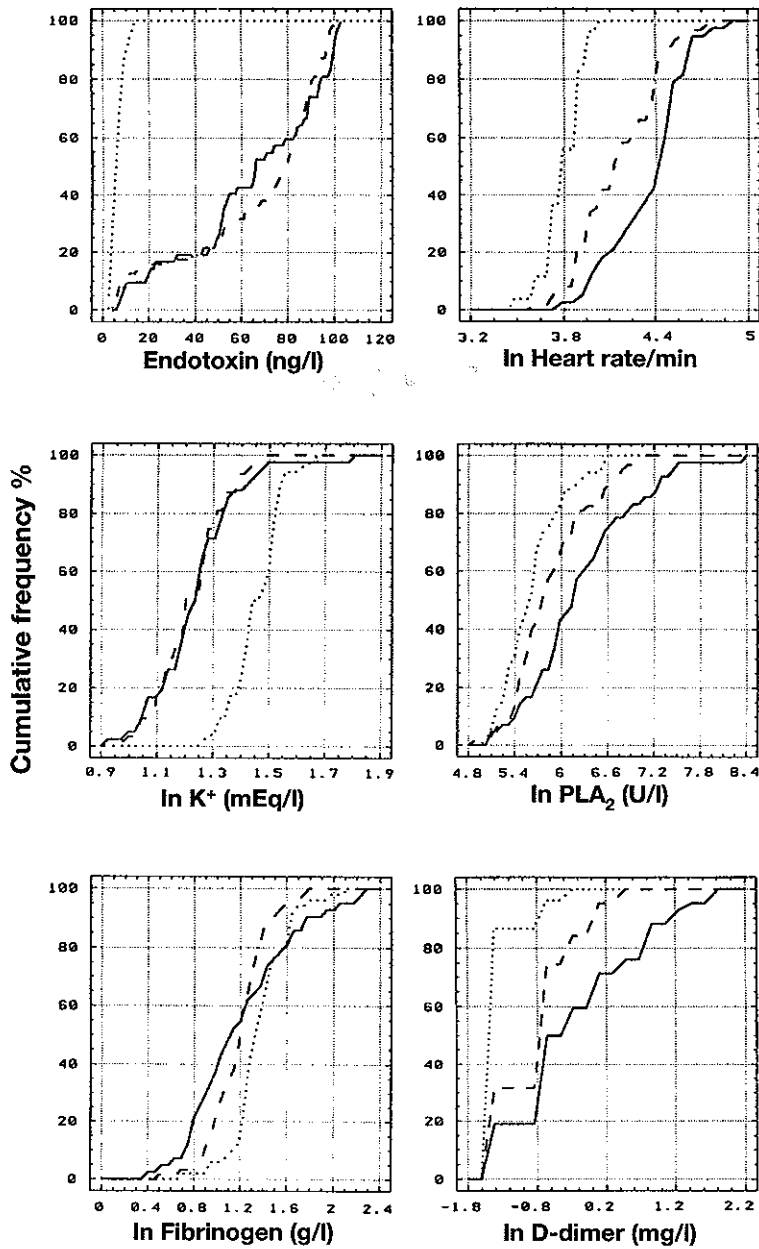
Table 3. Spearman's rank correlation matrix including admission data and the diagnostic category (control = 0), (gastrointestinal colic = 1). The significance (p) is given below each pairwise correlation estimate.

