Title

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The comparative pathology of enterocolitis caused by *Clostridium perfringens* type C, *Clostridioides difficile*, *Paeniclostridium sordellii*, *Salmonella enterica* subspecies *enterica* serovar Typhimurium, and nonsteroidal anti-inflammatory drugs in horses

Fábio S. Mendonça, Mauricio A. Navarro, Francisco A. Uzal[1]

Abstract. To determine if there were significant differences produced by 5 of the most prevalent causes of equine enterocolitis, we studied retrospectively the gross and microscopic pathology of 90 cases of enterocolitis submitted to the San Bernardino laboratory of the California Animal Health and Food Safety Laboratory. Included were cases caused by *Clostridium perfringens* type C (CP; $n=20$), *Clostridioides difficile* (CD; $n=20$), *Paeniclostridium sordellii* (PS; $n=15$), *Salmonella enterica* subspecies *enterica* serovar Typhimurium (ST; $n=20$), and NSAID intoxication (NS; $n=15$). Grossly, necrotizing hemorrhagic typhlocolitis was seen most frequently in cases of CD, ST, and NS disease. Cases of CP and PS had enteritis or colitis in similar percentages. Congestion, hemorrhage, and pleocellular inflammatory infiltrates followed by mucosal and submucosal necrosis were the main lesions found in horses with enteritis or colitis produced by any of the etiologic agents investigated. Severe lesions were more frequent in cases of CD and CP than in cases associated with any of the other 3 etiologies. Pseudomembranes were observed with similar prevalence in the small intestine and colon affected by all agents studied. Thrombosis of the lamina propria and/or submucosa was observed in ~50% of the cases of enteritis and colitis by all etiologies, except for PS, in which the majority of the cases had thrombosis. Gross and microscopic lesions of enterocolitis were not sufficiently specific for any of these etiologic agents to enable these enteritides to be distinguished by gross and/or histologic examination.

Keywords: *Clostridioides difficile*; *Clostridium perfringens* type C; enterocolitis; horses; nonsteroidal anti-inflammatory drugs; *Paeniclostridium sordellii*; *Salmonella enterica* ser. Typhimurium.

The large variety of inflammatory disorders of the equine gastrointestinal tract includes infectious and noninfectious diseases. Although gastritis is uncommon in horses, except for that associated with gastric ulceration,[28] enteritis and colitis are among the most common causes of disease of the alimentary tract in this species, and they remain challenging to diagnose and treat.[1,13,16,26,28]

Among the most common infectious inflammatory conditions of the small and large intestine in horses are those produced by *Clostridium* spp. and *Salmonella* spp. Noninfectious conditions, such as those produced by nonsteroidal anti-inflammatory drugs (NSAIDs) are also commonly associated with colitis in horses. Other causes of enterocolitis reported with different incidence include *Neorickettsia* spp., coronavirus, rotavirus, *Cryptosporidium parvum*, and *Strongylus* spp.[1,12–15,28]

Most of these agents, acting alone or in combination, can cause a rapid onset of clinical disease, which includes one or more of the following: decreased appetite, fever, tachycardia, tachypnea, dehydration, diarrhea, abdominal distention, colic, circulatory failure, and frequently death.[1,14,24] Secondary complications such as thrombophlebitis, laminitis, and renal failure may also occur.[11] The gross and microscopic lesions within the alimentary tract of horses with enterocolitis are often similar, regardless of etiology, but the literature is incomplete in this area.[1,12–14,17]

A diagnosis of equine enterocolitis may be based on clinical, gross, and microscopic findings. Determination of the etiology, however, usually requires the use of one or more ancillary tests, including detection of microorganisms by culture, fluorescent antibody test, immunohistochemistry, and/or PCR; detection of bacterial toxins by ELISA[1,12,13,18,27]; and others.

We hypothesized that there are differences in the gross and microscopic lesions of enterocolitis in horses diagnosed

