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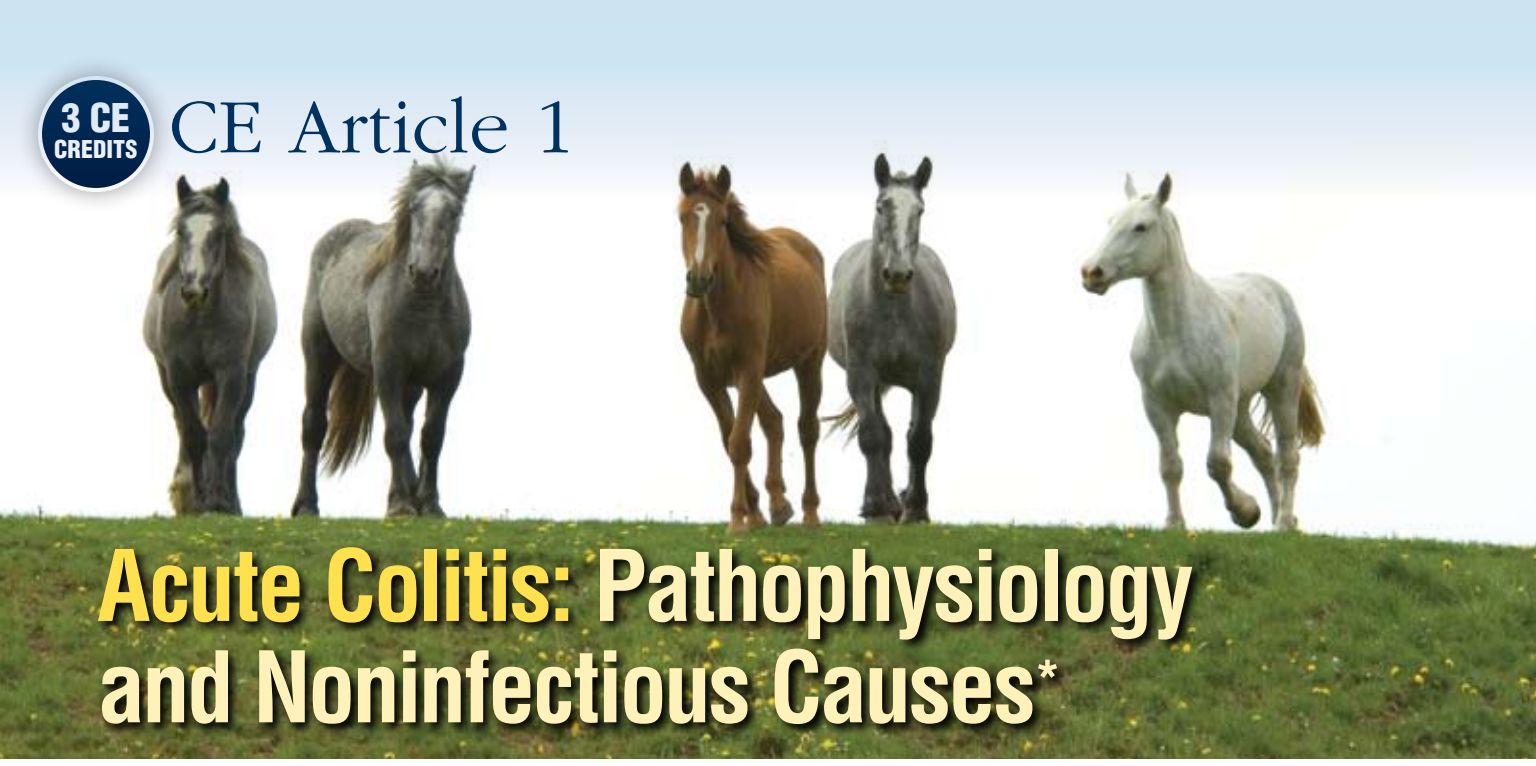

Acute Colitis: Pathophysiology and Noninfectious Causes*

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At a Glance

*A companion article on infectious causes begins on page 375.

