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Acute Diarrhea in the Adult Horse: Case Example and Review

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Acute diarrhea is a clinical sign of large intestinal (typhlocolic) disease in adult horses. Frequently, the major clinical signs also include colic, dehydration, and endotoxemia, which sometimes rapidly progress to shock and, occasionally, to death. Underlying pathologic causes are mostly colonic flora disturbances resulting in pathogen overgrowth and gastrointestinal motility alterations as well as intestinal fluid losses and electrolyte and acid-base imbalances. Diarrhea is defined as increased water content in the feces compared with homeostasis. Acute diarrhea may differ somewhat in foals and adult horses because of differences in causative infectious agents, the intestinal site affected, and different colonic absorptive capacity. The initiating cause of the problem of acute diarrhea is frequently (>60% of cases) not determined. Acute colitis also produces rapidly severe catabolic conditions with marked acute weight loss.

Acute undifferentiated diarrhea in a 4-year-old Thoroughbred stallion

A 4-year-old Thoroughbred stallion was presented with acute onset of severe diarrhea of 7 hours' duration. The pertinent history was unremarkable, and the horse had been in full training and racing at the local racetrack. On clinical examination, the horse was depressed, clinically estimated to be 10% dehydrated, mildly colicky, and mildly tachycardic, but the temperature was normal. Venous blood gases and electrolytes showed mild metabolic acidosis with hyponatremia, hypochloremia, absolute and relative

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hypoproteinemia, an increased anion gap, a marked increase in the strong ion gap (lactate) compatible with the problems of fluid and electrolyte losses, inflammation of the colon, and general decreased tissue oxygenation as a result of severe dehydration (Table 1). A complete blood cell count (CBC) showed leukocytosis with a left shift and hyperfibrinogenemia, which were both compatible with severe toxic colitis (Table 2). The horse had received penicillin, gentamicin, and flunixin meglumine treatment by the referring veterinarian on the day of presentation.

Initial *Clostridium difficile* toxin A and B screening of feces was negative. Initial treatment consisted of parenteral fluid treatment using lactated Ringer's solution (LRS) spiked with one half of the deficit of sodium bicarbonate, calculated as 0.4 (sodium bicarbonate space) × body weight × negative base excess (as reported on blood gas results; note that the base excess is calculated from normal human bicarbonate concentrations and that the real base excess in this patient is higher at approximately 12 mmol/L; normal bicarbonate values of the horse are 28.3 ± 3.4; see Table 1). The rate of fluid administration in severely dehydrated animals may go up to 1 L/min for the first 30 minutes so as to improve hydration status. This can be accomplished with a fluid pump system. The remaining fluid deficit (% dehydration × body weight = fluid deficit in liters) should be corrected over 12 hours. The horse was also started on oral potassium supplementation using potassium chloride (KCl), 50 g, administered orally every 12 hours. As an adjunct treatment for undifferentiated diarrhea, the horse was also given oral zinc bacitracin (10 mg/kg) twice daily for the first 24 hours, followed by administration once daily until firm feces were observed. The horse was also treated flunixin meglumine at a rate of 0.25 mg/kg every 8 hours for its purported antiendotoxic effects.

The horse responded well to the supportive treatment in the first 24 hours, and vital signs were normal on day 2. Parenteral antibiotic

Table 1
Venous blood gases, total solids, and electrolytes at admission

	Case	Reference range
pH	7.20	7.4 ± 0.05
P_{CO_2}(mm Hg)	43.1	40 ± 2
P_{O_2}(mm Hg)	45.7	40 ± 4
HCO_3^- (mmol/L)	16	28.3 ± 3.4
Base Excess (mEq/L)	−8	0 ± (2–4)
Anion gap (AG; mmol/L)	20.4	12 ± 4
Strong ion gap (AG-A^-) (mmol/L)	11.3	0 ± 2
Sodium (mmol/L)	125	139 ± 4.2
Potassium (mmol/L)	3.4	4.5 ± 0.04
Chloride (mmol/L)	92	101 ± 4
SID (Na^+ K^-Cl^- HCO_3) (mmol/L)	36.4	40 ± 2
TP g/L	50	64 ± 10
A^- (TP × 0 .175) (mmol/L)	9.1	12 ± 4

Abbreviations: SID, strong ion difference; TP, total protein.

