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Gastritis, Enteritis, and Colitis in Horses

Francisco A. Uzal, DVM, MSc, PhD[a,*], Santiago S. Diab, DVM[b]

KEYWORDS

• Enteritis • Gastritis • Colitis • Horse

KEY POINTS

- The most prevalent bacterial causes of enteritis/colitis include *Clostridium perfringens* type C, *Clostridium difficile*, *Clostridium piliforme*, *Salmonella* spp, *Rhodococcus equi*, *Ehrlichia risticii*, and *Lawsonia intracellularis*.
- Equine rotavirus and coronavirus are the most prevalent viral agents of enteric disease.
- *Cryptosporidium parvum* and strongyles are the most prevalent parasitic agents of enteric diseases in this species.
- Nonsteroidal antiinflammatory drugs are responsible for ulceration of most of the alimentary tract.

INTRODUCTION

There are a large variety of infectious and noninfectious inflammatory diseases that affect the gastrointestinal system of horses (**Table 1**).[1–8] For many years the percentage of these conditions in which a cause was found was low, but increased knowledge along with more and better laboratory diagnostic techniques now available for routine use in diagnostic laboratories has increased the number of cases with a confirmed cause. Nevertheless, there is a still a significant percentage of severe inflammatory conditions of the intestinal tract in which a cause is never found; this is frustrating for pathologists, clinicians, and owners. Frequently in the past and occasionally nowadays, severe, often fatal enteric inflammatory lesions of horses of unknown cause were referred to as colitis X. Because the name colitis X does not refer to a specific disease condition, but rather to a group of unknown causes that lead to a similar lesion and clinical outcome, it has been recommended that this term be no longer used. This recommendation is further supported by several enteric diseases of horses having been better characterized in recent years, and it has been shown that several different

[a] California Animal Health and Food Safety Laboratory, School of Veterinary Medicine, University of California Davis, 105 West Central Avenue, San Bernardino, CA 92409, USA; [b] California Animal Health and Food Safety Laboratory, School of Veterinary Medicine, University of California Davis, One Shields Avenue, Davis, CA 95616, USA
* Corresponding author.
E-mail address: fuzal@cahfs.ucdavis.edu

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Table 1
Summary of clinical signs, pathologic changes, and diagnostic tools and criteria for the main causes of enteric disease in horses

Agent or Disease	Main Clinical Signs	Main Age Affected	Main Pathologic Findings	Diagnostic Tools/Criteria	
				Presumptive	Definitive
Gastric ulceration	Usually asymptomatic	All ages	Ulceration (mostly pars esophagea)	Clinical signs	Gastroscopy; gross changes
Clostridium perfringens type C	Diarrhea, colic, fever, sudden death	Neonates; adults may occasionally be affected	Enterotyphlocolitis, necrotizing	Clinical signs; gross and microscopic findings; isolation of *C perfringens* type C from feces/ intestinal content	Detection of beta toxin in feces/intestinal content (ELISA)
Clostridium difficile	Diarrhea, fever, dehydration, colic	All ages	Enterotyphlocolitis, necrotizing; mucosal edema; volcano lesions	Clinical signs; gross and microscopic findings; isolation of toxigenic *C difficile* from feces/ intestinal content	Detection of toxins A and/ or B of *C difficile* in feces/ intestinal content (ELISA)
Clostridium piliforme	Diarrhea, weakness, lethargy, anorexia, dehydration, fever, icterus	Foals	Colitis, hepatitis, myocarditis	Clinical signs; gross findings	Microscopic findings; PCR; culture of *C piliforme* in embryonated egg
Salmonella spp	Diarrhea, colic, fever	All ages	Enterotyphlocolitis, necrotizing	Clinical signs; gross and microscopic findings	Detection of *Salmonella* spp in feces/intestinal content by culture and/ or PCR
Rhodococcus equi	Diarrhea, colic	Foals, up to 5 mo of age	Colitis, pyogranulomatous	Clinical signs; gross and microscopic findings	Detection of virulent strains of *R equi* in feces/ intestinal content by culture and/or PCR

Ehrlichia risticii	Diarrhea, colic, fever, anorexia, depression, leucopenia	All ages	Typhlocolitis, necrotizing	Clinical signs; gross and microscopic findings (including observation of organisms in silver-stained sections)	Detection of *E risticii* in feces/intestinal content by PCR
Lawsonia intracellularis	Diarrhea, fever, lethargy, hypoproteinemia, edema, weight loss	Weanling foals	Proliferative enteropathy	Clinical signs; gross and microscopic findings (including observation of organisms in silver-stained sections)	Detection of *L intracellularis* in feces/ intestinal content by culture and/or PCR
Rotavirus	Diarrhea, fever, depression, anorexia, dehydration	Foals up to 3–4 mo of age	Liquid content in small and large intestine; villus atrophy	Clinical signs; gross and microscopic findings	Detection of equine rotavirus in feces/ intestinal content by ELISA, latex agglutination assay, polyacrylamide electrophoresis, electron microscopy, RT loop-mediated isothermal amplification, and/or PCR
Coronavirus	Colic, diarrhea, fever, depression, anorexia. Occasionally, neurologic alterations	Adults	Necrotizing enteritis	Clinical signs; gross and microscopic findings	Detection of equine coronavirus in feces/ intestinal content/ intestinal tissues by PCR, immunohistochemistry, and/or electron microscopy

(*continued on next page*)

Table 1
(*continued*)

Agent or Disease	Main Clinical Signs	Main Age Affected	Main Pathologic Findings	Diagnostic Tools/Criteria	
				Presumptive	Definitive
Cryptosporidium spp	Diarrhea	Foals 5–6 wk old	Liquid content in small intestine and sometimes colon; villus atrophy	Clinical signs; gross findings	Genus: demonstration of oocysts in feces/intestinal content by Giemsa, modified Ziehl-Neelsen, auramine O, fluorescent antibody technique, ELISA; demonstration of oocysts in intestinal tissue by histology Species: PCR, loop-mediated isothermal DNA amplification
Large strongyles	Larvae: colic Adults: anemia, ill thrift	All ages	Larvae: endoarteritis; may produce colonic infarction Adults: nodules in subserosa of cecum or colon, loss of condition, anemia	Clinical signs; gross and microscopic findings; hyperbetaglobulinemia	Genus: large numbers of strongyle eggs in feces Species: larval culture
Small strongyles	Diarrhea, anorexia, weight loss, edema of ventral parts	All ages (more prevalent in horses up to 1 y old)	Nodules in cecal and colonic mucosa	Clinical signs; gross and microscopic findings	Genus: large numbers of strongyle eggs in feces Species: larval culture
NSAID intoxication	Diarrhea, colic, ulceration of upper alimentary system, hypoproteinemia, hypoalbuminemia	All ages	Ulceration of upper and lower alimentary tract (particularly right dorsal colon); renal papillary necrosis	Clinical signs; gross and microscopic findings; history of NSAID administration	No specific tests available

Abbreviations: ELISA, enzyme-linked immunosorbent assay; NSAID, nonsteroidal antiinflammatory drug; PCR, polymerase chain reaction; RT, reverse transcription.

agents can produce clinical signs and lesions that are similar or identical to those of the so-called colitis X.[8] This article discusses here the main inflammatory conditions of the gastrointestinal system of horses, with special emphasis on the diagnostic criteria.