Abstract: *Acute colitis is a common and potentially devastating condition in adult horses. While supportive care is critical in treating acute colitis, timely provision of appropriate therapies can maximize the chance for recovery. This article reviews the normal physiology of the equine large intestine and illustrates how disruption of normal gastrointestinal function in acute colitis leads to common pathologic changes, regardless of the underlying etiology. The most common noninfectious etiologic agents of acute colitis in horses are discussed to permit development of an appropriate treatment plan.*

Acute colitis is a debilitating condition that can affect horses and ponies of any breed, age, or sex.[1] By definition, colitis is associated with inflammation of the colonic mucosa that invariably leads to development of diarrhea; however, diarrhea may not be present on initial examination. The degree of colonic inflammation can be profound, leading to severe losses of fluid and electrolytes and possible permanent intestinal injury. Despite aggressive treatment, the clinical status of an affected equine patient can deteriorate rapidly, and the mortality rate can be high.[2] While the literature regarding the fatality rate of acute colitis in horses is limited, fatality rates of 32% to 60% for salmonellosis and 15% to 35% for Potomac horse fever have been reported.[3,4]

Determining the underlying etiology of acute colitis can be challenging. Few causes of acute colitis in adult horses have been documented compared with causes in other animals and humans. In one report, a definitive diagnosis was reached in only approximately 35% of cases of acute equine colitis.[5] In addition, identification of a specific etiologic diagnosis may be complicated by multiple potential pathogens. Regardless of the cause, similar clinical signs (i.e., diarrhea, abdominal pain, pyrexia, cardio-

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vascular failure) or even sudden death may be seen, representing derangement in the normal physiologic process of the large intestine (e.g., the colon and cecum). This article describes the normal physiology of the equine large intestine and the fundamental pathophysiology associated with acute colitis. It also reviews the common noninfectious etiologic agents of acute equine colitis (**TABLE 1**).

Normal Physiology

The equine large intestine includes the cecum, large colon, transverse colon, small colon, and rectum. The cecum has an average length of 1 m and a fluid capacity of 33 L, while the large colon is 3 to 4 m in length and has a capacity of as much as 130 L. The small colon is narrow and has a small total capacity, but it can be up to 4 m in length.[6] The large intestine is the principal site of digestion and water balance in horses; on a normal daily basis, it secretes and recovers a volume of fluid approximately equal to the total extracellular fluid volume of the horse—approximately 100 L/day.[7] Up to 75% of the energy requirement of horses is obtained through carbohydrate metabolism by microbial fermentation in the cecum and colon; specifically, the most important products are volatile fatty acids (VFAs; e.g., acetic, propionic, and butyric acids). A stable luminal environment is required for efficient functioning of the cecum and colon; therefore, luminal pH should be tightly maintained between 6.8 and 7.2, and colonic and cecal luminal osmolality should be kept at approximately 300 mOsm.[8]

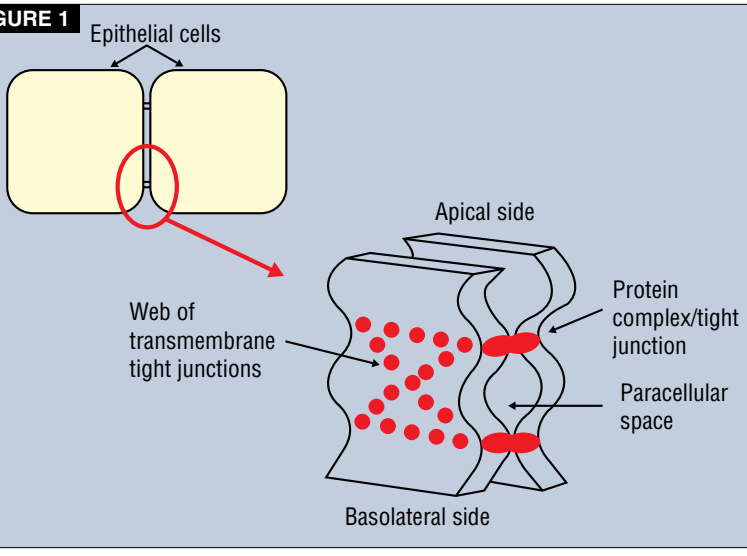
Passage of fluid and digesta through the cecum and large colon is relatively slow to allow adequate time for microbial digestion, fermentation, and absorption of the products of digestion. Fluid can take up to 50 hours to move through the large colon, and digesta can take 2 to 3 days, with times varying according to the type of digesta.[9] The cecum and colon have three phases of motor activity: mixing, retention, and retropulsion of ingesta.[10] Motility in the cecum consists of mixing contractions in which the haustra alternately contract and relax. In addition, every few minutes, a strong, mass movement–type contraction forces some of the cecal contents through the cecocolic orifice into the colon.[11] Within the colon, mixing and haustral contractions efficiently blend the ingesta and expose it to the mucosal surface for absorption of water, electrolytes, and VFAs produced by bacterial fermentation.[9]

Under normal physiologic conditions, water moves into or out of the intestine until the osmotic pressure of the intestinal contents equals that of plasma.[9] The absorption of water depends on absorption of nutrients (e.g., sugars, amino acids) and ions. Absorption is mostly transcellular because tight junctions form intercellular contacts that regulate solute movement through the paracellular pathway (**FIGURE 1**). The ion shifts of primary importance in the equine colon include net absorption of sodium