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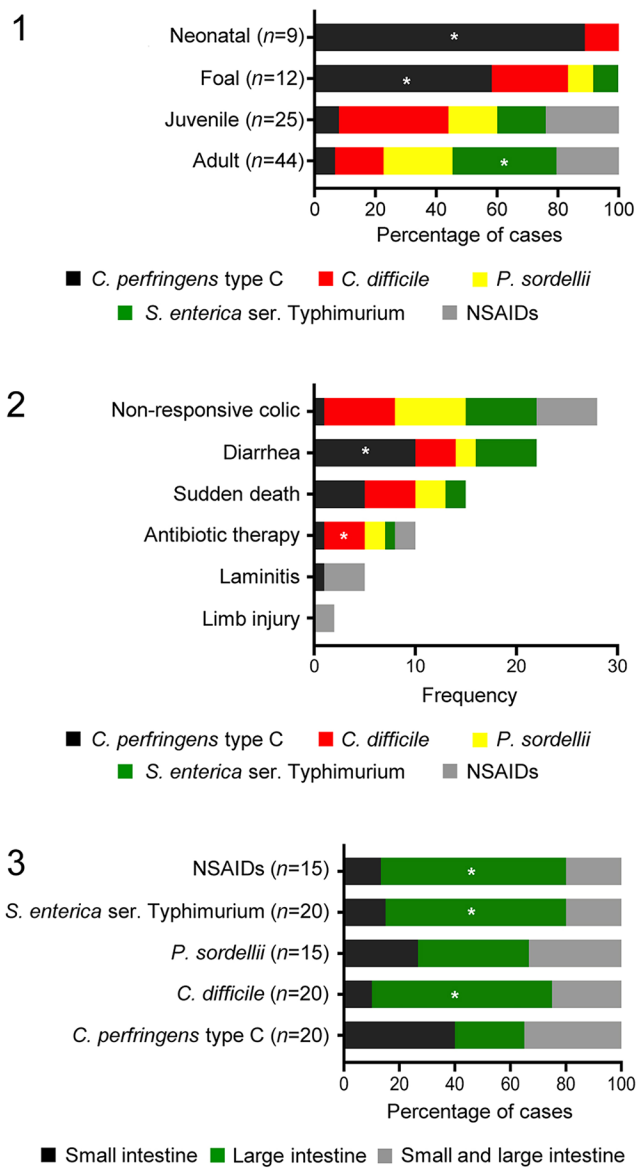
in our laboratory over the past 30 y as a result of 5 major causes, namely *Clostridium perfringens* type C, *Clostridioides difficile*, *Paeniclostridium sordellii*, *Salmonella enterica* subspecies *enterica* serovar Typhimurium, and NSAID intoxication,[16] and that a detailed gross and microscopic examination of tissues might help to establish a more precise etiology. To test our hypothesis, we studied 90 cases of equine enterocolitis caused by these agents and characterized and compared the main gross and microscopic lesions.

Materials and methods

We included horses with a diagnosis of enteritis, colitis, or enterocolitis caused by *Clostridium perfringens* type C ($n=20$), *Clostridioides difficile* ($n=20$), *Paeniclostridium sordellii* ($n=15$), *Salmonella enterica* subspecies *enterica* serovar Typhimurium (*S. enterica* ser. Typhimurium; $n=20$), or NSAIDs ($n=15$). The cases had been received at the San Bernardino laboratory of the California Animal Health and Food Safety Laboratory between 1 March 1990 and 31 October 2019. All cases had been subjected to autopsy by one of 14 different pathologists. The autopsy reports were analyzed for age, history, main gross and microscopic findings, and results of ancillary tests.

Horses ≤7 d old were considered neonates, 8 d to 1 y old as foals, 1–4 y old as juveniles, and those >4 y old as adults (Fig. 1). Included were 28 Thoroughbreds, 17 Quarter Horses, 8 Arabians, 7 Missouri Fox Trotters, 6 Miniature Horses, 5 Paint Horses, 3 Friesians, 2 Andalusians, 2 Appaloosas, 1 Paso Fino, 1 Peruvian Paso, 1 Mustang, 1 Morgan, and 1 Fjord. In 7 cases, the breed was not reported. Twenty-five animals were male, 14 were geldings, and 41 were female. In 10 cases, the sex was not reported.

In all cases, a morphologic diagnosis of enteritis, enterocolitis, or colitis had been established based on gross and microscopic findings. Confirmation of the etiology was determined as follows. The diagnosis of infection by *C. perfringens* type C was confirmed by detection of beta toxin with or without isolation of this microorganism from intestinal content, followed by PCR typing. The diagnosis of infection by *C. difficile* was established based on the detection of toxins A and/or B of this microorganism with or without isolation of *C. difficile* from intestinal content. A diagnosis of infection by *P. sordellii* was made based on detection of this microorganism in intestinal content by culture and/or PCR, coupled with detection of the same microorganism in intestinal tissues by immunohistochemistry (IHC) and ruling out other common causes of equine enterocolitis, including all of the agents investigated in this paper, plus equine coronavirus, Potomac horse fever, and cyathostomes. The diagnosis of infection by *S. enterica* ser. Typhimurium was based on detection of this microorganism in the intestinal content by culture and/or PCR. A diagnosis of NSAID intoxication was based on exclusion of most common causes of enterocolitis, coupled with a clinical history including use of these drugs, and, in some cases, the presence of lesions compatible with NSAID intoxication in organs outside the gastrointestinal tract (i.e., renal crest necrosis).