GASTRITIS

Gastritis in horses is uncommon, except for those associated with gastric ulceration and parasitic causes.

Gastric Ulceration

Most cases of gastric ulceration in horses are nonspecific and are associated with stress related to diet, enteric disease, colonic impaction, ileus, surgery, nonsteroidal antiinflammatory drug (NSAID) therapy, or conditions that eventually produce duodenal reflux.[7–9] The most common ulcers are those of the pars esophagea and, although the pathogenesis is unclear, it has been suggested to be similar to that in swine. It has been proposed that abnormal fluid content associated with feeding patterns allows acids, enzymes, and bile reflux into the cranial portion of the stomach, where, when the pH decreases to levels less than ~4.0, it damages the nonglandular gastric mucosa and leads to ulceration.[8] Reflux of acidic content into the cranial part of the stomach is also thought to occur as a consequence of gastric compression associated with exercise-induced increased intra-abdominal pressure.[10] This process would explain the high prevalence of ulceration of the pars esophagea seen in racehorses under intensive training.[8,11–13] For as-yet unexplained reasons, ulcers of the pars esophagea tend to be located close to the margo plicatus (Uzal and Diab, unpublished observation, 2015). These ulcers in racehorses are most often considered an incidental necropsy finding, with no clinical significance. However, in rare cases, very deep ulcers may lead to tearing of the stomach wall and gastric rupture.[7] Unlike what often happens in pigs, the ulcers of the pars esophagea in horses do not cause massive internal bleeding. Ulcers of the pars esophagea in horses tend to be chronic, multifocal to coalescing, variably sized (ranging from less than 1 cm to several centimeters), round to irregularly shaped, with elevated borders, and a dark red or pale ulcer bed (**Fig. 1**). The depth of the mucosal damage varies from superficial erosions or shallow ulcers to very deep ulcers. On rare occasions, the damage from deep ulcers can extend into the underlying submucosa, muscularis, and serosa and lead to tearing of the wall and even stomach perforation or rupture, especially if the animal develops gastric impaction or bloat for other reasons. Microscopically, subacute and chronic ulcers have an ulcer bed of granulation tissue of variable thickness and maturity, which is surrounded by an infiltrate of mixed inflammatory cell population. A thin layer of necrotic debris is usually observed overlying the ulcers.[8] Although ulcers of the glandular stomach are considered rare by many veterinarians (including the authors of this review), others suggest that they may be more common than is generally believed (Uzal and Diab, unpublished observation, 2015). These lesions have been associated with administration of NSAIDs.[7,8] The only way to establish a definitive diagnosis of gastric ulcers in the live horse is by gastric endoscopy.[10] In dead horses these ulcers are readily visible during postmortem examination.[8]

Parasitic Gastritis

Gasterophilus spp

Gasterophilus spp larvae (botflies) are the most common parasites of the stomach in horses.[8] The genus *Gasterophilus* comprises 6 species: *Gasterophilus intestinalis*, *Gasterophilus nasalis*, *Gasterophilus haemorrhoidalis*, *Gasterophilus pecorum*,

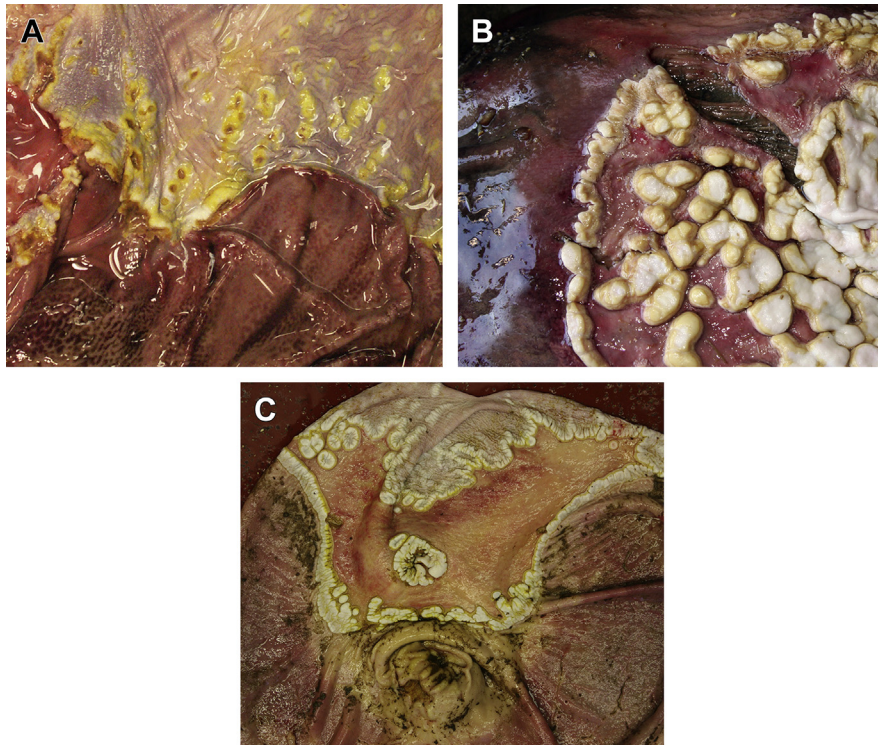

Fig. 1. Different stages of ulceration of the nonglandular mucosa of the stomach in thoroughbred racehorses. (*A*) Mild, multifocal, superficial erosion and ulceration close to the margo plicatus; (*B*) moderate, multifocal to coalescing, chronic ulceration adjacent to the margo plicatus, with tearing of the underlying submucosa; (*C*) severe, locally extensive, chronic ulceration of the nonglandular mucosa likely developing from prior multifocal coalescing ulcers.