TABLE 1 Most Common Noninfectious and Parasitic Diagnostic Differentials for Acute Colitis in Adult Horses

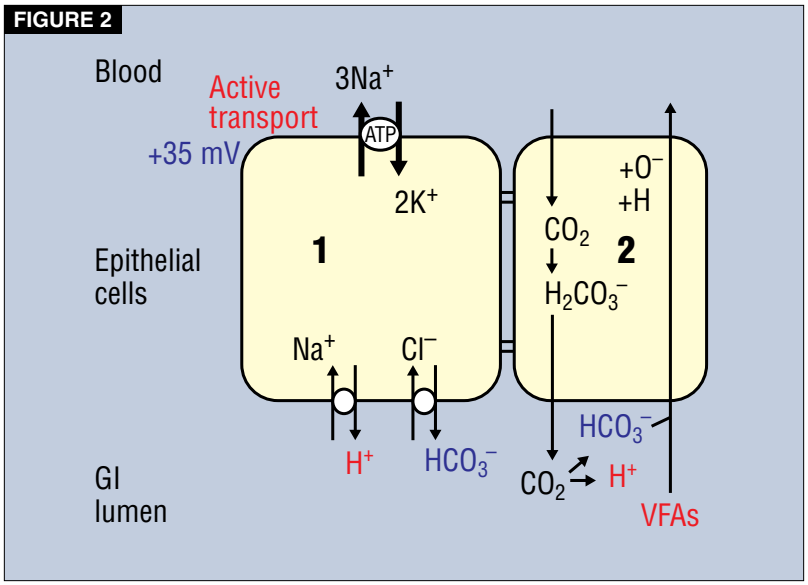
Category	Differential	Etiologic Factor
Parasitic	Strongylosis	*Strongylus vulgaris*
	Cyathostomiasis	Small strongyles
Toxic	NSAID use	Excessive dose or prolonged therapy
	Antimicrobial use	Increased risk with oral antimicrobials and β lactams
	Cantharidin	Blister beetle ingestion
	Plants	Different toxic agents of variable potency
Miscellaneous	Carbohydrate overload	Excessive consumption of soluble carbohydrates

FIGURE 1



Tight junctions seal the spaces between adjacent epithelial cells, preventing free movement of water and electrolytes between the GI lumen and the interstitium.

FIGURE 2



Transport mechanisms in the equine colon. (1) The Na^+-K^+-ATPase pump uses ATP; by its action, Na^+ is pumped out of GI cells via primary active transport. The Na^+-H^+ and Cl^--HCO_3^- pumps use energy from other sources and are examples of secondary active transport. Tight junctions between the cells and the electrochemical gradient prevent free paracellular movement of ions. (2) After ingestion of feed by the horse, the volatile fatty acid (VFA) concentration increases in the colonic lumen. CO_2 is absorbed across the cells, hydrates to form carbonic acid, and then dissociates into bicarbonate and hydrogen ions in the colonic lumen. Concurrently, Na^+-H^+ exchange is inhibited by the high level of VFAs; therefore, the HCO_3^- concentration increases. Once the VFAs have been absorbed, the Na^+-H^+ exchange activity increases again and the H^+ enters the lumen to buffer the HCO_3^-.

and chloride ions and net secretion of bicarbonate ions (**FIGURE 2**). The transport mechanisms for these ions involve passive and active forces. Passive forces include the intrinsic permeability of intestinal epithelial cells, osmotic pressure gradient exerted by the contents of the intestinal lumen, electrical potential difference across intestinal epithelial cells, concentration gradient of solutes across intestinal epithelial cells, and pH of luminal contents.[8] Active transport mechanisms include primary and secondary processes. Primary active transport involves movement of an ion against its electrochemical gradient using energy. In the equine colon, sodium is actively transported by the sodium–potassium–adenosinetriphosphatase (Na^+-K^+-ATPase) pump present in the basolateral cell membranes of the colonic epithelial cells. This pump actively moves three sodium ions out of the cell into the interstitium while moving two potassium ions into the cell. This creates an electrochemical gradient of approximately 35 mV across the mucosal surface of colonic epithelial cells, which facilitates movement of sodium from the colonic lumen into epithelial cells. The secondary active transport systems use "free energy" derived from passive diffusion of one ion down its electrochemical gradient to transport another ion against its electrochemical gradient. Sodium–hydrogen ion and chloride–bicarbonate exchange systems of this type have been identified in the mucosal surface of equine colonic epithelial cells.[8]