	Healthy-colic	Heart rate	Breath rate	PCV	K^+	Na^+	Cl^-	HCO_3^-	Anion gap	Endotoxin	Total plasma protein	Fibrinogen	Phospholipase	SDH	GLDH	D-dimer
Healthy colic	1.000 (0.000)															
Heart rate	0.686 (0.000)	1.000 (0.000)														
Breath rate	0.723 (0.000)	0.612 (0.000)	1.000 (0.000)													
PCV	0.416 (0.000)	0.520 (0.000)	0.367 (0.000)	1.000 (0.000)												
K^*	-0.707 (0.000)	-0.383 (0.000)	-0.523 (0.000)	-0.281 (0.001)	1.000 (0.000)											
Na^+	0.138 (0.084)	0.115 (0.159)	0.156 (0.057)	0.311 (0.000)	-0.032 (0.690)	1.000 (0.000)										
Cl^-	-0.346 (0.000)	-0.301 (0.000)	-0.298 (0.000)	-0.050 (0.537)	0.413 (0.000)	0.000 (0.000)	1.000 (0.000)									
HCO_3^-	-0.121 (0.134)	-0.219 (0.007)	-0.040 (0.624)	-0.269 (0.001)	-0.039 (0.629)	-0.144 (0.073)	-0.187 (0.020)	1.000 (0.000)								
Anion gap	0.382 (0.000)	0.496 (0.000)	0.348 (0.000)	0.438 (0.000)	-0.165 (0.041)	0.354 (0.000)	-0.026 (0.750)	-0.781 (0.000)	1.000 (0.000)							
Endotoxin	0.753 (0.000)	0.540 (0.000)	0.553 (0.000)	0.376 (0.000)	-0.493 (0.000)	0.256 (0.002)	-0.111 (0.167)	-0.139 (0.087)	0.314 (0.000)	1.000 (0.000)						
Total plasma protein	0.210 (0.009)	0.236 (0.004)	0.041 (0.617)	0.386 (0.000)	-0.170 (0.034)	0.243 (0.002)	0.147 (0.067)	-0.349 (0.000)	0.313 (0.000)	0.177 (0.028)	1.000 (0.000)					
Fibrinogen	-0.312 (0.000)	-0.156 (0.055)	-0.314 (0.000)	-0.154 (0.055)	0.249 (0.002)	-0.162 (0.044)	0.125 (0.120)	-0.080 (0.322)	-0.095 (0.239)	-0.407 (0.000)	0.232 (0.004)	1.000 (0.000)				
Phospholipase	0.323 (0.000)	0.336 (0.000)	0.266 (0.001)	0.280 (0.001)	-0.211 (0.008)	0.118 (0.139)	-0.063 (0.435)	-0.311 (0.000)	0.323 (0.000)	0.272 (0.001)	0.313 (0.000)	0.046 (0.566)	1.000 (0.000)			
SDH	0.407 (0.000)	0.412 (0.000)	0.342 (0.000)	0.422 (0.000)	-0.294 (0.000)	0.200 (0.013)	-0.207 (0.010)	-0.237 (0.003)	0.479 (0.000)	0.317 (0.000)	0.147 (0.067)	-0.059 (0.467)	0.355 (0.000)	1.000 (0.000)		
GLDH	0.349 (0.000)	0.333 (0.000)	0.239 (0.004)	0.379 (0.000)	-0.255 (0.002)	0.237 (0.003)	-0.099 (0.216)	-0.224 (0.005)	0.375 (0.000)	0.305 (0.000)	0.219 (0.006)	-0.114 (0.156)	0.270 (0.001)	0.732 (0.000)	1.000 (0.000)	
D-dimer	0.547 (0.000)	0.453 (0.000)	0.397 (0.000)	0.221 (0.006)	-0.350 (0.000)	0.037 (0.642)	-0.299 (0.000)	-0.225 (0.005)	0.430 (0.000)	0.398 (0.000)	0.318 (0.000)	-0.006 (0.943)	0.347 (0.000)	0.380 (0.000)	0.309 (0.000)	1.000 (0.000)

Table 4. Spearman's rank correlation matrix on colic horses including admission data and the fate of the horse (survivors = 0), (nonsurvivors = 1). The significance (p) is given below each pairwise correlation estimate.