Figures 1–3. Age, clinical history, and location of enteric gross and microscopic lesions of 90 horses that died from enteric infections produced by 5 different causes. The stars indicate statistical differences for that particular agent. **Figure 1.** Age. **Figure 2.** Clinical history. **Figure 3.** Location of gross and microscopic lesions.

For bacterial anaerobic culture, small and large intestinal contents collected from grossly affected areas of the intestine of each horse were inoculated onto pre-reduced anaerobically sterilized *Brucella* blood agar (Anaerobic Systems), pre-reduced anaerobically sterilized phenylethyl alcohol sheep blood agar (Anaerobic Systems), and egg yolk agar (Anaerobic Systems) and incubated anaerobically at 37°C for 48 h. Small and large intestinal content from each horse was also inoculated onto cycloserine–cefoxitin–fructose agar (Veterinary Media Services, University of California–Davis, Davis, CA) and incubated anaerobically at 37°C for 48 h. All isolates were identified by conventional biochemical techniques and/or MALDI-TOF MS.

Samples of small and/or large intestinal contents from each animal, as well as individual or pooled samples of liver, spleen, kidney, joint fluid, or blood, were inoculated onto Columbia 5% sheep blood agar (Hardy Diagnostics) and MacConkey agar plates (Hardy Diagnostics) and incubated aerobically or microaerobically, respectively, at 37°C for 48 h. *C. perfringens* isolates were typed by PCR using primers for alpha, beta, epsilon, iota, and beta2 toxins and enterotoxin as described previously.[23] A few *C. difficile* isolates were typed by PCR for the genes of toxins A (tcdA) and B (tcdB) as described previously.[10] *C. perfringens* alpha (CPA), beta (CPB), and epsilon (ETX) toxins were also investigated in intestinal content using a capture ELISA kit (Bio-X), following the manufacturer's instructions. Purified CPA, CPB, or ETX was used in positive control wells; toxins were replaced by buffer in negative control wells. *C. difficile* toxins A and B were investigated using an ELISA kit (Tox A/B II ELISA kit; Techlab), according to the manufacturer's instruction.

Equine coronavirus and *Neorickettsia* spp. were ruled out in most cases, based on negative results of PCR for the agents on small and large intestinal content and tissue. Small strongyles (cyathostomes) were ruled out in all cases based on negative fecal float technique and absence of larvae of these parasites in colonic tissues.

Tissues collected for histopathology included lung, heart, liver, spleen, kidney, adrenal gland, skeletal muscle, tongue, stomach, small intestine, cecum, colon, and/or brain. These tissues were fixed in 10% neutral-buffered formalin and processed by routine histologic methods to obtain 5-µm thick H&E-stained sections. Selected small intestinal and colonic sections were stained with Gram. IHC for *P. sordellii* was performed on sections of the small intestine and colon of horses as described previously.[21] Briefly, a streptavidin–biotin kit (LSAB peroxidase K675; Dako) was used according to the manufacturer's instructions. Primary rabbit polyclonal antibodies against *P. sordellii* (VMRD) were used. Positive controls consisted of muscle sections of a horse from which *P. sordellii* had been isolated. Negative controls consisted of sections incubated with normal rabbit serum instead of the primary antibody, and of intestinal sections of a healthy horse from which no anaerobes had been isolated.

The tissue sections from all the cases were blindly examined by one of the authors (F. Mendonça). The following lesions were recorded in all intestinal segments: congestion, hemorrhage, edema, fibrin, thrombosis, necrosis, pseudomembrane formation, inflammatory infiltrate, and intralesional gram-positive rods. A semi-quantitative severity score was assigned to each lesion using a scale from 0 (no lesions observed) to 4 (most severe), with scores of 1–3 indicating progressive severity. Pearson chi-squared or Fisher exact tests were used to determine any statistically significant differences among the observed frequencies in the analyzed categories. Statistical analyses were performed using R for Mac (v.3.2.6; https://cran.r-project.org/bin/macosx/). A p-value ≤ 0.05 was regarded as statistically significant.