Digestion in the colon is primarily by bacterial fermentation (normal large intestinal flora in horses is primarily composed of anaerobes and streptococci) in conjunction with cellulolytic bacteria (in the equine colon), which appear to be similar to those found in the rumen of ruminants.[12] Fermentation of soluble and insoluble carbohydrates yields VFAs, carbon dioxide, methane, and lactate. VFAs, the primary energy source in horses, are passively absorbed through the mucosa of the colon and cecum into the blood and are transported to the liver to be metabolized. Their absorption is tightly regulated by the luminal environment of the large intestine. At a normal pH of large intestinal contents (e.g., 6.8 to 7.2), 99% of VFAs are ionized (dissociated).[8] However, this form is poorly absorbed compared with the un-ionized (undissociated) form.[13] VFAs become un-ionized by transfer of hydrogen ions, primarily from carbon dioxide. Carbon dioxide diffuses into cells of the cecal and colon walls, hydrates to form carbonic acid, and then dissociates into bicarbonate and hydrogen ions.[8] In addition, bicarbonate ions are actively secreted via transporters in the basolateral membrane of colonic cells into the colonic lumen and then accumulate in luminal fluid. High luminal concentrations of VFAs inhibit the Na^+-H^+ exchange. However, as VFAs become un-ionized and are absorbed, this pump activity increases, and hydrogen ions enter the colonic and cecal lumens and buffer the increased level of bicarbonate ions.[8] Hydrogen ions are also used to transport sodium ions into the cell, which drives water absorption (**FIGURE 2**).

Tight regulation of the resident gastrointestinal (GI) microbial population is important, as normal flora protects the host from pathogenic bacteria through colonization resistance (i.e., in competing for space and nutrients, the normal flora inhibits colonization and proliferation of pathogenic bacteria).[14] Normal flora competes with potentially pathogenic organisms for attachment sites on the epithelial surface of the mucosa.

VFAs produced by normal flora further block bacterial attachment by inhibiting growth of pathogenic bacteria. Normal flora also produces bacteriocins that inhibit growth of potential pathogens.[14] Any disturbance in the normal flora impairs these defense mechanisms, increasing susceptibility of the intestine to colonization by pathogenic organisms. Specific host defenses that further preclude the growth of pathogenic bacteria include gastric pH, GI motility, the mucosal barrier, and mucosal immunity.

Pathophysiology

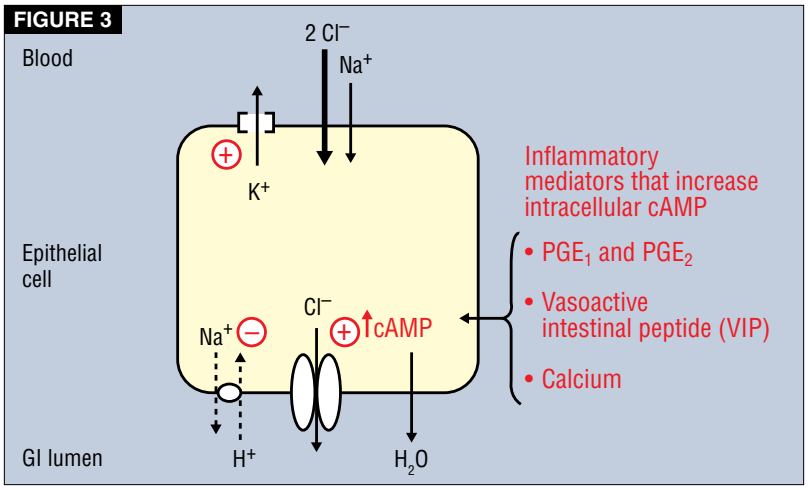
The pathophysiologic mechanisms of acute colitis can be divided into inflammation, abnormal passive and active secretion, and decreased transit time. The inflammatory process is complex: it has many different components. The equine large intestine is poised to mount an inflammatory response to antigenic stimuli through numerous lymphoid follicles and mast cells distributed throughout the mucosae of the cecum and colon and by neutrophils and macrophages that are normally within the colonic mucosa and submucosa.[15] Unfortunately, the process by which inflammatory cells attack foreign antigens is not always specific or well regulated and may lead to secondary damage to host tissues. Neutrophil, eosinophil, mast cell, and mononuclear cellular responses and inflammatory mediators such as prostaglandins and leukotrienes can all result in cellular and tissue damage. In a recent equine colitis study, the prostaglandin E_2 (PGE_2) level increased with time after a castor oil challenge and correlated with granulocyte infiltration.[16] However, neutrophil influx is not definitively detrimental because neutrophil-associated PGE_2 and interleukin (IL)-1β have been shown to promote tissue repair and healing.[17]

