

# Clinicopathologic evidence of disseminated intravascular coagulation in horses with acute colitis

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**Objective**—To detect subclinical disseminated intravascular coagulation (DIC) in horses with colitis and to determine any association between the diagnosis of subclinical DIC and outcome or occurrence of complications in horses with colitis.

**Design**—Prospective study.

**Animals**—37 horses admitted to a veterinary teaching hospital for treatment of acute colitis.

**Procedure**—Coagulation profiles were obtained on each horse 0, 24, and 48 hours after admission. Six tests were performed: platelet count, plasma fibrinogen concentration, prothrombin time, activated partial thromboplastin time, antithrombin activity, and serum fibrin degradation products concentration.

**Results**—A clinicopathologic diagnosis of subclinical DIC was made if 3 of the 6 tests had abnormal results at any 1 sample period. No horse had clinical signs of DIC at the time of sampling. Twelve of 37 (32%) horses met the criteria for diagnosis of subclinical DIC within a 1-year period. Outcome was defined as survival or nonsurvival. Five of 12 horses with subclinical DIC and 2 of 25 horses without subclinical DIC did not survive. Crude odds ratio analysis revealed a horse with acute colitis was 8 times as likely to die or be euthanatized if a diagnosis of subclinical DIC was made.

**Conclusions and Clinical Relevance**—Clinicopathologic evidence of DIC is common and is significantly associated with a poor outcome in horses with acute colitis. Treatment of subclinical DIC may influence outcome in horses with acute colitis. (*J Am Vet Med Assoc* 2002;220:1034–1038)

**D**isseminated intravascular coagulation (DIC) is a syndrome described in multiple species and develops secondary to a variety of primary illnesses.<sup>1-3</sup> Disseminated intravascular coagulation is a pathologic activation of the coagulation system leading to inappropriate hypercoagulation and secondary hemorrhage throughout the body.<sup>1</sup> This process may lead to multiple sites of hemorrhage and thrombosis and subsequent organ dysfunction or failure. Thromboses are more insidious, and potentially much more damaging, than hemorrhage, and clinical signs of end-organ failure may not be immediately apparent. In human med-

icine there is a inclination to diagnose DIC early (ie, subclinical DIC) by laboratory testing and initiate treatment prior to the onset of overt clinical signs, the rationale being that mortality rates could be improved and fulminant DIC could be avoided.<sup>1,4,5</sup> Studies in humans have supported this approach, with decreased mortality rates in treatment of subclinical DIC versus treatment of fulminant coagulopathy.<sup>4</sup>

In horses DIC has been documented secondary to sepsis, localized infections, neoplasia, immune-mediated disease, and acute gastrointestinal tract disease, and mortality rates in these reports<sup>3,6,7</sup> are high. Several studies<sup>6,8-10</sup> have documented coagulation abnormalities in horses with colic. Previous reports<sup>3,6,11</sup> of clinical DIC in veterinary medicine, as in human medicine, define it as a clinical diagnosis when 2 basic criteria are met: 1) 3 abnormal coagulation test results and 2) clinical signs of hemorrhage or thrombosis at multiple sites. Prospective studies<sup>8-10</sup> of coagulation testing in horses with colic have shown an association between abnormal clotting function and mortality rate.

Acute colitis is a serious and occasionally life-threatening disease of horses, and development of secondary complications such as thrombophlebitis, laminitis, and renal failure is common in affected horses. These horses are often the most critically ill in a hospital population. There are reports of DIC developing in horses with acute colitis.<sup>11</sup> To our knowledge, no prospective studies have been performed evaluating subclinical DIC in horses with acute colitis. The purpose of the study presented here was to prospectively evaluate horses with acute colitis for the development of laboratory evidence of DIC, irrespective of overt clinical signs of coagulopathy. Our hypotheses were that subclinical DIC develops commonly in this population of horses and that subclinical DIC is associated with a poor outcome.