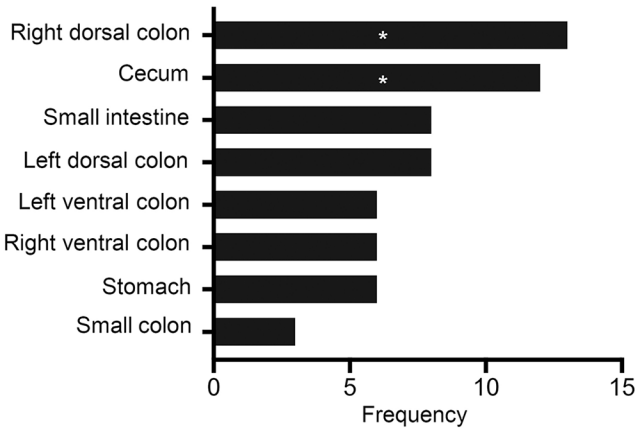


Figure 4. Detailed distribution of gross and microscopic lesions in the gastrointestinal tract of horses that died as a result of intoxication by nonsteroidal anti-inflammatory drugs. The stars indicate statistical differences for that particular location.

Results

Acute colic nonresponsive to treatment was the main clinical history associated with enteritis, enterocolitis, or colitis in horses, and this complaint was observed with similar frequency in cases caused by *P. sordellii* ($n=7$), *C. difficile* ($n=7$), *S. enterica* ser. Typhimurium ($n=7$), and NSAIDs ($n=6$). Diarrhea was the second most frequent clinical presentation, most commonly seen in animals with *C. perfringens* type C infection ($p<0.05$), followed by sudden death. Other clinical histories less frequently mentioned for most causes of enteric disease included antimicrobial therapy, laminitis, and limb injuries. A history of antimicrobial therapy was most frequently seen in cases of *C. difficile* infection ($p<0.05$; Fig. 2).

The most common cause of enteric disease in neonates and foals (90% in neonates and 58% in foals) was *C. perfringens* type C (Fig. 1). Ten percent of neonates were infected by *C. difficile*; the cause of enteric disease in 42% of foals was *C. difficile*, *P. sordellii*, or *S. enterica* ser. Typhimurium. The incidence of the 5 etiologies that we investigated was statistically similar in juvenile horses. *S. enterica* ser. Typhimurium was the main cause of enteric disease in adult horses (38%); the other 4 causes of enteric disease were observed with a similar incidence in this age group ($p<0.05$).

Lesions in animals with NSAID intoxication or infected with *S. enterica* ser. Typhimurium or *C. difficile* were mostly seen only in the colon ($p<0.05$); a small percentage of animals had lesions in the small intestine or the small intestine and the colon (Fig. 3). Animals infected with *P. sordellii* or *C. perfringens* type C showed more or less equal distribution of lesions in the small intestine, colon, and small intestine plus colon. Most reports of cases of NSAID intoxication had detailed information about the specific areas within the alimentary canal that were affected. The right dorsal colon and the cecum were the segments most frequently affected by NSAIDs (Fig. 4). No such detailed information on lesion distribution was available for the other 4 etiologies involved in our study.