Proinflammatory cytokine production also plays a significant role in the development of inflammation within the colonic mucosa. For example, murine acute colitis models have demonstrated increased levels of IL-1α/β, IL-6, IL-18, and granulocyte colony-stimulating factor within the colonic mucosa.[18] Bradykinin and histamine are released by neutrophils and mast cells during inflammation, and studies have shown that they increase secretion and impair absorption by the colonic mucosa.[19] The production and liberation of oxygen free radicals, which are directly cytotoxic, lead to further injury of the colonic mucosal epithelium. Oxygen free radicals may potentiate activity of proteolytic enzymes released by phagocytic cells during the inflammatory process. They can also inhibit antiproteases, which are naturally within colonic mucosa and prevent protease-induced cellular damage. When tissue injury becomes severe, mucosal epithelial cells are lost, leading to erosion and ulceration.[19] Overall, disruption of colonic mucosa leads to a reduction in epithelial surface area, loss of absorptive cells, and failure of tight junctions, with a net result of increased fecal water secondary to impaired reabsorption and increased passive secretion. Recent studies that tried to correlate cytokine concentrations and macroscopic colonic lesions found an increase in interferon-γ and IL-6 related to the presence of necrosis of the colonic mucosa.[20]

Passive fluid loss from the vasculature is minimized in healthy horses because the capillary endothelium is relatively impermeable to macromolecules (e.g., albumin). These macromolecules produce tissue oncotic pressure that resists movement of fluid into the interstitium. However, in acute colitis, the endothelium is often damaged, resulting in increased capillary permeability to macromolecules and loss of albumin from the capillaries to the interstitium.[21] Agents that may increase capillary permeability in equine colitis include endotoxins, enterotoxins, oxygen free radicals, histamine, and prostaglandins.[15] Normally, small fluctuations in the driving forces for fluid movement do not cause interstitial edema because of factors that resist expansion of the matrix (edema safety factors).[22] However, in acute colitis, diminished oncotic pressure across the capillary wall leads to decreased fluid retention by the remaining protein within the capillary lumen. As a result, fluid leaks from the circulation into the interstitium and hypoproteinemia worsens. Therefore, development of interstitial edema becomes a self-perpetuating process.[23] Movement of albumin into the interstitium promotes this fluid shift because tissue oncotic pressure is maintained by albumin despite increasing fluid accumulation. This results in progressive tissue edema and plasma protein loss into the interstitium and, eventually, the intestinal lumen.

CriticalPoint

The large intestine performs microbial digestion of fibrous feed material through a tightly regulated and physiologically complex environment.



Increased cAMP due to endogenous agents such as PGE_1, PGE_2, VIP, and calcium leads to increased Cl^- secretion. Inflammatory mediators increase intracellular cAMP concentration, which leads to opening of chloride channels. Chloride secretion increases, and water follows passively. Luminal sodium increases due to inhibition of the Na^+-H^+ pump by an increased cAMP level. Increased cAMP also increases K^+ transport out of intestinal cells, increasing intracellular chloride levels.

CriticalPoint

A definitive diagnosis may be elusive in cases of acute colitis; therefore, understanding the pathophysiology of colitis can facilitate the development of an appropriate treatment plan.

In many horses with colitis, there is also active secretion of solutes and water by inflamed colonic mucosa.[24] As discussed earlier, the fluid and electrolyte transport processes in colonic epithelial cells are tightly governed by many different processes. While many of these processes have not been studied in detail in horses, research performed in many species indicates that the single most important secretory event leading to increased fecal water (diarrhea) and electrolyte loss is probably increased chloride ion secretion, which is primarily mediated by increased intracellular cAMP.[22] An increase in chloride secretion directly increases water secretion because water passively follows chloride ions. Additionally, a compensatory increase in water reabsorption is prevented by the inhibitory effect of increased intracellular cAMP on the Na^+-H^+ pump, leading to decreased sodium reabsorption and associated reabsorption of water. Increased cAMP also increases potassium transport out of the intestinal cells via a basolateral potassium pump, thereby increasing intracellular chloride levels and further enhancing chloride secretion down the concentration gradient. Endogenous agents that can increase intracellular cAMP include PGE_1, PGE_2, calcium, and vasoactive intestinal peptide[8] (**FIGURE 3**).