Gasterophilus nigricornis, and *Gasterophilus inermis*. The first 2 are the most common.[7] In all cases, the flies lay eggs on the hairs of the face, intermandibular region, or of the ventral part of the body and legs. When the eggs hatch, the first-stage larvae penetrate the oral mucosa, molt, emerge, and migrate through the alimentary canal. *G intestinalis*, the most common species, attaches to the mucosa of the pars esophagea, most commonly close to the cardia but also in other parts of this region, where it completes the subsequent molts. *G nasalis* attaches to the pyloric mucosa and the duodenal ampulla. *G haemorrhoidalis* attaches to the rectal mucosa.[8,14] All of these parasites occasionally attach themselves to the pharynx and esophagus, but consequences to the host are minimal to none. The exception is *G pecorum*, which may cause pharyngitis. In the summer, after the deposition of the ova, the larvae leave the stomach and pass out in the feces to pupate.[8]

The clinical relevance of *Gasterophilus* spp infestation is generally assumed to be minimal, although bot larvae infestations have been associated with gastric ulceration, peritonitis, gastroesophageal reflux, splenitis, and pleuritis.[15,16] Grossly, the larvae can be seen attached to the alimentary tract mucosa. In the pars esophagea of the stomach, the area of attachment of the larvae is surrounded by a thin area of hyperplastic squamous epithelium (**Fig. 2**). Typically round and well-demarcated multifocal ulcers can be seen after the larvae detach from the mucosa.[8,14–16]

Fig. 2. Numerous larvae of *Gasterophilus* sp (horse bots) attaching to the nonglandular mucosa of the stomach. Note the multifocal, round ulcers with raised, hyperplastic margins left by the larvae on detachment.

Diagnosis of infection by *Gasterophilus* spp can be achieved by direct observation of the eggs on the hair, and larvae occasionally attached to the oral cavity of horses. Larvae attached to the lower alimentary tract can be visualized by endoscopy or by direct examination during necropsy. An enzyme-linked immunosorbent assay (ELISA) to detect *Gasterophilus* spp antigens has recently been developed.[17]

Draschia megastoma, Habronema majus, and Habronema muscae

These are spirurid nematodes that occasionally also parasitize the stomach of horses. The adult worms are between 1 and 2 cm long. The 2 *Habronema* spp mentioned earlier are not considered to cause significant gastric disease in horses. Draschia megastoma can produce large nodules by burrowing into the submucosa of the stomach, inciting a severe granulomatous reaction.[8,14] Grossly, these lesions appear as protrusions of ~5 cm in diameter with a small opening. The nodules are usually not clinically significant, although they can cause abscesses and even stomach perforation if infected with pyogenic bacteria.[8,14] Gross lesions and adult worms found during necropsy are diagnostic, as are eggs or larvae found in feces.

ENTERITIS AND COLITIS

Most inflammatory conditions of the small and large intestine in horses are of infectious origin, although there are a few noninfectious inflammatory conditions of importance that are discussed here (see **Table 1**). As stated earlier, a significant number of severe inflammatory lesions in the small or large intestine remain of undetermined cause.

Infectious Diseases

Bacterial disease

Infections by Clostridium perfringens type C and Clostridium difficile are considered the most common enteric clostridial diseases of horses. Although C perfringens type A has been, and sometimes still is, blamed for cases of enterocolitis in horses,[18–20] diagnostic criteria have not been established for this microorganism, mostly because type A can be found in the intestine of most healthy horses[21] (Uzal and Diab, unpublished observation, 2015) and mere isolation of this microorganism from a horse with enteric disease has no diagnostic significance. However, it is possible that certain strains of *C perfringens* type A carry virulence factors that are

not present in commensal strains. If that is the case, determining those virulence factors would help ascribing a pathogenic role to strains of this microorganism isolated from horses with intestinal disease. However, until such information is available, determining a pathogenic role to *C perfringens* type A is difficult, if not impossible.

***Clostridium perfringens* type C** *C perfringens* type C disease occurs mostly in neonates, although cases in older foals and adult horses are occasionally seen. Foals can contract the disease as early as a few hours after birth and most cases occur in the first 2 weeks of life.[3,22] Isolates of *C perfringens* type C must carry the genes to encode for alpha and beta toxins, although individual isolates may also produce a variety of other so-called minor toxins.[23] Experimental evidence has clearly shown that the main virulence factor of *C perfringens* type C is beta toxin, a highly trypsin-labile protein.[24,25] Because of this, animals with low levels of trypsin activity in the intestine, such as neonatal individuals caused by the trypsin inhibitory effect of colostrum, are particularly susceptible to type C disease.[3] Trypsin inhibitors in the diet, such as those present in sweet potatoes, may also be involved in the pathogenesis of type C disease in some species,[25] but this does not seem to be an important predisposing factor in horses.[3,22]

The disease caused by *C perfringens* type C is clinically characterized by yellow to hemorrhagic diarrhea, colic, dehydration, and weakness, usually followed by death within 24 hours of onset. It tends to appear in small clusters of cases and it seems to be recurrent year after year in the same properties. Occasional cases of sudden death without any clinical signs may also occur.[3,26] On necropsy, the jejunum and ileum are most frequently affected (**Fig. 3**), although lesions are often also observed in the colon and cecum (**Fig. 4**). Gross findings include segmental to diffuse hemorrhagic and necrotizing enteritis, colitis, or typhlocolitis, with hyperemic intestinal wall and mesentery, and gray dull or diffusely bright red intestinal mucosa that may or may not be covered by a pseudomembrane. The intestinal contents are often fluid and bright or dark red (hemorrhagic) and may have strands of fibrin.[3,8] Gross lesions observed outside the intestinal tract are often the result of endotoxemia and include serous or serosanguineous fluid in the pericardium, multifocal hemorrhages of thoracic and abdominal serous membranes, subendocardial and epicardial hemorrhages, and pulmonary edema and congestion.[3,8]

A presumptive diagnosis of type C disease can usually be established based on the young age of the affected animals, coupled with compatible clinical signs and

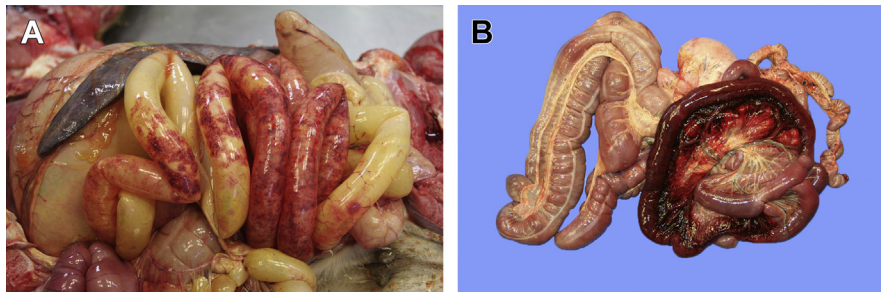

Fig. 3. *C perfringens* type C enteritis in foals. (*A*) The small intestine is dilated by gas and shows multifocal areas of transmural hemorrhage readily visible on the serosal surface. (*B*) A segment of the small intestine and mesentery is diffusely dark red as the result of severe necrosis, transmural congestion, and hemorrhage. (*Courtesy of* [*B*] Farshid Shahriar, DVM, PhD, DACVP, University of California Davis, San Bernardino, CA.)