## Material and Methods

**Selection of horses and sample collection**—From December 1998 to December 1999 horses were admitted to the study on the basis of the following inclusion criteria: 2 months of age or older and an admitting complaint of colitis, indicated by the presence of diarrhea of < 8 days' duration. Blood was collected at the time of admission and at 24 and 48 hours after admission. Twenty milliliters of blood was collected by direct venipuncture of the jugular vein or a peripheral vein and immediately placed in tubes with EDTA (2 ml), sodium citrate (15 ml), and Bothrops atrox venom with soybean trypsin inhibitor for determination of serum fibrin degradation products (FDP; 2 ml) concentration.<sup>a</sup>

**Clinical laboratory tests**—Serum was separated and stored at -20 C, with FDP determination performed within 1 month of collection. Serum FDP concentrations were mea-

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sured by use of a commercial latex agglutination kit as previously described for horses.<sup>5</sup> Serum FDP concentrations were determined according to manufacturer's recommendations at dilutions of 1:5 and 1:20.<sup>a</sup>

Blood collected in EDTA tubes was used for immediate platelet and WBC counts, using an automated cell counter.<sup>b</sup> Samples collected with sodium citrate were immediately processed and centrifuged at 1,240 × g, and the citrated plasma was separated and stored at -20 C. Plasma fibrinogen concentration, prothrombin time (PT), activated partial thromboplastin time (aPTT), and antithrombin (AT) activity were determined from citrated plasma within 1 month of collection, using an automated system.<sup>c</sup> Prothrombin time was determined by use of lyophilized rabbit brain calcium thromboplastin to activate the extrinsic coagulation pathway.<sup>12</sup> Activated partial thromboplastin time was determined by use of rabbit brain phospholipids and calcium chloride to activate the intrinsic coagulation pathway.<sup>12</sup> Anti-thrombin activity was determined by incubating thawed plasma with bovine Factor Xa in heparin and then quantifying the residual Factor Xa activity via a chromogenic assay.<sup>12</sup> The described techniques were performed by use of standard protocols according to the manufacturer's recommendations.<sup>12</sup> Other laboratory tests included determination of plasma creatinine concentration, PCV, plasma total solids concentration, and plasma lactate concentration. Plasma creatinine concentration was determined by use of commercially available reagents utilizing a colorimetric assay.<sup>d</sup> Plasma lactate measurement was performed by enzymatic reaction, using a standard protocol according to the manufacturer's recommendations.<sup>e</sup> Except for determination of plasma lactate concentration, all of the tests were performed on at least a daily basis for each horse with the most abnormal value recorded. Plasma lactate concentration was determined only at admission.

**Identification of affected horses**—Abnormal coagulation test results were defined as follows: plasma fibrinogen concentration < 150 mg/dl (reference range, 200 to 375 mg/dl), PT > 12.5 seconds (reference range, 8 to 10 seconds), aPTT > 50 seconds (reference range, 29 to 40 seconds), AT activity < 110% (reference range, 150 to 220%), and serum FDP concentration > 10 µg/ml (reference range, < 10 µg/ml). Subclinical DIC-positive horses were identified when 3 of the listed tests had abnormal results at any sampling time. Subclinical DIC-negative horses were identified once 3 complete profiles were performed and the described criteria were not met. Clinical signs of DIC were not considered in the determination of subclinical DIC-positive horses. Observations were recorded for signalment, outcome, complications, signs of coagulopathy, and physical and clinico-

pathologic abnormalities in each horse. A complete necropsy was performed on each horse that did not survive, and the reports were evaluated. Mortality rate was defined by euthanasia or death occurring during hospitalization. Individual circumstances surrounding death or the decision for euthanasia, such as financial constraints placed by the owner and emotional concerns, were not evaluated in determining mortality rates.