Intestinal motor function is vital to normal digestion and absorption. Fluid will not traverse the intestinal tract unless propelled by contractile activity.[9] Propulsive and segmental activity of muscle layers within the intestinal tract mixes food with intestinal secretions, alters the surface area of intestine exposed to luminal contents, and regulates the rate of intestinal transit and contact time during which mucosal absorption occurs. Abnormal smooth muscle activity has been shown to occur in acute colitis and may be a response of the bowel to irritation and/or increased intraluminal volume.[25] When inflammation occurs, smooth muscle contractions decrease due to endogenous myosin phosphatase inhibitor CPI-17 suppression and altered activity of muscarinic receptors and ion channels.[26] Typically, abnormal motility involves an increased rate of transit due to decreased segmental contractions that normally impede intestinal flow.[27] This increased rate of transit leads to decreased contact time for fluid absorption, resulting in increased fecal water content and increased frequency of defecation (i.e., diarrhea). In addition, there is reduced clearance of bacteria from the large intestine, which may contribute to the virulence of potentially pathogenic organisms.[28]

Parasite-Associated Colitis

While parasite-associated colitis is most often clinically associated with chronic diarrhea, sudden-onset diarrhea has been reported in horses.[29] Cyathostomes (small strongyles) and large strongyles are important equine parasites associated with acute colitis.[30,31] In cyathostome infestation, injury to colonic mucosa is thought to be related to simultaneous maturation and release of hypobiotic cyathostome larvae from the cecal and colonic mucosae. This phenomenon is seasonal; therefore, the disease is expected to occur only in late winter and early spring, although the stimulus for larval emergence is not clear.[29] Emergence of encysted larvae causes mucosal injury, ulceration, and inflammation, all of which may be responsible for development of clinical disease.[14] Alternatively, diarrhea associated with large strongyle infestation (most importantly, infestation with *Strongylus vulgaris*) is typically acute and occurs within several days of infestation. Fourth-stage larvae migrate from

the lumen through the mucosa and submucosa into arterioles of the intestine, causing mural edema, hemorrhage, and infiltration of the wall by inflammatory cells.[32] Increased secretion and decreased absorption of fluid and electrolytes stimulated by inflammatory mediators such as prostaglandins and histamine may also play a role in colitis induced by large strongyles.

Antimicrobial-Associated Colitis

Antimicrobial administration can be associated with colitis in equine patients.[2] The resulting condition can be very severe, and horses with antimicrobial-associated diarrhea are reported to be 4.5 times less likely to survive than those with diarrhea from other causes.[2] Antimicrobials may precipitate diarrhea by disrupting GI flora and depleting the normal population of obligate anaerobes and streptococci. This interferes with colonization resistance.[33] Additionally, normal anaerobic bacteria in the GI tract produce short-chain fatty acids and other metabolites toxic to facultative anaerobic bacteria. Loss of normal anaerobic flora leads to depletion of these short-chain fatty acids, which are also important for carbohydrate fermentation and absorption of sodium and water by colonic mucosa.[12]

Antimicrobials that are highly concentrated within the GI lumen exert a more profound effect on GI flora than other antimicrobials. Antimicrobials that are administered orally or excreted in bile that undergo enterohepatic circulation (e.g., oxytetracycline, doxycycline) are of greatest concern.[34] Broad-spectrum antimicrobials such as tetracyclines and β-lactams are most commonly associated with colitis in humans; in horses, trimethoprim–sulfamethoxazole, macrolides, cephalosporins, and tetracyclines have been reported to cause colitis.[34–38]

NSAID Toxicosis

NSAIDs are well recognized as having potential toxic effects on the equine GI tract; these effects may lead to diarrhea. PGE_2 and PGI_2 are critical for maintaining normal mucosal blood flow within the GI tract; therefore, inactivation of COX enzymes by NSAIDs can lead to decreased prostaglandin production, which, in turn, impairs mucosal blood flow, leading to mucosal injury and inflammation.[39] In addition, the administration of COX inhibitors has been shown to inhibit epithelial cell migration and mucosal restitution.[40] NSAID toxicosis manifests as two clinical syndromes called *generalized NSAID toxicosis* and *right dorsal colitis*. In patients with the generalized form, mucosal ulceration occurs throughout the GI tract, and oral and gastric lesions are very common; in patients with right dorsal colitis, the ulceration is focal and severe. Why the ulceration is expressed only in the right dorsal colon in some horses is unknown, but both clinical syndromes are often associated with the development of diarrhea.

The detrimental effects of NSAIDs are typically dose dependent; in most reported cases of NSAID toxicosis, affected horses were receiving higher-than-recommended doses, often over many days.[41] The toxic dose of phenylbutazone in healthy horses has been reported to be 8 to 10 mg/kg/day for several days; doses of 15 mg/kg/day or higher, when given on multiple days, were found to be lethal, with death occurring as early as day 4 of treatment.[42] Flunixin meglumine appears to be less toxic than phenylbutazone, but foals given 1.1 mg/kg/day for 30 days developed signs of toxicosis.[43] In another study, flunixin meglumine dosed at 6.6 mg/kg/day IV for 5 days was necessary to produce clinical signs of toxicosis in a group of neonatal foals.[44] Combining nonsteroidal therapies (commonly called *stacking*) increases the potential for toxicosis. Significant GI ulceration and protein-losing enteropathy were reported when a combination of phenylbutazone and flunixin meglumine was administered to 13 adult horses, even though each drug was administered at the published, and seemingly appropriate, dose for 5 days.[45] Although NSAID toxicosis is usually dose dependent, there are reports of idiosyncratic toxicoses in which horses that received recommended doses of phenylbutazone developed right dorsal colitis.[46]