Table 2
Hemogram at admission

CBC	Case	Reference values
WBC (×10E9/L)	18.5	5.3–11.0
RBC (×10E12/L)	14.56	6.5–11.6
HGB (g/L)	190	109–188
HCT (L/L)	0.60	0.29–0.53
PLTS (×10E9/L)	100	80–397
Segmented	7.03	2.1–6.0
Bands	0.74	0.0–0. 2
Lymphocytes	9.25	1.7–5.0
Monocytes	0.74	0.0–0.6
Fibrinogen (g/L)	5.0	<2.9
Rouleaux	+++	

Abbreviations: CBC, complete blood cell count; HCT, hematocrit; HGB, hemoglobin; PLTS, platelets; RBC, red blood cells; WBC, white blood cells.

treatment was not continued, and by day 3, there were firm feces present, parenteral fluid therapy was discontinued, and the horse recovered uneventfully. The main abnormalities noted on a biochemical profile were mild hypoalbuminemia (2.7 g/dL, normal range: 2.9–3.6 g/dL) and mild prerenal azotemia.

Bacteriologic culture of feces for *Salmonella* and *Clostridium* spp were repeatedly negative, as was a toxin assay testing for *C difficile* toxins A and B as well as for *C perfringens* enterotoxin (*C perfringens* Enterotoxin Test and *C difficile* tox A/B test; Techlab, Blacksburg, Virginia). The exact initiating cause of the diarrhea problem in this horse could not be established. The horse was not tested for Potomac horse fever (PHF). The final working diagnosis was acute undifferentiated diarrhea attributable to bacterial colonic overgrowth of unidentified pathogenic organism(s).

Pathophysiology of acute diarrhea

In approximately 40% of horses presented with the complaint of acute diarrhea, a causal association may be established, and in approximately 60% of cases, the originating cause is never found [1]. Diarrhea represents a disturbance of the normal fluid balance, including an imbalance of electrolyte secretion to absorption in the large intestine [2]. Because of the massive absorptive capacity of the large colon, small intestinal lesions do not usually cause diarrhea in adult horses as compared with other species. Small intestinal diarrhea may be seen in foals. Different mechanisms are involved in the development of diarrhea; these include hypersecretion, increased permeability (exudation), malabsorption, and abnormal motility [3,4]. Patients with severe acute diarrhea are usually also presented with signs of active inflammatory processes primarily localized in the large colon. Central to the problem of acute diarrhea is the cecocolic intestinal flora. Any ''upsetter'' of the flora may create a milieu that releases bacterial toxins (eg,

lipopolysaccharide [LPS]) inducing inflammation (cytokines and other inflammatory mediators), resulting in net fluid loss into the intestinal lumen and damage to the cell layers and vascular bed of the cecocolic mucosa as well as local edema formation, exudation, and toxin absorption into the bloodstream. The net result is massive fluid, electrolyte, anticoagulant, and procoagulant substances and protein losses with secondary signs, such as hypovolemia, acidemia, hypoalbuminemia, coagulation disturbances, and cardiovascular and endotoxic shock [5].

Specific disease conditions associated with acute diarrhea include *C difficile* enterocolitis, *C perfringens* enterocolitis, antibiotic-associated diarrhea (AAD), salmonellosis, PHF, and nonsteroidal anti-inflammatory (NSAID)–associated diarrhea.