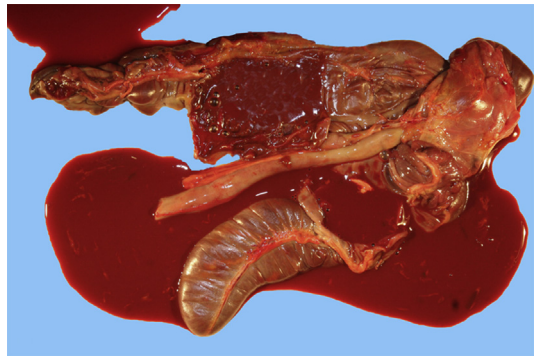

Fig. 4. *C perfringens* type C typhlocolitis in a foal. The large colon and cecum are filled with abundant bright red (hemorrhagic) fluid.

lesions.[3,8] However, the clinical, gross, and microscopic findings of foals with *C perfringens* type C disease may be similar to those produced by other enteric pathogens (notably *Salmonella* spp, *C difficile*, and *Ehrlichia risticii*). Therefore, a definitive diagnosis cannot be based on pathologic findings alone.[3,8] Confirmation of type C disease requires the detection of beta toxin in intestinal contents and/or feces, most frequently by ELISA.[27] However, a negative result does not preclude a diagnosis of *C perfringens* type C infection because this toxin is very sensitive to trypsin and it is frequently broken down if diagnostic samples are not readily collected and properly preserved. Freezing and/or adding trypsin inhibitor to intestinal content specimens preserve the lifespan of beta toxin for several weeks.[22] Isolation of *C perfringens* type C from intestinal contents or feces of animals with necrotizing enteritis is diagnostically significant because this microorganism is rarely found in the intestine of normal animals.[8] Typing is done by polymerase chain reaction (PCR), for which several protocols are available.[27] However, although at low prevalence, type C can be found in the intestine of healthy horses. Isolation of *C perfringens* type C from horses without intestinal disease is therefore of no diagnostic significance.[3] (Uzal and Diab, unpublished observation, 2015). Combined infections by *C perfringens* type C and *C difficile* have been described in foals in which the gross and microscopic findings were almost identical to those described in the diseases caused by each of the microorganisms individually (**Fig. 5**).[28] This observation stresses the need to perform a complete

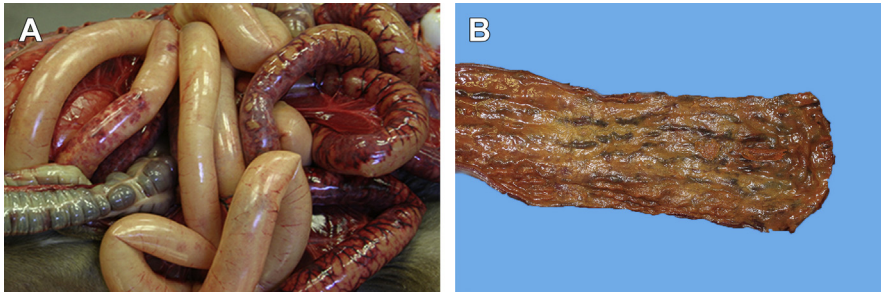

Fig. 5. Coinfection between *C perfringens* type C and *C difficile* in a foal. (*A*) The small intestine is dilated by gas and shows multifocal areas of transmural hemorrhage readily visible on the serosal surface. (*B*) The mucosa of the small intestine is diffusely necrotic and multifocally covered by a thin, yellow to orange pseudomembrane. (*Courtesy of* Pat Blanchard, DVM, PhD, DACVP, University of California Davis, Tulare, CA.)

diagnostic work-up in foals with enteric disease, because detection of one agent does not preclude the presence of others as well.

Clostridium difficile *C difficile* is a ubiquitous gram-positive rod that may be found in the soil and the intestine of many mammals and birds.[4,5,29] Although the major predisposing factors for *C difficile* infection for humans and horses are antibiotic treatment and hospitalization,[29] in the past few years there have been cases in people and animals that have not received antibiotics or been hospitalized; these are called community-associated cases.[4,5] In horses, *C difficile* infection seems to be most frequently associated with β-lactam antibiotics, but this is probably a consequence of the high prevalence of their use, because virtually any antibiotic can predispose disease by this microorganism.[29] Horses of any age may be affected.[4,5,29]

Because highly virulent ribotypes of *C difficile* that are responsible for human outbreaks (ie, 027 and 078) have been also found producing disease in horses and other animal species, it has been speculated that *C difficile* infection could be a zoonosis.[30] Although controversy still exists about the importance of the role of each of the toxins of *C difficile*–associated disease for the virulence of this microorganism, it is now well accepted that both main toxins of this microorganism (ie, toxin A [TcdA] and B [TcdB]) are important for the virulence of *C difficile*.[4,5,31,32]

Clinical signs of *C difficile*–associated disease in horses are highly variable, both in terms of type of signs and severity, and they are by not specific. The cardinal clinical sign is diarrhea, which may be accompanied by 1 or more of the following: colic, fever, red mucous membranes, fever, prolonged capillary refill time, tachycardia, tachypnea, dehydration, and abdominal distention.[4,5,8] The lethality rate in foals may vary between 0% and 42%. In older horses, the lethality seems to be lower, although no specific information is available in this regard.