	Survival-death	Heart rate	Breath rate	PCV	K*	Na+	Cl-	HCO3-	Anion gap	Endotoxin	Total plasma protein	Fibrinogen	Phospholipase	SDH	GLDH	D-dimer
Survival-death	1.000 / 0.000															
Heart rate	0.351 / 0.001	1.000 / 0.000														
Breath rate	0.139 / 0.172	0.193 / 0.058	1.000 / 0.000													
PCV	0.275 / 0.005	0.461 / 0.000	0.203 / 0.046	1.000 / 0.000												
K*	0.034 / 0.728	0.231 / 0.022	-0.094 / 0.356	0.051 / 0.605	1.000 / 0.000											
Na+	-0.062 / 0.527	0.067 / 0.506	0.111 / 0.275	0.307 / 0.002	0.165 / 0.091	1.000 / 0.000										
Cl-	-0.243 / 0.013	-0.074 / 0.464	-0.099 / 0.331	0.073 / 0.458	0.353 / 0.000	0.736 / 0.000	1.000 / 0.000									
HCO3-	-0.152 / 0.124	-0.225 / 0.026	0.096 / 0.345	-0.347 / 0.000	-0.208 / 0.035	-0.167 / 0.089	-0.197 / 0.046	1.000 / 0.000								
Anion gap	0.266 / 0.007	0.371 / 0.000	0.080 / 0.432	0.441 / 0.000	0.112 / 0.258	0.293 / 0.003	0.022 / 0.923	-0.840 / 0.000	1.000 / 0.000							
Endotoxin	0.011 / 0.914	0.063 / 0.531	0.064 / 0.529	0.148 / 0.131	0.135 / 0.170	0.223 / 0.023	0.252 / 0.010	-0.136 / 0.167	0.111 / 0.261	1.000 / 0.000						
Total plasma protein	0.070 / 0.417	0.181 / 0.072	-0.180 / 0.076	0.405 / 0.000	0.013 / 0.896	0.190 / 0.053	0.199 / 0.043	-0.355 / 0.000	0.293 / 0.003	0.038 / 0.698	1.000 / 0.000					
Fibrinogen	-0.048 / 0.628	0.026 / 0.799	-0.259 / 0.011	-0.076 / 0.438	0.019 / 0.847	-0.095 / 0.331	0.024 / 0.805	-0.099 / 0.314	0.016 / 0.875	-0.271 / 0.006	0.287 / 0.003	1.000 / 0.000				
Phospholipase	0.276 / 0.005	0.205 / 0.041	0.066 / 0.513	0.303 / 0.002	0.060 / 0.539	0.115 / 0.240	0.017 / 0.861	-0.346 / 0.001	0.337 / 0.001	-0.008 / 0.932	0.293 / 0.003	0.041 / 0.678	1.000 / 0.000			
SDH	0.378 / 0.000	0.270 / 0.008	0.123 / 0.230	0.352 / 0.000	-0.011 / 0.913	0.152 / 0.123	-0.133 / 0.177	-0.268 / 0.007	0.483 / 0.000	0.045 / 0.647	0.115 / 0.242	0.007 / 0.941	0.386 / 0.000	1.000 / 0.000		
GLDH	0.211 / 0.033	0.213 / 0.035	0.021 / 0.835	0.324 / 0.001	-0.032 / 0.746	0.198 / 0.044	-0.005 / 0.957	-0.178 / 0.072	0.315 / 0.002	0.072 / 0.463	0.211 / 0.033	-0.056 / 0.571	0.254 / 0.010	0.740 / 0.000	1.000 / 0.000	
D-dimer	0.286 / 0.004	0.139 / 0.113	-0.029 / 0.778	0.099 / 0.315	0.064 / 0.517	0.018 / 0.857	-0.100 / 0.307	-0.177 / 0.073	0.319 / 0.001	-0.010 / 0.922	0.267 / 0.006	0.171 / 0.081	0.280 / 0.004	0.351 / 0.000	0.245 / 0.013	1.000 / 0.000

Figure 2. Cumulative frequency distribution graphs on selected parameters at admission. The nonsurvivors among the colic horses are indicated by solid line (___), the survivors by dashed line (– –) and the healthy controls by dotted line (...).

Table 5. Diagnostic sensitivity and specificity of individual parameters and acceptable combinations to predict intestinal colic (A) or nonsurvival (B). The specificity and sensitivity values derive from observed frequencies by placing the threshold at a level where the % of correct predictions was at its maximum (when the number of samples in both groups are the same). The values in parenthesis are predictions from logistic regression where the decision threshold was set at the 0.5 probability level.

| | A | | B | |
| | Health or disease? | | Survival or nonsurvival? | |
Parameter	Sensitivity	Specificity	Sensitivity**	Specificity**
Heart rate/min	74 (90)	96 (73)	74 (70)	58 (71)
Breath rate/min	80 (84)	94 (83)	73 (50)	43 (64)
PCV %	57 (71)	90 (56)	53 (69)	85 (70)
K^+ mEq/l	86 (89)	91 (82)	NA*	NA*
Na^+ mEq/l	17, 31[#] (§)	95, 92[#] (§)	NA*	NA*
Cl^- mEq/l	62 (66)	79 (21)	50 (53)	71 (63)
HCO_3^- mEq/l	36, 25[#] (§)	95, 92[#] (§)	78 (*)	59 (*)
Anion gap mEq/l	76 (68)	65 (41)	41 (68)	87 (68)
Endotoxin ng/l	88 (97)	100 (78)	52 (*)	54 (*)
Tot. plasma prot. g/l	10, 47[#] (§)	100, 84[#] (§)	65 (*)	49 (*)
Fibrinogen g/l	60 (67)	79 (33)	28, 29[#] (§)	93, 90[#] (§)
D-dimer mg/l	73 (92)	87 (62)	50 (80)	75 (67)
PLA_2 U/ml	66 (69)	67 (53)	72 (60)	57 (65)
SDH U/l	68 (69)	76 (70)	54 (50)	73 (61)
GLDH U/l	75 (*)	62 (*)	74 (67)	47 (62)
Combination	(100)	(100)	(78)	(77)
(logistic model)	(endotoxin, K^+, heart rate, D-dimer)		(D-dimer, Cl^-, heart rate)	

** Diagnostic sensitivity to predict nonsurvival is the percentage of nonsurviving horses which were designated as nonsurvivors by the diagnostic test. The specificity is the percentage of surviving horses which were designated as survivors by the same threshold setting.