**Statistical analyses**—Odds ratio (OR) and confidence interval (CI) determinations were performed by use of computer analysis.<sup>f</sup> The Fisher exact test was performed to determine qualitative relationships between complications and the exposure of subclinical DIC. Any significant relationship was subsequently analyzed quantitatively by logistic regression. Logistic regression analysis was then used to study the effects of any confounding variables. Significance was set at  $P \leq 0.05$ . Packed cell volume, plasma total solids, plasma creatinine concentration, and WBC count were examined for confounding effects as dichotomous variables, with 2 possibilities being normal and abnormal. Plasma lactate concentration was also examined for confounding effects as a continuous variable. Plasma total solids concentration and AT activity were evaluated for any relationship, using continuous variables and regression analysis.

## Results

Thirty-seven horses met the inclusion criteria for our study. Of 37 horses, 30 were febrile at the time of admission, 23 had leukopenia, and all horses had evidence of dehydration and diarrhea on physical examination. Twelve horses met the criteria for a clinicopathologic diagnosis of subclinical DIC (group 1), and 25 did not (group 2; Table 1). None of the horses in either group had clinical signs of DIC at any sampling period. Of 12 group-1 horses, 5 died. Of 25 group-2 horses, 2 died. Subclinical DIC and a poor outcome were significantly related. The odds of survival of a horse with subclinical DIC were reduced 8 fold relative to a horse without subclinical DIC ( $P = 0.025$ ; 95% CI, 1.29 to 51.99).

Azotemia was defined as plasma creatinine concentration of > 2.0 mg/dl. The BUN was not routinely determined in the horses of our study. Azotemia was significantly ( $P = 0.005$ ) associated with a diagnosis of subclinical DIC. High plasma lactate concentrations were significantly associated with a diagnosis of subclinical DIC (OR, 2:1;  $P = 0.023$ ; CI, 1.10 to 3.88) but

Table 1—Mean (± SE) values of coagulation profiles during the first 3 days of hospitalization of horses with acute colitis

Test	RR	Group-1 survivors			Group-1 nonsurvivors			Group-2 survivors			Group-2 nonsurvivors		
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Platelet count (× 1,000 cells/µl)	100–300	112 ± 16 (7)	142 ± 16 (6)	103 ± 16 (5)	105 ± 6 (5)	79 (1)	NA	138 ± 8 (23)	133 ± 7 (23)	139 ± 9 (23)	156 ± 17 (2)	170 ± 43 (2)	144 ± 43 (2)
Prothrombin time (s)	8–10	10.9 ± 0.9 (7)	11.1 ± 0.6 (6)	11.6 ± 1.2 (5)	10.3 ± 0.2 (5)	14.1 (1)	NA	9.2 ± 0.2 (23)	9.4 ± 0.4 (23)	9.1 ± 0.2 (23)	8.6 ± 0.5 (2)	9.8 ± 0.7 (2)	10.1 ± 0.2 (2)
Partial thromboplastin time (s)	29–40	53.9 ± 7.2 (7)	61.1 ± 4.8 (6)	58.8 ± 6.8 (5)	60.5 ± 5 (5)	117 (1)	NA	42.8 ± 2.9 (23)	40.5 ± 1.6 (23)	39.1 ± 2.1 (23)	39.5 ± 5.1 (2)	47.3 ± 4.9 (2)	43.7 ± 0.9 (2)
Antithrombin (% activity)	150–220	105 ± 0.2 (7)	90 ± 14 (6)	79 ± 10 (5)	92 ± 10 (5)	80 (1)	NA	131 ± 5 (23)	122 ± 5 (23)	123 ± 5 (23)	172 ± 77 (2)	114 ± 24 (2)	95 ± 1 (2)
Fibrinogen (mg/dl)	200–275	551 ± 77 (7)	481 ± 56 (7)	529 ± 73 (4)	356 ± 52 (5)	227 (1)	NA	451 ± 32 (23)	493 ± 27 (23)	503 ± 34 (23)	4.5 ± 211 (2)	421 ± 34 (2)	556 ± 48 (2)

RR = Reference range. NA = Not applicable.  
Numbers in parentheses indicate number of horses. Group-1 horses had clinicopathologic evidence of subclinical disseminated intravascular coagulation; group-2 horses did not.

not outcome (OR, 1.2:1;  $P = 0.093$ ; CI, 0.97 to 1.47). Mean plasma lactate concentration at admission for group-1 horses ( $n = 11$ ) was  $6.46 \pm 1.6$  mmol/L and for group-2 horses (18) was  $1.82 \pm 0.25$  mmol/L.