Clostridium difficile enterocolitis

C difficile enterocolitis is an inflammation of the colon caused by overgrowth of toxigenic strains of *C difficile*, most commonly causing diarrhea and varying degrees of toxemia [6–9]. Proliferation of this organism occurs because of a disruption of the normal colonic flora. Two toxins are produced, a cytotoxin and an enterotoxin, which work synergistically, with the net result of mucosal damage, local inflammation, and fluid secretion causing a vicious circle. Historically, there may be recent antibiotic use, which upsets the normal stable colonic bacterial milieu. Diagnosis is made by the presence of toxin in the feces using a commercial ELISA test [10,11]. A positive culture of *C difficile* in feces is not necessarily diagnostic, because there are toxin-positive and toxin-negative strains of this organism present [11,12]. Viability of the organism in collected feces is poor even if kept refrigerated, whereas viability of the toxin is long term when feces are stored at 4°C [12,13]. The supportive treatment is identical to the case scenario. In addition, if feces are toxin-positive, a course with oral metronidazole at a rate of 15–25 mg/kg administered every 8 hours is indicated until feces are toxin-negative and are firming up [14]. Most of the isolates of *C difficile* at the Ontario Veterinary College clinic were sensitive to metronidazole but in vitro resistant to zinc-bacitracin [13]. The antibiotic vancomycin (20–40 mg/kg administered two times daily to four times daily intravenously or orally) should be reserved for severe resistant infections and should not be used in the horse if possible. Di-tri-octahedral smectite [15] has been shown in vitro to bind clostridial toxins and inhibit growth of *C difficile* but has not been critically evaluated as an adjunct treatment in horses with *C difficile*–induced colitis or in horses with undifferentiated acute colitis [16].

Clostridium perfringens enterocolitis

C perfringens has been associated with colitis in horses [9,17]. *C perfringens* is classified based on the pattern of exotoxin production into five types:

A, B, C, D, and E (importance of type E in disease is questionable). *C perfringens* type A is the type most frequently associated with colitis in horses but is also isolated in normal horses. The main toxin that the virulent strains produces is the α toxin, which interferes with glucose uptake and energy production and triggers arachidonic acid metabolism and activation of secretion in enterocytes [10]. There is a novel toxin designed β_2 produced by *C perfringens* that could be described as similar to type A and has been found only in horses with colitis [18]. It biologic activity includes enterocyte necrosis, ulceration, intestinal hemorrhage, and inflammation. Virulent *C perfringens* also produces enterotoxin that alters permeability to water macromolecules, resulting in cell necrosis [10]. Diagnosis can be made by isolation of *C perfringens*, and demonstration of associated toxins in the absence of other pathogens is the strongest evidence of its causative role. The treatment approach is identical to *C difficile* therapeutic measures.

Antibiotic-associated diarrhea

Antibiotics that have been used experimentally to induce acute colitis in horses include lincomycin, clindamycin, oxytetracycline, and low-dose erythromycin ethylsuccinate [13,14,19,20].

Parenteral or oral antibiotics that have been temporally associated with the onset of acute diarrhea include tetracyclines, lincomycin, erythromycins, cephalosporins, trimethoprim-sulfas, and penicillins. Cases of colitis have also been associated with the administration of cloxacillin, florfenicol, ampicillin/sulbactam, chloramphenicol, and metronidazole as well as with ciprofloxacin more recently [21].

The core of the problem is the disruption of the normal cecocolic flora [22]. Theoretically, any broad-spectrum antibiotic has the potential to upset the local protective flora and to allow potential pathogens to "overgrow" and cause disease. In human beings, the main factors implicated in AAD are related to loss of colonization resistance through alterations in the gastrointestinal microflora, changes in fermentative conditions, and resulting increased toxin production by pathogenic organisms (eg, *C difficile* toxins) [23]. To date, only erythromycin ethylsuccinate has been implicated with *C difficile* as the specific pathogen causing acute colitis in the horse [6,19]. In many clinical cases, it is difficult to establish a pathogen and the antibiotic as the linked causative factors in disease. Most classes of antibiotics have been implicated in human AAD, but there is a greater association with cephalosporins, penicillins, and clindamycin [8,23].