Cantharidin Toxicosis

Cantharidin is the toxic principle found in beetles of the genus *Epicauta*, which are commonly known as *blister beetles*. These beetles feed on alfalfa flowers and can be incorporated into hay if the alfalfa is cut and processed simultaneously, as by crimping. Horses then ingest beetles with the hay. Cantharidin is a potent GI irritant, causing acantholysis and vesicle formation when applied topically.[47] This

CriticalPoint

The use of some common drugs (e.g., NSAIDs, antimicrobials) can precipitate acute colitis.

TABLE 2 Plants That May Induce Acute Colitis in Adult Horses

Plant	Toxic Agent	Clinical Signs
Acorn/oak ***(Quercus* spp*)***	Tannins	Acute onset of severe abdominal pain, rectal straining, hemorrhagic diarrhea, marked intestinal borborygmi
Oleander ***(Nerium oleander)***	Cardiac glycosides	Sudden death; cardiac irregularities; profuse, watery, bloody diarrhea
Buttercup ***(Ranunculus* spp*)***	Ranunculin (protoanemonin)	Oral irritation, salivation, abdominal pain, diarrhea that may be bloody
Nightshades ***(Solanum* spp*)***	Solanine	Salivation, abdominal pain, increased borborygmi and diarrhea
Rhododendron, azaleas ***(Rhododendron* spp*)***	Grayanotoxins (glycosides)	Salivation, diarrhea, abdominal pain, tremors, cardiac abnormalities, death
Pokeweed ***(Phytolacca americana)***	Phytolaccatoxin, phytolaccigenin	GI irritation (colic, diarrhea that may be bloody), anemia (rare), death
Castor bean ***(Ricinus communis)***	Ricin	Abdominal pain, diarrhea, depression, incoordination, profuse sweating, increased body temperature

CriticalPoint

While many of these processes have not been studied in detail in horses, research performed in many species indicates that the single most important secretory event leading to increased fecal water (diarrhea) and electrolyte loss is probably increased chloride ion secretion, which is primarily mediated by increased intracellular cAMP.

leads to severe ulceration and inflammation of the GI mucosa throughout the GI tract, resulting in severe diarrhea, which is often fatal. For more on cantharidin toxicosis, see the article beginning on page 353.

Plant Toxicosis

Plant toxicosis appears to be an uncommon cause of acute colitis, although this may be related to the difficulty of determining that plant toxicosis is the cause of the diarrhea. A wide range of toxic plants can induce diarrhea in horses[48] (**TABLE 2**). Signs can vary from chronic to peracute and life-threatening, depending on the toxic agent and dose ingested. Most plant toxicoses are associated with signs beyond simple diarrhea—oral ulceration and cardiac complications are common.

Carbohydrate Overload

Overconsumption of soluble carbohydrates overwhelms the absorptive capabilities of the small intestine, causing a high percentage of soluble carbohydrates to enter the large intestine. The subsequent pathogenesis for acute colitis primarily involves toxic effects on microbial flora in the large intestine.[14] An increased amount of soluble carbohydrates reaches the cecum and colon, resulting in rapid fermentation by gram-positive, lactic acid–producing bacteria and a sudden increase in organic acid production. The intestinal pH decreases rapidly, and the buffering capacity of the large intestine is overwhelmed. This profoundly acidic condition results in death of the resident microbial flora. In turn, lactic acid increases the osmotic load within the large intestine, leading to development of secretory diarrhea. The acidity also results in necrosis, erosion, and inflammation of large intestinal mucosa, exacerbating water, protein, and electrolyte loss into the intestinal lumen. In addition, bacterial endotoxins and other toxic principles are absorbed across the inflamed large intestinal mucosa. Subsequently, inflammatory cytokines are produced at a level sufficient to induce systemic inflammation, which may lead to systemic disease, such as endotoxemia and laminitis.

Conclusion

Knowledge of the pathophysiology and etiology of acute colitis allows clinicians to formulate rational diagnostic and therapeutic plans, maximizing the potential for positive outcomes in these challenging cases. While treatment is fundamentally supportive in nature, therapies targeting the appropriate etiologic agent may aid in decreasing mucosal inflammation and injury, thereby diminishing the severity of diarrhea and the systemic inflammatory response. Supportive treatment modalities directed toward the underlying pathophysiologic mechanisms may be beneficial even if the etiology is unknown.