The gross lesions of *C difficile* infections in young foals are usually restricted to the small intestine, but may also involve the cecum and/or colon (**Fig. 6**). A more caudal distribution of lesions is seen in older foals and adult horses, in which the colon and cecum are usually involved and the small intestine typically spared (**Fig. 7**). Exceptions to this age-related distribution of lesions may occur and therefore the disease cannot be ruled in or out based on lesion location only.[4,5,29] The lesions tend to be similar regardless of the localization within the gastrointestinal tract, and they include hemorrhagic and/or necrotic mucosa that may or may not be covered by a multifocal or diffuse pseudomembrane, mesenteric and serosal hyperemia, and hemorrhage. When the colon is affected, the wall is typically thickened by clear or hemorrhagic,

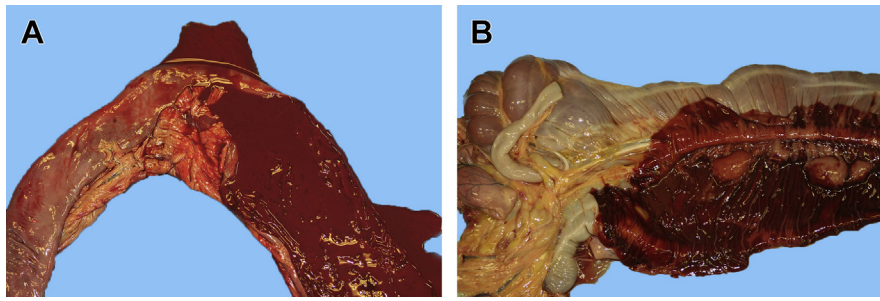

Fig. 6. *C difficile*–associated disease in foals. (*A*) Segment of the small intestine showing hemorrhagic content and a diffusely dark red mucosa. (*B*) The large colon of a foal with diffuse hemorrhagic necrosis of the mucosa. (*Courtesy of* [*A*] Francisco Carvallo, DVM, MSc, PhD, DACVP, University of California Davis, San Bernardino, CA.)

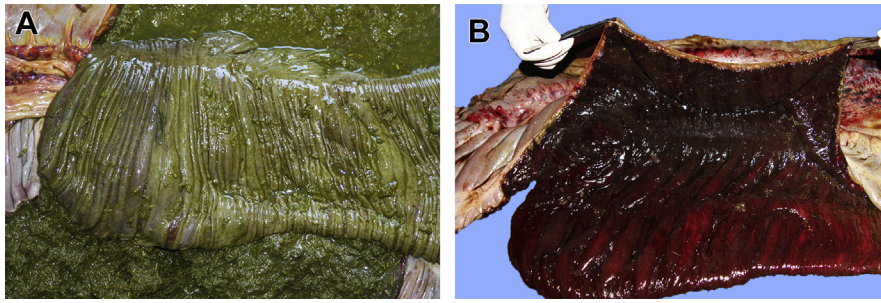

Fig. 7. *C difficile*–associated disease in adult horses. (*A*) The mucosa and submucosa of the large colon show diffuse, marked, clear, gelatinous edema and the colon contents are a mix of well-chopped green roughage and abundant green fluid. (*B*) A more hemorrhagic form of the disease shows similar mucosal and submucosal edema but the mucosa is diffusely dark red as the result of necrosis, hyperemia, and hemorrhage.

gelatinous, submucosal and mucosal edema. The small intestinal content in foals is most frequently hemorrhagic, but it may be yellow and pasty or green/brown and watery. In older foals and adults, the large intestinal contents may be hemorrhagic or composed of abundant green fluid. As in the case of infections by *C perfringens* type C, gross lesions outside the gastrointestinal may include hydropericardium, hemorrhages of serous membranes, subendocardial and epicardial hemorrhage, and pulmonary edema and congestion.[4,5,29]

A presumptive diagnosis of *C difficile*–associated disease can usually be established based on clinical and pathologic findings. However, because the clinical signs and gross and microscopic findings in *C difficile*–associated disease are nonspecific, a definitive diagnosis should be made by detection of toxins A, B, or both in intestinal content or feces. Several tests are currently available, but the ELISA test is the most frequently used.[4] Isolation of toxigenic strains *C difficile* from these specimens is also of moderate diagnostic significance because this microorganism is usually found at a low prevalence in the intestine of normal horses (usually <10%).[4] Typing of isolates is necessary because nontoxigenic strains exist and isolation of those is not diagnostically significant. Typing is routinely performed by PCR.[4,5,29]

Clostridium piliforme *C piliforme* is the agent of Tyzzer disease.[8] This microorganism is the only gram-negative species of the pathogenic clostridia. Young foals are usually affected.[33] The disease in many animal species has been traditionally characterized by clinical signs associated with a classic triad of lesions involving the heart, intestinal tract, and liver.[34] In horses, however, most cases present only with changes in the liver and present clinically as acute liver failure.[33] Alimentary manifestations of Tyzzer disease in foals are unusual, but, when present, they are clinically characterized by semiliquid diarrhea, which may or may not be combined with other clinical signs, including weakness, lethargy, anorexia, dehydration, fever, tachycardia, and icterus.[33] Gross and microscopic changes in the digestive tract include catarrhal to fibrinohemorrhagic colitis, with long, thin bacilli forming pick-up-sticks arrays in the cytoplasm of enterocytes.[8] Although these rods can be seen faintly in hematoxylin and eosin–stained tissue sections, they are better shown with silver stains or Giemsa.[8] In the liver, the typical lesion is multifocal, random foci of acute hepatocellular necrosis, with minimal inflammation and long and thin bacilli, arranged as described earlier, observed in the cytoplasm of hepatocytes at the periphery of the lesion.

Because *C piliforme* cannot be cultured in conventional media, the diagnosis is usually based on the characteristic microscopic lesions, coupled with the demonstration of intracellular bacilli with the classic morphology of this microorganism.[8] Culture in embryonated eggs and more recently PCR has also been used to detect the presence of this microorganism in tissues of affected foals.[33,35]

***Salmonella* spp** The most common cause of salmonellosis in horses is *Salmonella enterica* subspecies *enterica* serovar Typhimurium but other serovars may also be responsible for cases of equine salmonellosis.[8] *Salmonella* spp can be found in the intestine of clinically healthy horses. Stress and antibiotic treatment are considered the main predisposing factors for clinical salmonellosis to occur. The former is particularly significant when antibiotic resistant strains of *Salmonella* spp are present in the intestine.[8,36–38]

Clinically, salmonellosis in horses may be peracute, acute, or chronic. The peracute form is usually septicemic, tends to occur in foals, and is beyond the scope of this article. The acute and chronic forms are primarily enteric and occur most frequently in older foals and adult horses. The disease may occasionally be seen in young foals with clinical and pathologic characteristics similar to those of older horses.[8,36] Clinical signs of acute salmonellosis include diarrhea and fever for 1 to 2 weeks; full recovery or death may be the outcome of this form of the disease. In chronic salmonellosis, the clinical signs may persist for weeks or months and include soft feces, anorexia, and loss of condition.[7,8]

The gross lesions of the enteric form of salmonellosis may be similar, if not identical, to those produced by other bacterial agents of enterocolitis, such as *C perfringens* type C and *C difficile*. They are characterized by diffuse and severe fibrinohemorrhagic to necrotizing inflammation of the cecum and colon, although the small intestine (**Fig. 8**) may also be affected. A tan, gray or red pseudomembrane is usually present loosely attached to the necrotic mucosa.[8] Chronic cases of enteric salmonellosis may have diffuse or multifocal, fibrinous or ulcerative lesions of the cecum and colon. Occasionally, lesions resembling button ulcers are seen, and edema of the submucosa is usually present.[8]