Of 12 group-1 horses, 4 developed laminitis. Of 25 group-2 horses, 2 developed laminitis. Thrombophlebitis developed in 3 of 12 group-1 horses versus 4 of 25 group-2 horses. Disseminated intravascular coagulation was not significantly associated with thrombophlebitis ( $P = 0.66$ ) or laminitis ( $P = 0.073$ ).

Packed cell volume, plasma total solids, lactate, and creatinine concentrations and WBC count were examined for confounding effects, and none were found. An association between plasma total solids concentration and AT activity at admission or 24 hours after admission was not found. Anti-thrombin deficiency was correlated with hypoproteinemia at 48 hours after admission ( $P < 0.001$ ). In group-1 horses AT deficiency and prolonged PTT were the most common abnormalities detected (Table 1). In group-2 horses high serum FDP concentration was the most common abnormality. Of 62 samples tested, 26 had high serum FDP concentrations; 19 were between 10 and 40  $\mu\text{g/ml}$ , and 7 were  $> 40$   $\mu\text{g/ml}$ . Platelet counts were abnormal in 9 of 24 determinations in group-1 horses and in 7 of 75 determinations in group-2 horses. These findings represented thrombocytopenia in 6 of 12 horses in group 1 and 4 of 25 horses in group 2. Plasma fibrinogen concentrations were within reference range limits in all horses.

Of the 5 group-1 nonsurvivor horses, 3 died, 1 was euthanatized at surgery when it was determined there was no viable large colon as a result of infarction, and 1 was euthanatized after it had become agonal. Two of these horses developed fulminant DIC prior to death with prolonged bleeding from catheter sites, intestinal infarction, and pulmonary hemorrhage. At necropsy examination the first horse had renal infarcts, necrohemorrhagic enterocolitis, periarticular hemorrhage, serosal intestinal petechiae, and intestinal microthrombi. The second horse had hematuria, perirenal hemorrhage, adrenal hemorrhage, pulmonary hemorrhages, petechiae of the central nervous system, epicardial ecchymosis, and endocardial hemorrhage, whereas the third horse had necrohemorrhagic colitis, transmural intestinal hemorrhages, splenic petechiae, bladder petechiae, subpleural ecchymoses, intestinal microthrombi, renal microthrombi, adrenal hemorrhage, and microthrombi. The fourth horse had intestinal hemorrhage, perivascular hemorrhage, and colonic infarction, and the fifth horse had severe liver disease leading to hepatic fracture and intestinal petechiae. An infectious cause was not found in any of these horses.

No horses in group 2 developed fulminant DIC. Group-2 nonsurvivor horses were euthanatized on days 4 and 5 of hospitalization. Necropsy results of the first horse revealed severe laminitis and 1 site of microthrombosis in the intestinal vasculature. Necropsy of the second horse revealed mild large colon inflammation.

## Discussion

Disseminated intravascular coagulation is an elusive syndrome to diagnose and treat. Even postmortem

examination is not a definitive diagnostic tool for this syndrome, largely because if tissue fixation is not rapidly performed thrombi may no longer be detectable.<sup>13,14</sup> In the past, diagnosis of DIC was made on the basis of clinical signs of hemorrhage. This standard is not helpful in affected horses, because once they reach this stage little can be done to reverse fulminant coagulopathy. Results of our study indicate that horses with acute colitis are in a high-risk group for subclinical DIC.