* NA "not applicable": The distributions were closely identical. The p = 0.5 threshold setting did not distinguish between the groups.

Two optimal threshold settings were found.

§ Due to nonmonotonic behaviour, the logistic model was not applicable.

sult in a simple combination in terms of acceptable sensitivity and specificity. In the latter approach, all the 15 predictors were included in the model and backward elimination was used as the means to eliminate less important and collinear predictors.

Results

Of the 105 colic horses, 63 survived but 42 failed to survive the intestinal colic episode. The mortality was 44% among the operated horses and 28% among the conservatively treated horses. The analysis of the 15 variables to classify the groups (52 controls, 63 survivors and 42 nonsurvivors) correctly gave the following results.

Single parameters

The measured values of blood samples collected at admission to the clinic are summarized in Table 2. Most of the parameters except plasma HCO_3^- and Na^+ showed significant differences between the colic and control horses. The correlation matrixes (Spearman's rank
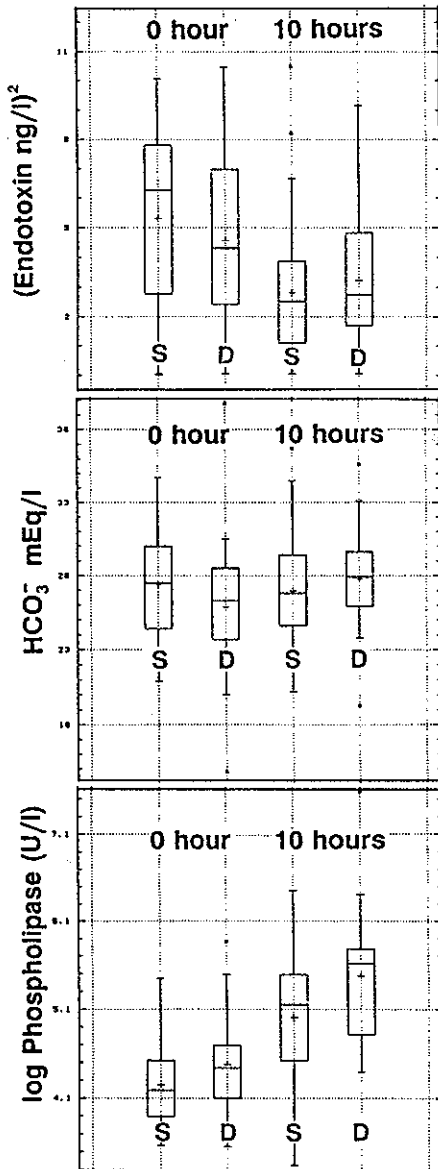
Fig. 3. Box-and-Whisker plots on plasma endotoxin, bicarbonate and phospholipase-A2 levels at admission (0 hour) and 10 h later in colic horses going to survive (S), n = 42, or die (D), n = 25. The increase in bicarbonate between 0 and 10 h was significantly higher in nonsurvivors compared with the survivors (p = 0.003).

correlations) including the binary correlation with the health (0) or disease (1 = gastrointestinal colic) are presented in Table 3. The correlation matrix on admission data from colic horses, including the binary correlation with the future of the horse (survivors = 0, nonsurvivors = 1), is presented in Table 4.

The results of the admission levels of plasma endotoxin, heart rate, plasma potassium, PLA_2, fibrinogen and D-dimer distinguishing between healthy and colic horses as well as survival and nonsurvival are given as cumulative frequency distribution graphs in Fig. 2.

Compared with survivors, horses that failed to survive the intestinal colic episode had significantly different median admission levels of plasma SDH, heart rate, D-dimer, PLA_2, PCV, anion gap, Cl⁻, and GLDH, listed in the order of statistical significance (Table 2). The binary correlation of each parameter with survival (0) – death (1) were similar (Table 4). The plasma samples of control horses were visually clear. However, 12.7% of the plasma samples from colic horses (n = 229) appeared lipaemic (turbidity, visual evaluation). Of the 29 lipaemic samples of colic horses, 22 originated from nonsurvivors.

Table 5 reports the diagnostic sensitivity and specificity of individual admission parameters A) to place healthy and colic horses in the correct groups, and B) to predict death or survival within the colic group. Endotoxin was the best discriminator between healthy and colic horses; the optimum threshold setting was 13 ng/l (Fig. 2). No diagnostically distinguishing features were found in the comparison of the site of intestinal disorder (small vs large intestinal impaction or obstruction).