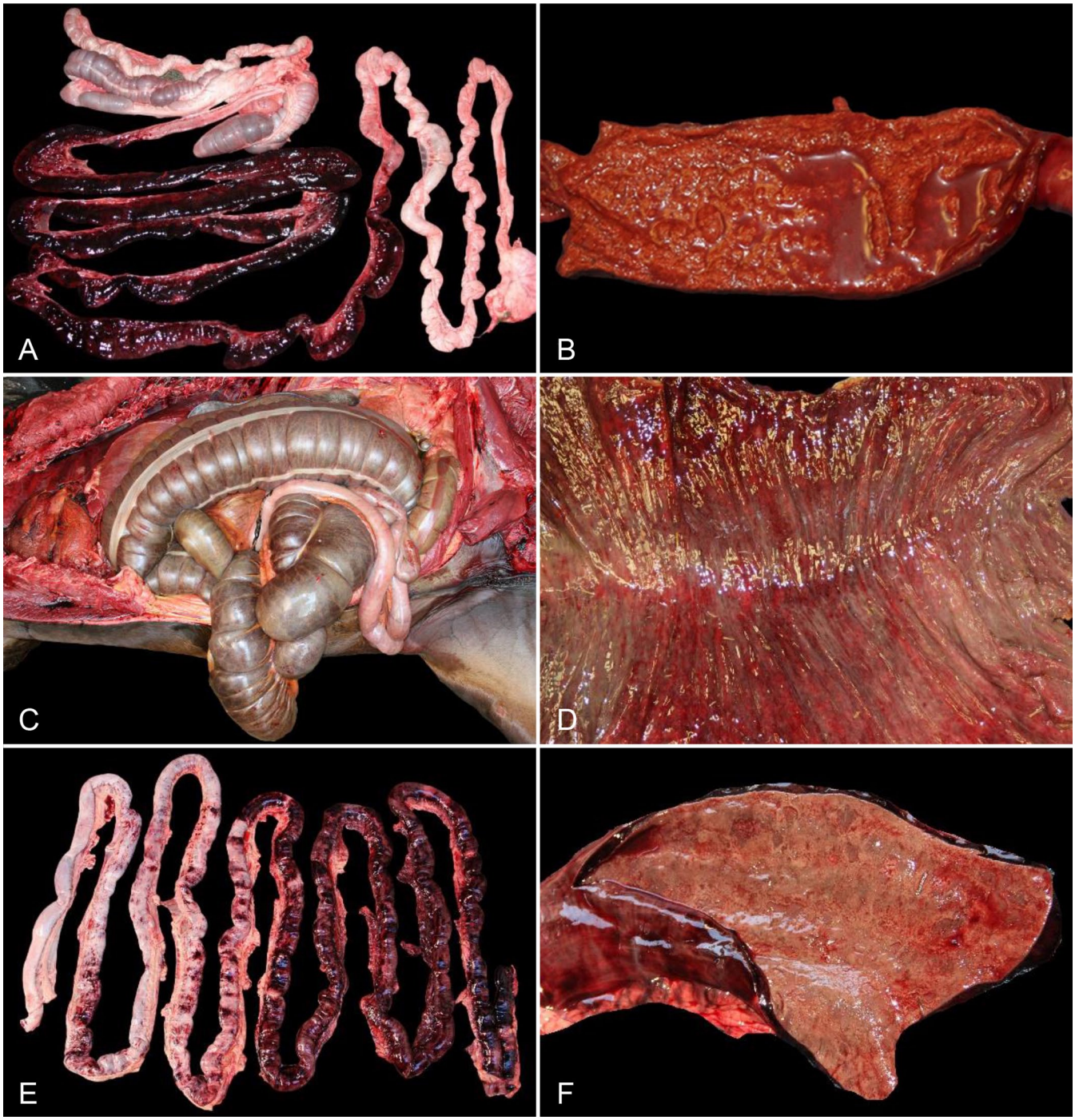


Figure 5. Gross changes in the alimentary tract of horses that died as a result of infection by *Clostridium perfringens* type C, *Clostridioides difficile*, *Paeniclostridium sordellii*, *Salmonella enterica* subspecies *enterica* serovar Typhimurium, or by intoxication by nonsteroidal anti-inflammatory drugs. Infections by *C. perfringens* type C with **A**. severe serosal hemorrhage and **B**. mucosal necrosis in the small intestine; *C. difficile* with **C**. serosal congestion and **D**. mucosal necrosis and hemorrhage in the colon; and *P. sordellii* with **E**. severe serosal hemorrhage and **F**. mucosal necrosis of the small intestine.

The main gross lesions of the small and/or large intestine caused by any of the agents that we investigated included one or more of the following: necrosis, hemorrhage and edema of mucosa and submucosa, pseudomembrane overlying the mucosa, and distention by gas and/or red liquid content (Figs. 5–7). Necrosis and hemorrhage of the mucosa and submucosa of the large intestine was more frequent in horses with *C. difficile* infection ($p < 0.05$); similar changes in the