A presumptive diagnosis of salmonellosis can be based on clinical signs and gross and microscopic lesions. As stated earlier for *C perfringens* type C enterotoxemia and *C difficile*–associated disease, the clinical signs and lesions are nonspecific and

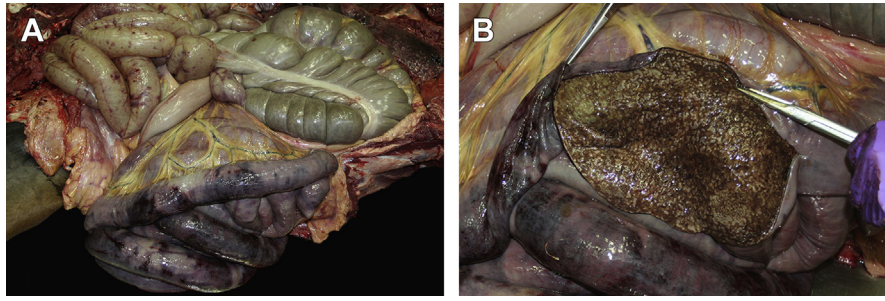

Fig. 8. Enteric salmonellosis in an adult horse. (*A*) A long segment of the small intestine (bottom of the image) shows thickening and multifocal transmural areas of hemorrhage and necrosis readily visible from the serosal surface. (*B*) The mucosa of the small intestine from image *A* is dull, thickened, and diffusely mottled light/dark brown as the result of fibrinonecrotizing enteritis. (*Courtesy of* Mark Anderson, DVM, PhD, DACVP, University of California Davis, Davis, CA.)

confirmation of the diagnosis should rely on demonstration of the organism in intestinal content and/or intestinal tissue by culture and/or PCR.[39] Serogrouping and serotyping of isolated strains provides specific identification of the isolated serovar.

Rhodococcus equi *Rhodococcus equi* is an intracellular gram-positive pleomorphic bacillus that may be part of the normal intestinal flora of horses and can be also found in the soil. *R equi* produces respiratory and, less frequently, intestinal disease in foals from a few weeks to ~5 months of age.[40] The strains isolated from foals carry a virulence plasmid named pVAPA1037, which is essential for disease in horses because it provides the microorganism with the capacity to replicate in macrophages.[40–42] *R equi* is traditionally associated with pneumonia in foals and approximately 50% of these cases may also develop enterotyphlocolitis, mesenteric lymphadenitis, abscesses, and/or peritonitis.[41] The development of enteric lesions in foals with pneumonia is thought to be a consequence of swallowing of respiratory exudate containing *R equi*.[8,40]

The gross lesions of enteric disease produced by *R equi* may occur in the small and large intestine, but are more common and most severe in the cecum, large colon, regional lymph nodes, and over Peyer patches in small intestine (**Fig. 9**). The intestinal and mesenteric lymph node lesions are characteristic and provide reasonable diagnostic certainty. The intestinal lesions consist mainly of many multifocal, elevated, and crateriform mucosal and submucosal nodules with a central ulcer. These ulcerated nodules range between 1 and 2 cm in diameter and are often covered by a pseudomembrane. Mesenteric lymph nodes are typically markedly enlarged and firm. Nodal lesions without concurrent enteric lesions are occasionally seen.[8,41]

Microscopically there are multifocal mucosal and submucosal pyogranulomas with variable numbers of gram-positive coccobacilli in the cytoplasm of macrophages. The presence of these intracellular bacteria is a useful diagnostic feature. Pyogranulomatous mesenteric lymphadenitis, often with intracellular bacteria, is another characteristic feature of the disease.[8,41]

Gross lesions are highly suggestive of *R equi* infection and, together with the microscopic detection of enteric and nodal pyogranulomas with intracellular bacteria, allow the establishment of a strong presumptive diagnosis. However, confirmation relies on isolation of *R equi* from tissues and/or intestinal content and determination of the virulence plasmid in isolated strains, because nonvirulent strains may also be present and are of no diagnostic significance.[7,8,40]

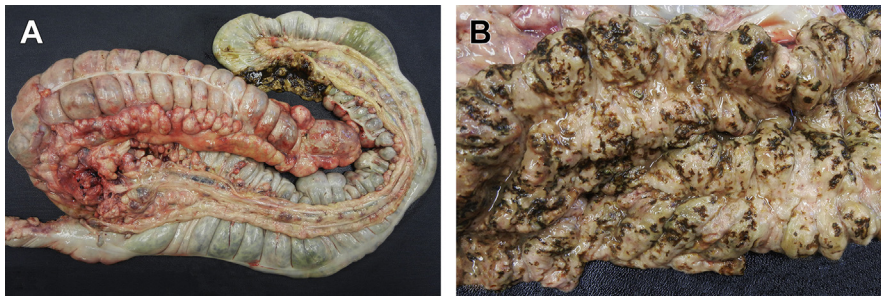

Fig. 9. *R equi* ulcerative colitis and mesenteric lymphadenitis in a foal. (*A*) Mesenteric lymph nodes along the mesocolon are diffusely markedly enlarged as a result of severe, pyogranulomatous lymphadenitis. (*B*) The mucosa of the colon from image *A* shows multifocal to coalescing, irregularly shaped, ulcerated mucosal and submucosal nodules, many of which are covered by a dark green pseudomembrane. (*Courtesy of* Peter Chu, DVM, PhD, University of California Davis, Davis, CA.)