Once subclinical DIC has been identified in horses, treatment for coagulopathy should be instigated prior to the development of hemorrhagic diathesis. In human medicine this practice has resulted in improved survival rates.<sup>4</sup> The first line of treatment for subclinical DIC involves decreasing coagulation in the hypercoagulable state with aspirin or heparin.<sup>1</sup> Low molecular weight heparin is a specific treatment aimed at blocking Factor Xa, without the adverse effects found with unfractionated heparin.<sup>4,15,16</sup> Replacement of depleted coagulation factors such as platelets and AT is also used in human medicine and may have a role in veterinary medicine.<sup>1,15</sup>

In our study, the 1-year incidence of subclinical DIC in horses with acute colitis was 32% (12/37 horses). Previous studies of DIC in horses required clinical signs of fulminant coagulopathy, explaining the disparity between findings in our report and previous studies. In a small study<sup>8</sup> of coagulation testing in horses with colic, the occurrence rate of any single clinicopathologic abnormality was 100%. In our study, 90% of the horses had at least 1 abnormality. The impact of subclinical DIC on outcome has been evaluated in people and dogs, revealing a significant relationship between subclinical DIC and poor outcome.<sup>2,4</sup> A causal relationship has not been evaluated in veterinary medicine, but human studies have shown improved treatment success rates when DIC is treated early in the course of disease.<sup>4</sup>

By inspection, laminitis and phlebitis appeared to develop more commonly in horses in our study with subclinical DIC, although significance was not reached. Disseminated intravascular coagulation is classically associated with microangiopathic thrombi and not large vein thrombosis. A hypercoagulable state such as DIC could lead to venous thrombosis if endothelial irritation such as an IV catheter was also present. A relationship between the presence of catheter related thrombosis and primary disease has been suggested.<sup>17</sup> Regarding the cause of laminitis, some recent reports<sup>18-20</sup> indicate that microthrombi may not be an important or consistent finding in the developmental phase of laminitis. In our collective experience, DIC and laminitis are sequelae to gastrointestinal tract inflammation and may play unrelated but important roles in determining outcome.

As a result of several factors, DIC is a difficult syndrome to diagnose. Primary amongst these factors is a lack of a consensus definition for DIC in human and veterinary patients and our inability to define precisely when the onset of DIC occurs as a result of its presentation as a continuum of clinical and hemostatic abnormalities. We chose our definition for subclinical DIC

on the basis of availability of tests of hemostatic indices validated for horses and previous definitions in the literature.<sup>3,6,11</sup> Other factors include the variety of primary diseases that predispose horses to DIC, the variable clinical signs associated with DIC, including microthrombi and subsequent damage that may not be evident by routine examination, and variable conventional coagulation test results depending on the stage of disease (ie, hypercoagulation vs hemorrhagic diathesis). Because of these vagaries a new diagnostic plan has been suggested in human medicine, calling for specific testing for the detection of hypercoagulation and inhibitor consumption, clinical diagnosis of DIC, and also grading of severity, all without any influence of the primary disease on these criteria.<sup>1</sup> Using the new diagnostic plan, clinicopathologic diagnosis of subclinical DIC requires abnormalities in 4 areas: 1) procoagulant activation, 2) fibrinolysis activation, 3) inhibitor consumption, and 4) end-organ damage.<sup>1</sup>

Conventional coagulation tests do not allow for the use of this schematic diagnostic plan, and novel diagnostic methods are necessary for a specific and sensitive testing approach. New tests are being evaluated in human and veterinary medicine to aid in early detection of what is termed compensated or subclinical DIC.<sup>1,5,21-24</sup> D-dimer is a fibrinolysis-specific degradation product.<sup>1</sup> Thrombin-antithrombin complexes are an indicator of increased coagulation.<sup>1</sup> Both compounds have proven to be more sensitive indicators of DIC than conventional tests and show promise for affected horses.<sup>5,21-24</sup> These tests can increase the ability of the veterinarian to detect subclinical DIC patients.