The examination of single variables of colic horses in relation to the time after admission showed that the prediction of nonsurvival clearly improved with K^+ when moving from samples taken at admission to samples col-

Table 6. Diagnostic sensitivity (correct classification % of nonsurvivors) and specificity (correct classification % of survivors) of multiple logistic regression models to predict nonsurvival among colic horses: I) "classical" parameters, II) "classical" parameters with the model-improving new parameters and III) a simple and good theory-independent combination.

		Combination	Sensitivity	Specificity
I)	Classical	Heart rate Breath rate PCV Anion gap	64	71
II)	Classical + New	D-Dimer PLA_2 Cl^-	70	73
III)	A simple and good combination	D-Dimer Cl^- Heart rate	78	77

lected 10 hours later. Plasma potassium was generally low in colic horses in samples collected at admission (Table 2, Fig. 2) and decreased further for the first 10 hours. The discriminatory ability of GLDH increased slightly from 0 hour samples to 10 hour samples. PLA_2 retained its discriminatory ability from 0 hour to 10 hour samplings. Therapy complicated the picture of all the other parameters; the 10 hour samples were inferior to the admission samples in discriminating between death and survival. The significance of anion gap as a predictor for death or survival lost its discriminating capacity completely during the first 10 hours at the clinic. The colic horses that subsequently died showed a significantly higher relative increase in bicarbonate (Fig. 3, p = 0.003) and a decrease in anion gap (p = 0.018) during the first 10 hours at the clinic, compared with the survivors. The change in plasma sodium correlated positively with the change of bicarbonate in the horses that did not survive (p = 0.07). GLDH was the only single enzymatic parameter that increased its discriminatory ability in the predic-

tion of nonsurvival when 0-10 hour differences were used, rather than absolute values. Plasma endotoxin levels generally decreased but plasma D-dimer and phospholipase increased in colic horses during the first 10 hours at the clinic but these changes were not related to survival (Fig. 3).

Combined data (Logistic regression)
A) Health or disease? When the physiological variables and laboratory values on blood samples collected from healthy and colic horses at admission were included in the model to place healthy and colic horses into correct groups, the most important predictor variables were endotoxin, potassium, heart rate, and D-dimer. The diagnostic sensitivity and specificity of the discrimination analysis based on the above model was 100% (Table 5). Endotoxin was a good predictor alone (Fig. 2, Table 5).
B) Survival or nonsurvival? Only colic horses were included. When admission samples from colic horses were analyzed to predict survival or nonsurvival and the "classical" pa-

rameters (heart rate, breath rate, PCV, anion gap) were included, only the pulse rate was statistically significant (Wald-test, p-value 0.027).

Addition of all the "new" variables together (endotoxin, fibrinogen, D-dimer, PLA_2, SDH, GLDH and Cl^-) to the model containing the "classical" parameters significantly improved the model fit. The improvement G^2 was 17.43 on 5 degrees of freedom, p < 0.001. In this model, according to the Wald tests, only D-dimer and Cl^- could be regarded as statistically significant (p = 0.068 and 0.057). The model suffered from inclusion of too many predictors; if the "classical" and "new" parameters were included together (n =11) in the model, even heart rate was not significant (p = 0.135).

When the effect of the "new" variables were added one by one to the model including the classical variables, the most significant ones were (based on the improvement G^2), D-dimer (p = 0.001), PLA_2 (p = 0.022) and Cl^- (p = 0.022). With these 3 variables added to the model the sensitivity and specificity of the prediction of nonsurvival were 70% and 73% (Table 6).

If the prediction model was constructed independent of assumptions of any parameters to be included, a simple and good combination of predictors included pulse rate, D-dimer and Cl^-. The sensitivity of the model (to predict nonsurvival) was 78% and specificity 77%. (Table 6). The logit model was:

$$\text{logit } (\pi) = 5.73204 + 0.03514 \text{ heart rate} - 0.09788 \text{ chloride} + 1.16992 \text{ D-dimer}$$

(π = probability of nonsurvival). Therefore, the risk for nonsurvival increased with pulse rate and D-dimer and decreased with Cl^-. If the value of the right hand side of the above equation is positive, the horse is considered a nonsurvivor.

Discussion

This study was designed to select, from among a set of physiological and biochemical variables, those prognostically useful in equine gastrointestinal colic, independent of the extent and the nature of the lesion. We were especially interested to see whether a combination of parameters would be superior to any individual parameters and how to combine the parameters in the best possible way. Multivariate statistical methods have both descriptive and predictive functions. The process of intestinal colic is dynamic and currently there is no safe indicator to tell the point at which the horse is "over the edge" and cannot be saved. It is clear that the prognostic value of a parameter is dependent on the time at which it is sampled in relation to the ongoing process. There is no way to standardize the sampling in relation to the process; the prognostic value of each parameter changes with time. Therefore, the discriminatory ability (death or survival) of samples collected at 2 time points after admission were examined for differences as time elapsed. The colic horses were sampled at 10h intervals, but as the number of nonsurviving colic horses decreased rapidly, we were not left with a sufficient sample for adequate statistical analysis beyond 10h. Whether the 0-10h changes reflected specific effects of colic, acute-phase response or therapy, was not determined. The therapy and quality of the surgery certainly complicates the evaluation of the changes.