Ehrlichia risticii *E risticii* is the causal agent of Potomac horse fever (equine monocytic ehrlichiosis, equine ehrlichial colitis, or equine neorickettsiosis). Horses of all ages can be affected. This disease is clinically characterized by diarrhea of not more than 10 days' duration, fever, anorexia, depression, and leucopenia; colic is occasionally seen.[7,8,43]

Grossly, there is congestion and ulceration of the mucosa of the cecum and colon, usually accompanied by enlargement of mesenteric lymph nodes. Microscopically, lesions are consistently found in the colon, although similar changes may be seen in the small intestine. The lesions consist of superficial epithelial necrosis, erosion, and fibrin effusion. With silver stains, the organisms can be seen as small clusters of dark dots (~1 μm in diameter) in the apical cytoplasm of crypt enterocytes and also in the cytoplasm of macrophages in the lamina propria.[8,44] Although a presumptive diagnosis is usually based on observation of necrotizing colitis and the presence of intracellular microorganisms on silver preparations, confirmation is achieved by demonstration of the agent in feces or peripheral buffy coat by PCR.[8,44,45]

Lawsonia intracellularis In horses, infection by *Lawsonia intracellularis* is infrequently observed and is called equine proliferative enteritis (EPE).[46–48] EPE affects mostly weanling foals and is clinically characterized by fever, lethargy, diarrhea, hypoproteinemia, edema, and weight loss.[49]

Grossly, there is thickening of the mucosa, mostly in the distal small intestine. Occasionally, gross lesions are not evident. In severe chronic cases, there can be marked irregular hyperplasia and thickening of the mucosa, which is covered by a fibrinonecrotic pseudomembrane and variable edema of the submucosa.[8] Intracellular curved bacteria can be seen microscopically in the apical cytoplasm of enterocytes using silver stains or by immunohistochemistry.[8]

A presumptive diagnosis of proliferative enteritis in any species can be based on typical gross and histologic lesions, and further supported by silver staining to visualize the intracellular bacteria.[8] Confirmation can be obtained by immunohistochemistry and/or by PCR.[8,48,50–52] Cultivation of *L intracellularis* is rarely attempted because it requires the use of tissue culture.[8]

Escherichia coli Although there are rare reports of enterotoxigenic *Escherichia coli* (ETEC) isolated from foals with diarrhea,[7] no evidence exists that this microorganism is responsible for disease, because inoculation of ETEC into foals failed to produce diarrhea or other clinical signs.[53] The other forms of colibacillosis frequently associated with enteric disease in other species have not been reported in horses. Current thinking is therefore that *E coli* has little significance in enteric disease of horses. Neonatal *E coli* septicemia may manifest with secondary nonspecific diarrhea in foals.[8]

Other bacterial agents of enteric disease in horses

Clostridium sordellii,[8] *Actinobacillus equuli*,[4,5] *Streptococcus equi*,[6] *Histoplasma* spp,[54] *Listeria monocytogenes*,[55,56] *Klebsiella pneumoniae*,[8] and others have been rarely associated with enteritis and/colitis in horses, although definitive evidence of their role in enteric disease is therefore lacking.

Viral Diseases

Rotavirus

Rotavirus is considered a significant cause of diarrhea in foals up to 3 or 4 months of age, although an age-related resistance to diarrhea starts to develop at 2 to 3 weeks of age.[7,8,57] As in other animal species, the disease usually presents in the form of

outbreaks. Coinfections with equine coronavirus, *Salmonella* spp, and *Cryptosporidium* spp may also occur.[8] Clinically, infection by rotavirus is characterized by fever, depression, anorexia, diarrhea, and dehydration.[7,57] Mortality is rare.[8,57]

Gross changes are subtle and consist of liquid content within the small and large intestine. Pathologic changes are nonspecific and the diagnosis has to be confirmed by detecting the virus in intestinal contents or feces. A variety of tests are currently available for this purpose, including ELISA, latex agglutination assay, polyacrylamide electrophoresis, electron microscopy, reverse transcription (RT) loop-mediated isothermal amplification, and PCR.[7,58–60]

Coronavirus

Equine coronavirus is a betacoronavirus that has been associated with enteritis in adult horses in the United States and Japan, but likely occurs also in other countries. The disease usually affects individual horses, but outbreaks have also been reported.[61] Clinical signs are nonspecific and include colic, fever, diarrhea, depression, and anorexia. Occasionally, some horses may show neurologic alterations, which are thought to be a consequence of hyperammonemia associated with the severe intestinal alterations.[61]

Gross and microscopic changes consist of necrotizing enteritis, which may be subtle but is usually severe, especially if the animal died of the disease or was euthanized because of poor prognosis. Lesions outside the alimentary tract include the presence of Alzheimer type II astrocytosis in the cerebral cortex, which is speculated to be a consequence of colitis-associated hyperammonemia.[8,61]

As with many of the bacterial diseases, clinical, gross, and histologic signs are nonspecific and testing to detect coronavirus in intestinal contents and tissues is increasingly being included in the routine testing of horses with diarrhea and enteritis or enterocolitis. Equine coronavirus should be investigated, especially when horses showing compatible clinical signs and lesions test negative for other infectious agents of enteritis. The diagnosis is confirmed by detection of equine coronavirus in intestinal contents or feces by PCR, in tissues by immunohistochemistry, or by direct electron microscopy of intestinal contents or affected intestinal tissue.[61,62]

Parasitic Diseases

Protozoa

Cryptosporidiosis *Cryptosporidium* is an apicomplexan protist that is found mostly on the epithelium of the gastrointestinal, biliary, and respiratory tracts of mammals, birds, reptiles, and fish.[8] *Cryptosporidium parvum* is responsible for cryptosporidiosis in immunologically normal and immunosuppressed foals between 5 days and 6 weeks of age.[7,63,64] Clinically, cryptosporidiosis is characterized by self-limiting diarrhea, which is mainly caused by malabsorption, villus atrophy, and a predominance of immature enterocytes. The covering of a significant part of the surface area of absorptive cells by the organisms is probably a contributory factor for the diarrhea. Mortality is rare.[8,65]

Grossly, there is liquid content throughout the small intestine and, sometimes, the colon.[7,8] Diagnosis is confirmed by microscopic demonstration of oocysts in smears of feces or intestinal content stained with Giemsa, modified Ziehl-Neelsen, or auramine O, or with the fluorescent antibody technique. An ELISA technique is also available for detection of oocysts in feces and intestinal content. Histology of the intestine is also diagnostic. However, these techniques allow only identification at the genus level; identification of the species involved requires molecular methods, including PCR and loop-mediated isothermal DNA amplification.[66]

Ciliated protozoa Ciliated protozoa (*Balantidium* spp) and coccidia (*Eimeria leuckarti*) are occasionally seen on the colonic mucosa of healthy and sick horses, including animals with enteric and nonenteric problems. Although a role for pathogenicity has been suspected for these organisms, definitive evidence of their pathogenicity is missing. For practical purposes, these ciliated protozoa are considered normal inhabitants of the intestine.[8]

Nematodes

Strongyloides

Equine strongylosis is produced by members of the subfamilies Strongylidae (large strongyles) and Cyathostominae (small strongyles), including several genera in each subfamily.