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1. **Which of the following has not been associated with acute diarrhea in adult horses?**
   - **a.** *S. vulgaris*
   - **b.** *Dictyocaulus viviparus*
   - **c.** cantharidin
   - **d.** flunixin meglumine
   - **e.** ceftiofur sodium

2. **Which of the following crosses the colon wall by primary active transport?**
   - **a.** sodium
   - **b.** water
   - **c.** potassium
   - **d.** bicarbonate
   - **e.** VFAs

3. **Which of the following regarding the normal physiology of the equine colon is false?**
   - **a.** The tight junctions in the colon are impermeable to water and electrolytes, aiding in the creation and maintenance of an electrochemical gradient across the mucosa.
   - **b.** Water passively follows the absorption or secretion of ions.
   - **c.** The Na^+-K^+-ATPase transporter is present in the luminal membrane of the colon.
   - **d.** Secondary active transport of ions requires ATP, which is commonly provided by the Na^+-K^+-ATPase pump.
   - **e.** The pH of the luminal contents of the colon is 6.8 to 7.2.

4. **Which statement regarding the Na^+-K^+-ATPase pump is true?**
   - **a.** It pumps three sodium ions out of the cell for every two potassium ions pumped in.
   - **b.** It creates an electrochemical gradient of approximately 100 mV across the colonic epithelial cells.
   - **c.** It moves ions passively.
   - **d.** It is a membrane transporter specific to the large intestine.
   - **e.** Na^+-K^+-ATPase stands for sodium-potassium-adenosine monophosphatase.

5. **Which of the following pathophysiologic mechanisms is not common in equine patients with acute colitis?**
   - **a.** abnormal secretion
   - **b.** decreased absorption
   - **c.** inflammation
   - **d.** fibrosis
   - **e.** abnormal motility

6. **Which statement regarding the physiology of colonic epithelial cells is false?**
   - **a.** cAMP is an important component in chloride ion transport.
   - **b.** A high level of cAMP increases the transport of potassium out of the cells.
   - **c.** Vasoactive peptide, PGE_1, and PGE_2 can increase cAMP.
   - **d.** An increase in cAMP blocks the basolateral chloride channels in the cells.
   - **e.** Luminal sodium increases when cAMP increases due to blockade of the Na^+-H^+ pump.

7. **Which statement regarding parasitic diarrhea is true?**
   - **a.** Cyathostomes rarely cause parasite-associated diarrhea.
   - **b.** Stage L5 cyathostomes can encyst.
   - **c.** *S. vulgaris* larvae do not migrate.
   - **d.** Parasite-associated diarrhea is due to inflammation, increased secretion, and ulceration within the large colon.
   - **e.** Parasite-associated diarrhea always causes death within a couple of days.

8. **Which statement regarding NSAID administration is false?**
   - **a.** NSAID toxicosis is typically associated with prolonged administration or abnormally increased doses of NSAIDs.
   - **b.** NSAID-associated acute colitis is due to GI ulceration.
   - **c.** NSAID administration leads to a decrease in prostaglandin production, which, in turn, impairs mucosal blood flow and leads to mucosal injury and inflammation.
   - **d.** The administration of phenylbutazone and flunixin meglumine concurrently is associated with a lower risk of toxicosis than the administration of two consecutive doses of phenylbutazone.
   - **e.** NSAIDs are often used to treat acute colitis because of their antiinflammatory and antiendotoxic effects.

9. **Which statement regarding carbohydrate overload is false?**
   - **a.** As the increased amount of soluble carbohydrates reaches the large intestine, the pH increases rapidly, becoming alkalotic.
   - **b.** The resident microbial flora is killed by rapid fermentation of soluble carbohydrates in the cecum and the large colon.
   - **c.** The change in pH results in necrosis, erosion, and inflammation of the intestinal mucosa.
   - **d.** Endotoxemia and laminitis are possible sequelae to carbohydrate overload.
   - **e.** The death of the patient from carbohydrate overload is usually secondary to laminitis or endotoxemia.

10. **Which statement regarding noninfectious agents that are potentially toxic to the equine colon is false?**
    - **a.** Cantharidin can cause ulceration of the entire GI tract when ingested.
    - **b.** NSAIDs most often cause ulceration of the right ventral colon.
    - **c.** Oral antimicrobial administration is more likely to lead to acute colitis than is intravenous antimicrobial administration.
    - **d.** If alfalfa hay is crimped, the risk of cantharidin toxicosis increases.
    - **e.** Cephalosporins have been associated with antimicrobial-induced colitis.