Salmonellosis

Salmonellosis causes different clinical syndromes and is usually characterized by an acute septic colitis with profuse diarrhea [24]. Its incidence

is low in nonhospital settings, but outbreaks occur occasionally on farms [25]. *Salmonella* species most frequently isolated from horses include *S typhimurium* (DT104), *S agona*, *S anatum*, and *S krefeld* [26,27]. *Salmonella* carrier horses have been reported with a frequency as high as 10% to 20%, but the frequency is thought to be between 1% and 2% in the general population [26]. The infection by *Salmonella* usually occurs orally and through the gastrointestinal tract. It can invade the pharyngeal, small intestinal, and colonic mucosa. It invades the intestinal M cells, is phagocytosed by macrophages and dendritic cells in the lamina propria and lymphoid tissue, and then passes into the bloodstream [24,25]. *Salmonella* causes diarrhea by different mechanisms involving virulent factors that promote infection. *Salmonella* produces a cytotoxin causing cell damage and altered permeability [28]. It also produces a thermolabile (LT) exotoxin similar to *Escherichia coli* that causes hypersecretion and may contribute to diarrhea [29], and the main cause of diarrhea is probably the ability of *Salmonella* to produce a severe intestinal inflammatory reaction [30]. The systemic effects caused by *Salmonella* can be attributed to LPS, often resulting in severe cardiovascular impairment and releasing factors triggering an inflammatory response of the host cumulating in further tissue damage and signs of endotoxemia [24,31]. Diagnosis of *Salmonella* is achieved by five serial fecal cultures that have a sensibility of 93% [32,33] or a positive fecal polymerase chain reaction (PCR) assay for *Salmonella* bacteria [34].

Potomac horse fever

PHF is an acute enterotyphlocolitis of horses caused by infection with the monocytotropic rickettsia, *Neorickettsia risticii* [35], formerly called *Ehrlichia risticii* [36]. The pathophysiology of PHF is poorly understood. *N risticii*, an obligate intracellular parasite, has a predilection for blood monocytes and tissue macrophages. Within days of infection, *N risticii* can be found in blood monocytes, and although readily phagocytosed by monocytes, *N risticii* survives within phagosomes in macrophages by inhibiting phagosome-lysosome fusion. The neorickettsemia persists throughout the clinical period [37].

The pathogen has a predilection for the cecum and large colon but is occasionally found in the jejunum and small colon. Colonic and small intestinal epithelial cells, colonic mast cells, and macrophages are the targets of infection. Even mild cases of PHF without diarrhea have evidence of colitis [38]. The major clinical signs observed resemble those of horses with salmonellosis or endotoxemia. It is possible that many pathophysiologic changes observed in horses affected with PHF are secondary to the effects of altered colonic flora (eg, diarrhea, endotoxemia).

Serology is the most commonly used method of diagnosing PHF. The indirect fluorescent antibody (IFA) test is the most widely used diagnostic test

for PHF [37]. The interpretation of results can be challenging. PHF is diagnosed by demonstrating a fourfold or greater increase or decrease in IFA titers between acute and convalescent serum samples. The acute sample should be collected as soon as first clinical signs are observed, and the convalescent sample should be collected 5 to 7 days later. Failure to seroconvert does not rule out PHF. The expected antibody titer of naturally affected horses is greater than 1:80. Persistence of high antibody titers (eg, 1:2560) for more than a year has been noted in clinical and subclinical cases after natural infection [37]. An ELISA is also available [39]. A nested PCR technique has been developed [40]. This detects the partial 16S rRNA gene of *E risticii* and seems to be as sensitive as blood culture for detecting infection with *E risticii*. Isolation of *E risticii* by blood culture is the most definitive method of diagnosis of PHF. It requires collecting heparinized blood (100–400 mL) and harvesting buffy coat for culture [40]. Because conventional PCR assays are time-consuming and prone to contamination, a new real-time PCR assay has been developed and allows detection of *N risticii* in 2 hours [41].

Diarrhea associated with nonsteroidal anti-inflammatory drugs

Clinically, NSAID toxicity is described to cause two clinical syndromes: generalized NSAID toxicity and right dorsal colitis (RDC) [40,42]. All NSAIDs are potentially capable of causing toxicity. RDC is a localized ulcerative inflammation of the right dorsal colon that has been associated with NSAIDs given in excessive amounts in the presence of dehydration. The exact cause is not known, but there are associations with a history of phenylbutazone or flunixin meglumine treatments.