Large strongyles *Strongylus vulgaris* is the most important of the large strongyles and is a common parasite of horses, although the development and use of improved anthelminthics has reduced the prevalence significantly

Horses of any age may be affected. The classic lesion produced by *S vulgaris* larvae is endoarteritis, most commonly involving the cranial mesenteric artery and its main branches, which in young horses may lead to arterial infarction of the colon. This condition manifests clinically as colic. Enlargement of the cranial mesenteric artery can be detected on rectal palpation and/or ultrasonography when the lesion is severe.[7,8] The adult forms of *S vulgaris* found in the intestine are responsible for anemia and ill thrift. An acute syndrome characterized by fever, anorexia, depression, weight loss, diarrhea or constipation, colic, and infarction of the intestine occurs in foals infected with large numbers of larvae for the first time, whereas this syndrome is uncommon in animals previously exposed to infection.[8]

The gross and histologic lesions of the larval form of the disease consist mostly of proliferative arteritis with thrombus formation and, when emboli are released from the large thrombi, they can obliterate smaller mesenteric arteries, arterioles, and capillaries, resulting in clearly demarcated areas of infarction in the colon. Gross lesions produced by adult large strongyles consist of encapsulated nodules in the subserosa of the cecum and colon.[8]

Diagnosis of *S vulgaris*–associated disease is based on clinical signs coupled with large numbers of strongyle eggs in feces and hyperbetaglobulinemia. The differentiation between large and small strongyle eggs cannot be achieved by microscopic examination alone and larval culture is required.[7,67]

Small strongyles (cyathostomes) This group includes more than 50 species, of which the larvae, and not the adult forms, are considered pathogenic.[68] Cyathostomiasis is more prevalent in horses up to approximately 1 year old, although the disease can occur in horses of any age. Clinical cyathostomiasis is the consequence of simultaneous emergence of large numbers of inhibited third-stage larvae from the cecal and colonic mucosa in the late winter, spring, and early summer in temperate climates. Encysted third-stage larvae may undergo hypobiosis, persisting in nodules in the colonic wall for as long as 2 years.[68] Over the past few years, cyathostomins have developed significant anthelmintic resistance.[69–71] Clinical signs of cyathostomiasis are nonspecific and include diarrhea, anorexia, weight loss, and edema of ventral parts.[8,68]

Gross findings include the presence of nodules of a few millimeters in diameter in the cecal and colonic mucosa. These nodules are formed by encysted larvae and are red or black and slightly elevated. The mucosa of the affected intestinal segments shows diffuse edema and congestion (**Fig. 10**).[8]

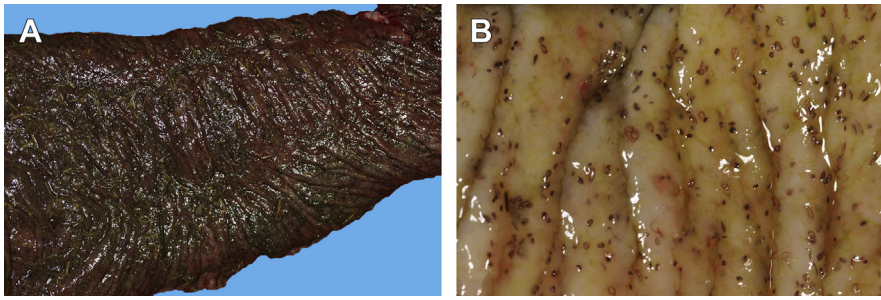

Fig. 10. Cyathostomiasis (small strongyles) in horses. (*A*) The large colon of a horse with diffusely reddened and edematous mucosa. (*B*) A close-up of the mucosal surface of a large colon with hundreds of coiled, red to brown, third-stage larvae encysted in the mucosa. (*Courtesy of* [*A*] Mark Anderson, DVM, PhD, DACVP, University of California Davis, Davis, CA; and [*B*] the Anatomic Pathology Service, School of Veterinary Medicine, UC Davis.)

Diagnosis of cyathostomiasis is based on clinical signs combined with increased strongyle egg counts in feces, anemia, and hyperbetaglobulinemia. Adult nematodes can occasionally be seen in feces. As explained earlier, larval culture is required to differentiate between large and small strongyle eggs.[7,67] A high fecal egg count is a useful diagnostic criterion and gives an idea of the number of adult parasites in the intestinal tract. However, the egg count is not representative of the encysted larval stage, for which the disease induced by the emergence of these larvae cannot be ruled out based on low egg count in feces. No diagnostic techniques are currently available for prepatent stages of *Strongylus* spp.[7]

Noninfectious or Parasitic Conditions

Inflammatory enteric disease in horses may be produced by intestinal displacements, and intoxication by nonsteroidal antiinflammatory drugs and other substances.

Intestinal displacements

Intestinal displacements that produce ischemic mucosal lesions but that are corrected with consequent reflow may cause chronic diarrhea and possibly cachexia. Because these lesions are initially noninflammatory, they are not discussed here.

Toxic enteric disease

Nonsteroidal antiinflammatory drugs These drugs are universally used to treat multiple ailments of horses and they have been associated with ulcerative colitis and typhlitis.

The pathogenesis of the syndrome is related to ischemia caused by reduced perfusion, which is a consequence of inhibition of synthesis of prostaglandin by inhibition of the cyclooxygenase enzyme.[72] Clinically, intoxication by NSAIDs is characterized by colic and diarrhea, and other signs associated with ulceration of the upper and lower alimentary system.[72] The most consistent clinicopathologic findings are hypoproteinemia and hypoalbuminemia.[72]

At necropsy, multifocal to coalescing widespread ulceration of the colonic and cecal mucosa is observed. Although the lesions tend to be most severe on the right dorsal colon (hence the name right dorsal colitis), the lesions can be found anywhere in the dorsal colon and occasionally in the ventral colon as well (Uzal and Diab, unpublished observation, 2015). Ulcers can also be seen in other locations, including the mouth, esophagus, and stomach. Renal papillary necrosis in the kidneys is a typical lesion but is not always present.[8,72,73]

No specific tests are available for the diagnosis of NSAID intoxication. A history of administration of NSAIDs coupled with hypoproteinemia and hypoalbuminemia is highly suggestive of intoxication by these drugs.[72] At necropsy, ulcerative lesions in the alimentary tract, mainly in the right dorsal colon, and the presence of necrotizing lesions in the renal papilla are suggestive of intoxication by NSAIDs, especially when other common causes of colitis have been ruled out.[8,72]

Other toxic causes of enteric disease Several substances[8,73] have an irritant effect on the alimentary tract of horses. Among these are cantharidin (the principal toxin of blister beetle),[74,75] *Nerium oleander*[76] and arsenic.[77] Neither the clinical signs nor the postmortem changes of these intoxications are specific. The diagnosis is based on the presence of compatible lesions (within the alimentary tract or other organs) and detection of these substances in intestinal contents or tissues of affected horses.

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