End-organ damage associated with DIC was suggested in our study by findings of hyperlactatemia and hypercreatinemia. Possible causes of end-organ damage in horses with colitis include endotoxemia, hypotension, hypovolemia, sepsis, and DIC. As DIC is rarely a primary problem, the cause of azotemia is often not clear in these horses. Nonetheless, serum creatinine concentration has been useful in human medicine as a part of the diagnostic evaluation for DIC. Findings in our study support this use of creatinine concentrations in the horses as well. High lactate concentrations may indicate tissue hypoperfusion or tissue damage secondary to poor oxygen metabolism leading to anaerobic metabolism in peripheral tissues.<sup>25,26</sup> The relationship between blood lactate concentrations and DIC is not clear. It may be that hyperlactatemia and hypercreatinemia are indicators of end-organ damage secondary to microthrombi found in horses with DIC.

The potential relationship between hypoproteinemia and AT deficiency was evaluated to determine if protein-losing enteropathy, which often develops in horses with acute colitis, affected AT activity. Low AT activity does not necessarily indicate consumption of AT by coagulation, as loss by the gastrointestinal or urinary tracts can also lead to AT deficiency. A relationship was found between hypoproteinemia and AT deficiency only at the third sampling time, 48 hours after admission. This finding may suggest that after rehydration, and as the acute colitis progresses, AT deficiency is not necessarily solely caused by consumption. Protein-losing enteropathy and, to a lesser

extent, protein-losing nephropathy are present in horses with acute colitis. Once rehydrated, low plasma AT activity may simply be another indication of nonspecific protein loss. This finding impacts our interpretation of AT deficiency in our horses. Anti-thrombin deficiency as a result of loss from the primary disease may be a contributor to abnormal coagulation and not a result of such a process. Primary AT deficiency has been documented to cause hypercoagulation in veterinary and human medicine.<sup>27,28</sup>

Plasma fibrinogen concentration has not proved useful in studies of DIC in dogs, and its use in horses is also not evident in our study.<sup>2</sup> No horse had a plasma fibrinogen concentration that was subnormal (reference range, 200 to 375 mg/dl). Interestingly, there was a downward tendency in horses with subclinical DIC (group 1). They had a decrease in mean plasma fibrinogen concentration in contrast to group-2 horses. Also observed was a precipitous drop of > 100 mg/dl in horses with DIC that did not survive (Table 1). These findings suggest that evaluation of serial plasma fibrinogen concentrations may be useful for evaluation of progression of subclinical DIC in horses.

In this study thrombocytopenia was detected in 6 of 12 horses in group 1 and in 4 of 25 horses in group 2, representing a similar proportion in the nonsurvivors and survivors in each group. Samples were collected in EDTA, and pseudothrombocytopenia has been documented in this anticoagulant.<sup>29</sup> In this study any horse with thrombocytopenia was screened via manual examination a blood sample for clumping of platelets. As with all tests of coagulation, thrombocytopenia alone is not diagnostic for DIC. In horses with colitis a variety of inflammatory processes may lead to thrombocytopenia.

Necropsy reports in group-1 nonsurvivor horses were consistent with DIC and supported the clinicopathologic antemortem diagnosis of DIC. Although necropsy examination may not be a sensitive test for DIC, because of dissolution of thromboses, the presence of thrombosis is highly suggestive, but not pathognomonic, for DIC.

<sup>a</sup>Thrombo-Wellcotest, Murex Laboratories, Norcross, Ga.

<sup>b</sup>Cell-dyne 3500, Abbott Co, Abbott Park, Ill.

<sup>c</sup>ACL, Instrumentation Laboratory Co, Lexington, Mass.

<sup>d</sup>Kodak Eckachem 250 Analyzer, Kodak Co, Rochester, NY.

<sup>e</sup>NOVA Sta Profile M, Nova Biomedical Corp, Waltham, Mass.

<sup>f</sup>Stata Press, College Station, Tex.

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