The most evident clinical signs of RDC are depression, anorexia, fever, colic, diarrhea, dehydration, and evidence of endotoxemia. Clinical signs of generalized NSAID toxicity may vary from no systemic signs to severe diarrhea along with the other sign of toxicity, such as anorexia, oral ulceration, fever, and peripheral edema [43]. NSAIDs inhibit cyclooxygenase activity (COX 1 and COX 2). It is believed that NSAIDs that are indiscriminately COX 1 and COX 2 inhibitors have a higher capacity to produce more toxicity (eg, phenylbutazone, aspirin). The gastrointestinal lesions caused by NSAIDs are manifested as mucosal ulceration, bleeding, protein-losing enteropathy, and a significant response to microbial products exposed to the lamina propria [43,44].

Therapeutic considerations in acute diarrhea cases

Because the net results of any case with severe acute diarrhea are massive fluid, electrolyte, and protein losses with secondary signs, such as hypovolemia, acidemia, and cardiovascular and endotoxic shock, the main goal of treatment is to re-establish homeostasis by supportive treatment. Based on

the previous described alterations of homeostasis, the goals of colitis treatment, regardless of the cause, may involve fluid and electrolyte replacement, correcting acid-base disarrangements, circulatory support, treatment of hypoproteinemia, control of inflammation, endotoxin control, pain management, mucosal protection and repair, and the use of antibiotics and anticoagulants.

To correct fluid losses, the amount of fluid required to be replaced is calculated by the formula: BW × % DH, where BW is body weight and DH is dehydration. The calculated amount is administered at a speed based on cardiovascular status. Severely dehydrated animals may need rapid administration and require the use of peristaltic pumps to achieve it. The speed used can be between 10 and 40 mL/k/h. The use of 7.5% hypertonic saline (5–7 mL/kg in 20 minutes) is a resuscitation maneuver to reverse hypovolemia; however, in colitis cases with severe hyponatremia, it needs to be administered cautiously [45]. It needs to be always followed by the administration of isotonic solutions, with the amount compared with the total fluid loss plus the animal's daily maintenance requirement calculated. To restore and maintain fluid balance, LRS or acetated Ringer's solution and sodium chloride (0.9%) are commonly used [46]. Colloidal solutions (eg, whole blood, plasma, hetastarch, dextrans) can be used to maintain the fluid in the vascular space [46,47]. Colloids should be initiated when plasma proteins are less than 4 g/dL. Colloids should be from a commercial source or from appropriate donors (Aa and Qa isoantibody–negative).

Sodium bicarbonate is used to treat severe metabolic acidosis that does not correct with volume expansion. To calculate needs, use the following formula: 0.4 mEq × body weight (kg) × (base deficit). Give half the dose slowly intravenously over 20 minutes, and give the rest of the dose in crystalloid fluids over 4 hours. Hypokalemia can be treated by adding KCl to the hydration solution and can be administrated safely if the rate of administration does not exceed 0.5 mEq/kg/h. To correct body deficits, KCl should be administered orally at 50 g twice a day for several days.

Inotropic agents can be given to increase systemic blood pressure when it drops markedly. Dopamine hydrochloride, 1 to 5 μg/kg/min, is given by continuous intravenous administration

Dobutamine, 2 to 5 μg/kg/min, is given by continuous intravenous administration [48]. NSAIDS (eg, flunixin meglumine, ketoprofen, phenylbutazone, aspirin) are frequently used for attenuation of the inflammatory cascade. Flunixin meglumine seems to have the most potent antiendotoxic effects at a rate of 1.1 mg/kg administered every 8 to 12 hours or at 0.25 mg/kg administered every 6 to 8 hours, or ketoprofen can be administered at a rate of 0.5 mg/kg every 6 hours. Aspirin also prevents thrombus formation. NSAIDS inhibit vasodilator prostaglandins; therefore, care must be taken with regard to renal damage [49].