The quality of the information provided by a clinical or biochemical quantity in the diagnosis of a disease is dependent on its capacity to discriminate whether the disease exists or whether the animal is going to die. The results of the most important variables, distinguishing both between healthy and colic horses, and between survival and nonsurvival among the colic horses, are given as cumulative fre-

quency percentage graphs (Fig. 2). This allows discrimination thresholds to be set at optimum levels when individual parameters are used. The smaller the overlapping area, the greater the diagnostic accuracy. The threshold setting can be adjusted according to the wanted diagnostic sensitivity and specificity. The predictive value can then be calculated according to these if the prevalence of the disease is known. Our study was designed to include about the same number of horses in each diagnostic category. This principle of including a similar number of horses in each category resulted in an apparent lower recovery figure than commonly experienced at the Hochmoor Animal Clinic.

Many parameters were quite effective in distinguishing between healthy and colic horses. The present investigation confirms the importance of heart rate, respiratory rate and PCV to be included in the clinical examination of the colic horse. However, these parameters were highly correlated (collinearity in regression models). Therefore the combination did not bring much additional information to the heart rate alone.

Plasma samples from colic horses were in several cases "milky" or haemolytic. Turbidity of plasma seems to be a marker of disease and poor prognosis. Because the evaluation was subjective, we did not include this information in the prediction model. The lipidaemic turbidity of plasma might indicate disturbance in lipid metabolism and ongoing membrane disrupting process. Plasma turbidity is known to increase in horses upon fasting. Due to the hyperlipidemic response to endotoxin, experimental animals might tolerate more endotoxin. Endotoxin-induced hyperlipoproteinemia might be a physiological defence mechanism whereby the body attempts to bind circulating endotoxin *(Wei & Floren* 1993).

Plasma endotoxin was an extremely safe parameter for identifying colic horses among healthy horses (Fig. 2, Table 5). This indicates that leakage of endotoxin from the gut into the blood is typical for gastrointestinal colic. Additional strength in the confirmation of the existence of the disease was gained by combining plasma K^+, heart rate and D-dimer with endotoxin in the regression model; by this logistic model all the horses became placed in their correct categories (healthy or colic).

Whenever the integrity of the mucosal barrier is lost due to inflammation or ischemia of the intestinal wall, endotoxins cross into the portal blood and peritoneal cavity and can be detected in the peripheral circulation. LPS has been detected in blood plasma of horses with gastrointestinal diseases that cause colic *(King & Gerring* 1988). Theoretically, the amount of endotoxin in the blood should reflect the extent of damage to the intestinal wall. However, the plasma endotoxin level proved to have no prognostic value whatsoever in differentiating between survivors and nonsurvivors (Fig. 2, Table 5).

Much of the pathophysiology of intestinal colic can be explained by the adverse effects of endotoxemia. Actually, many endotoxin effects are mediated by endogenous factors derived from endotoxin-responding host cells. Various cytokines (such as TNFα, IL-1 and IL-6) and other mediators that are produced by responding host cells cause aberrations in temperature regulation, haemodynamic-, haematologic-, and liver responses including regulation of the production of acute-phase proteins as well as regulation of the immunologic system *(Morris* 1991). Administration of IL-1 or TNFα to animals has been shown to induce many effects observed in Gram-negative and endotoxin-induced sepsis. When causing excessive response, LPS can cause irreversible multiple organ dysfunction known

as the systemic inflammatory response syndrome (SIRS). Our results indicate that the limiting factor that determines the outcome of the endotoxin response (shock) is probably the susceptibility of the host to endotoxin rather than the plasma endotoxin level. This might be determined by up- and downregulation of the complex cytokine network.

Inflammation is accompanied by the acute-phase response that comprises a constellation of metabolic, endocrinologic and immunologic alterations which start within hours of an initiating stimulus. Synthesis of acute-phase plasma proteins (APP:s) by the liver is a major component of acute-phase response. Therefore plasma fibrinogen and PLA_2 can be expected to increase in any inflammatory disease. Measurement of cytokines responsible for the endotoxin effects (eg $TNF\alpha$ or IL-6) may be a diagnostic aid during the first hours of an inflammatory state if the blood APPs have not yet begun to increase *(Morris* 1991, *Morris et al.* 1992). After the acute-phase protein genes have been switched on within the liver, it takes several hours before any increase in APPs can be detected in blood. This time period varies with different APPs.

Increased serum PLA_2 activity proved to be a good indicator of colic, and also distinguished between survivors and nonsurvivors (Fig. 2, Tables 3 & 4). In human beings, serum levels of PLA_2 activity are elevated in septic shock and rheumatoid arthritis *(Akira et al.* 1993). The secreted form of PLA_2 (group II), found in the serum, has its origin mainly in the liver. IL-6 is a major inducer of PLA_2 gene expression in hepatoma cells *(Crowl et al.* 1991). Therefore PLA_2 may be classified as APP. Cellular PLA_2 is an enzyme that plays an important role in inflammation by producing potent lipid mediators, such as leukotrienes, prostaglandins, and platelet activating factor. PLA_2, attacking the intestinal mucosa, is re-

garded as a central mediator of intestinal injury in inflammatory *(Almer et al.* 1991) and ischemic bowel disease in human beings *(Otamiri & Tagesson* 1989).

The present agar diffusion method of measuring phospholipase would be too slow to justify its use in a clinical situation in which the result would be urgently needed. On the other hand, PLA_2 could be replaced by SDH in the regression models without affecting the strength of the model. This reflects the multicollinearity problem in the multiple regression analysis. Two independent parameters (PLA_2 and SDH) were highly correlated as seen in the pairwise correlation matrix (Tables 3 & 4) and probably contained the same information. The strong association might indicate causation. PLA_2 is a membrane-disrupting enzyme which may be responsible for the release of SDH. SDH is known to be a cytosolic enzyme of hepatocytes and the intestinal epithelium, but is not considered as "APP" currently. If PLA_2 is APP, then SDH might prove to be APP in the equine species due to the close correlation between these 2 parameters.

The use of fibrinogen as a marker of acute-phase response in equine colic is intriguing. The colic horses who survived showed low fibrinogen levels at admission compared with control horses. In those colic horses who subsequently died, the variation of the fibrinogen values was high and the distribution was polarized: both high and low values were found (Fig. 1). However, the plasma fibrinogen level tended to increase in the nonsurvivors during the first 10h at the clinic. Theoretically, fibrinogen should increase because it is an important APP. On the other hand, thrombotic processes consume fibrinogen, resulting in low plasma fibrinogen in colic horses (Fig. 2, Table 2). The net content of fibrinogen depends on the sequence, whether enhancement of fibrinogen synthesis or fibrinolysis oc-

curred first. This was why we included D-dimer in the list of parameters. Imbalanced regulation of haemostasis has been shown to contribute to the pathogenetic features of equine colic *(Johnston & Crane* 1986, *Darien et al.* 1991). The horses with hypercoagulation might show thrombotic features and the condition is often associated with increased fibrinolysis resulting in disseminated intravascular coagulation *(Morris & Beech* 1983, *Prasse et al.* 1993). Plasma fibrinogen levels in the samples collected at admission were significantly lower in colic horses as compared with the controls. This indicates an increased consumption of fibrinogen. However, the level of fibrinogen at admission in a colic horse could not differentiate between survival or death. The wide variation of blood fibrinogen levels in nonsurviving colic horses at admission, and the increase of plasma fibrinogen towards death, indicate problems in regulation of haemostasis and APP synthesis.

Increased levels of D-dimer in plasma indicate that excessive amounts of fibrin have formed within the vascular tree but are undergoing fibrinolytic degradation. The NycoCard D-dimer test is an immunochemical test to analyze fibrinolytic problems in man. The function of this test in the equine species is not surprising. Despite the aberrant structure of equine fibrinogen, the cross-linking region of the A_α chain represents the conserved portion of the fibrinogen molecule with amino acid homology and immunogenicity from one species to another *(Sobel et al.* 1990). This is the section contained in the D-dimer fibrin(ogen) degradation product.

The NycoCard D-dimer test has high potential for horse-site testing. After separation of plasma, the result is obtained within 2 min. The test appeared to be practical and extremely useful for horse-site testing in emergency situations.

The importance of D-dimer in the final regression model reflects the disseminated intravascular coagulation (DIC) disorder in colic horses. The condition was more severe in nonsurvivors compared with survivors. The present analysis hints that development of DIC syndrome is the determining factor for nonsurvival. Elevated D-dimer indicates an ongoing thrombosis and fibrinolytic process. This information is valuable when designing pharmacological intervention.

When the survival (0) and death (1) of colic horses were used as the dependent variable and the other parameters on admission data as predictor variables, the binary correlations reported in Table 4 indicate that many parameters are prognostically valuable. However, when isolating the most important confounding predictor variables to be used together (Table 6), the apparent pattern changed; the most important set of variables to be used in combination on samples collected at admission were D-dimer, chloride and heart rate. Many parameters showed collinearity with these parameters and became eliminated from the final model.