Hyperimmune antisera or plasma is used in endotoxemia. O-chain–specific antisera work well, but because of the antigenic diversity between gram-negative (GN0) bacteria in this region, they are not clinically useful. Different gram-negative bacteria share common core antigens; therefore, antibodies are aimed at the LPS core [50]. These antibodies may promote opsonization and reticuloendothelial clearance and inhibit the interactions of LPS. J5 hyperimmune plasma is used at a dose of 4.4 mL/kg initially. Some studies have failed to show positive results, however [51].

The use of antibiotics in treating acute enterocolitis is controversial [52]. Although bacterial seeding to other organ systems is rare, in severely neutropenic patients, the use of broad-spectrum antibiotics seems to be indicated. Oral antibiotics used as adjunct treatments to the supportive care are metronidazole (15–25 mg/kg administered every 8 hours) in cases with confirmed *C difficile* toxin-associated colitis and zinc bacitracin (10 mg/kg administered every 12 hours) in *C difficile* toxin-negative acute colitis with an open diagnosis for the cause of the diarrhea [1,14]. Improvement should normally be noted within 2 to 3 days. Metronidazole is potentially teratogenic and should not be used in pregnant mares. Both adjunct oral antibiotics are used in an extralabel form and have not been critically evaluated for efficacy in a controlled clinical trial.

In *Salmonella* cases, there are different opinions regarding the use of antibiotics in adult horses. Septicemic foals with salmonellosis are routinely treated with antimicrobial drugs, however. There are reasons for using antibiotics (may kill existing *Salmonella* bacteria, may prevent spread of *Salmonella* bacteria in the gastrointestinal tract to other organs, and may prevent spread of enteric bacteria through damaged intestinal mucosa to other organs), but there are also reasons for not using them (probably do not kill existing *Salmonella* bacteria, killing gram-negative bacteria may release additional LPS into the system, may prolong fecal shedding of *Salmonella* bacteria, may contribute to antibiotic resistance, and may further upset the colonic flora). The antimicrobials used in the treatment of salmonellosis include the combination of penicillin and gentamicin, the combination of ceftiofur and gentamicin, and fluoroquinolones (eg, enrofloxacin, orbifloxicin) [53].

Specific treatment for PHF includes oxytetracycline administered intravenously at a rate of 6.6 mg/kg every 24 hours for 3 to 5 days as the treatment of choice. A rapid recovery and dramatic decrease in fatality are observed when oxytetracycline therapy is commenced within 24 hours after the development of fever. A response to therapy (eg, decreased temperature, improved attitude, appetite, intestinal sounds) can be observed within 12 hours [39]. The combination of oral erythromycin estolate (25 mg/kg administered every 12 hours) and rifampin (10 mg/kg administered every 12 hour) is also effective when given early in the clinical course; however, the clinical response is not as rapid as when oxytetracycline is given intravenously. The risk of upsetting the colonic flora must be borne in mind, however [19,52].

During the acute phase, these animals demonstrate pronounced catabolism and lose condition quickly. Leukopenic and hypoproteinemic patients profit from hyperimmune serum and/or plasma transfusions as well as from broad-spectrum parenteral antibiotics to prevent seeding of infection peripherally. The energy requirement of a 500-kg horse at rest in a normal state is 33 kcal/kg/d; a horse with severe acute colitis needs approximately 50 kcal/kg/d. To counteract the severe catabolism with acute colitis, partial parenteral nutrition has also been reported. At this hospital, we use the following regimen: 50% dextrose (2 L) is combined with 8.5% amino acids (1.5 L) and LRS (1.5 L). This yields a hypertonic solution; therefore, the parenteral intravenous infusion has to evolve over time slowly and should be started at 140 mL/h and then gradually increased to 280 mL/h and then to 560 mL/h. In our clinical experience, this treatment approach has reduced the amount of plasma used, reduced mortality, shortened the hospitalization time, and reduced the total bill.

With regard to the prognosis of cases with acute colitis, there are limited numbers of studies in the literature. In a retrospective study at a veterinary teaching hospital, the case fatality rate was 42% [54], although in a more recent study, the case fatality rate was 25.4% [52]. Horses that were severely dehydrated were seven times more likely to die [53], and horses with a history of administration of an antimicrobial for a problem preceding diarrhea were 4.5 times more likely to fail to survive [55].

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