Anion gap was itself a good discriminator at admission for distinguishing between healthy and colic horses. This is in agreement with earlier reports *(Gossett et al.* 1987, *Wirth* 1986). Because of collinearity, anion gap was dropped from the logistic regression model containing heart rate, D-dimer and Cl⁻ as predictor variables. This indicates that anion gap is contained in the information of those independent variables present in the model. Variables left out of the predictor set are not necessarily unimportant; they may simply be correlated with other variables in the predictor set. Anion gap lost its discriminating capacity totally at 10h sampling (due to correction of the acid base balance by alkalinizing fluids).

Acid-base disturbances are considered to contribute to colic-associated shock. Lactate typically accumulates in colic horses *(Gossett et al.* 1987, *Waterman* 1977). Anion gap was wide in colic horses when measured at admission. The acidotic condition was monitored carefully at the clinic and corrected by alkalinizing infusion solutions, when required. Therefore, the anion gap measured at 10h was not useful at all for predicting death or survival (p = 0.97). This indicates that careful monitoring and correction of the acid-base status by alkalizing infusion solutions took place according to currently accepted principles. However, it is worth noting that the colic horses that later died, showed significantly higher relative increase in bicarbonate and narrowing in anion gap during the first 10h compared with the survivors. The increase of bicarbonate was accompanied by a parallel increase in sodium (p = 0.07). This might indicate either that the rapid correction of the acidotic state by alkalizing, sodium-rich intravenous infusion solutions was detrimental to the horse, or the endogenous acid-base regulatory mechanism was disturbed in the dying horses.

The best combination of predictor sets of colic horses at admission shows that survival or nonsurvival can be predicted quite accurately by the predictor set containing D-dimer, Cl⁻ and heart rate (Table 6). The predictive value was surprisingly high considering other apparent sources of variation. These would certainly include the type of intestinal involvement, area of damaged intestinal wall, speed of initiating operation in respect to the onset of colic, age of the horse, time consumed in transport, transport stress, time consumed in the operation itself, surveillance of the horse including corrections in fluid-, ion-, acid-base balances and respiratory gas exchange, quality of the anaesthesiologist and the surgeon. Although the present results indicate that too

rapid correction of the acid-base balance had some association with death (or more correctly euthanasia) of colic horses, the other variables were difficult to measure or were not reported, or the number of the horses was too low in each category to allow any insight to the importance of the above sources of variation.

When considering screening and computerized decision-making for equine gastrointestinal colic, there must be an understanding that the natural history of the disease and early detection can play a role in the reversal of the clinical course. Standard multivariate procedures look at the various parameters in parallel. It might be that algorithmic judgement (decision trees) would result in similar or better prediction. Multiple regression procedures require knowledge about which parameters to include in the regression model. Algorithmic procedures require knowledge of the order as well. We actually did our analysis in two steps, first it was decided whether the horse suffered from gastrointestinal colic (in this respect plasma endotoxin was quite safe parameter) and secondly the population of colic horses were analyzed for separation whether they were going to die or not.

Conclusion

The study showed that the fate of the colic horse was already determined at the time of admission to the clinic (= before surgery). Endotoxaemia was a typical feature for horses with gastrointestinal colic. The individual response to this stimulus largely determined the survival. Increasing heart rate and D-dimer together with decreasing chloride was a typical risk factor for nonsurvival. Disseminated intravascular coagulation (DIC) was probably the key element. In searching for valuable predictor parameters for decision making, it seems important to have rapid horse-site test-

ing for the most important predictor variables. The NycoCard D-Dimer test appeared to be a practical horse-site test to detect fibrinolytic activity. An "online" method is suggested to combine the results in order to give an objective estimation of the future of the horse.

Acknowledgements

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Sammandrag

Plasma d-Dimer ökar prognosvärdet vid intestinal kolik hos häst.

Prognostiska värdet (kolikmorbiditet, -mortalitet) av 15 kliniska och laboratorieparametrar undersöktes med hjälp av logistiska modeller. Plasma endotoxin var den bästa enskilda parametern att skilja friska och kolikhästar från varandra. Ökad plasma D-dimer (fibrinolys produkt) och puls tillsammans med ett sänkt plasma kloridvärde var en riskfaktor för kolikmortalitet. Diagnostiska sensitiviteten (för prediktion an mortalitet) av denna modellen var 78% och specificiteten 77%. D-dimertesten från Nycomed rekommenderas som en praktisk och prognostiskt värdefull test för hästkliniker.