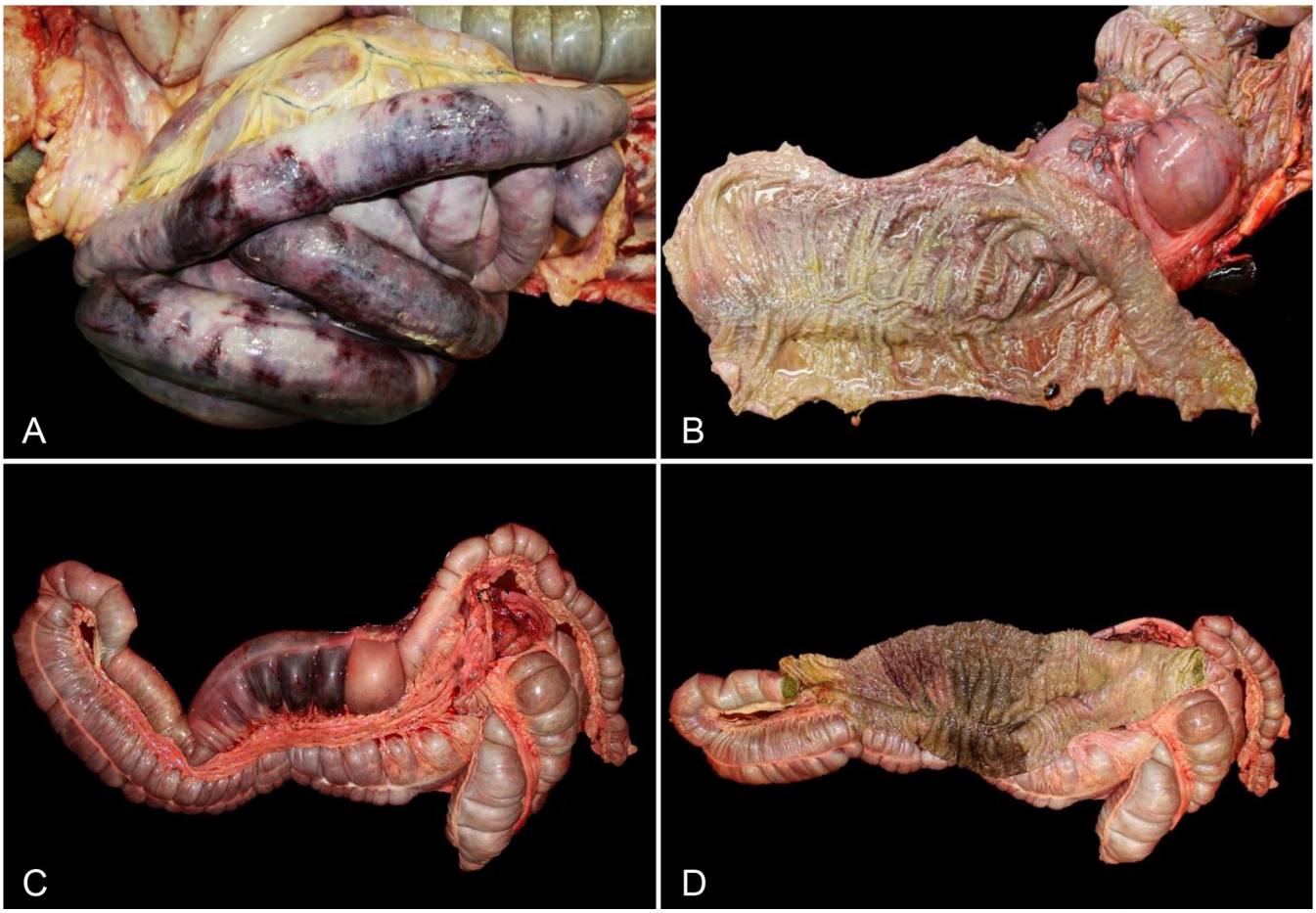


Figure 6. Infection by *Salmonella enterica* subspecies *enterica* serovar Typhimurium with **A**. severe serosal hemorrhage of the small intestine and **B**. mucosal necrosis with pseudomembrane on the colon; and intoxication by nonsteroidal anti-inflammatory drugs with **C**. serosal hemorrhage and **D**. mucosal necrosis of the right dorsal colon.

small intestine were more frequent in horses with *C. perfringens* type C infection ($p < 0.05$). All of the other gross changes described were observed in a non-statistically different frequency among all of the agents investigated here.

The main extraintestinal changes, regardless of the etiology involved, included, in decreasing order of frequency, congestion and/or hemorrhage of multiple organs, pulmonary edema, hepatic necrosis, pneumonia, hydrothorax, hydropericardium, ascites, gastric dilation, laminitis, splenomegaly, peritonitis, pododermatitis, and polyarthritis (Fig. 8).

The main microscopic lesions of the small and/or large intestine and their distribution caused by any of the agents that we investigated included congestion, edema, and hemorrhage of the mucosa and/or submucosa, necrosis of mucosa and/or submucosa, inflammatory infiltrate in mucosa and/or submucosa, including lymphocytes, plasma cells, neutrophils, eosinophils, and histiocytes (Figs. 9, 10), thrombosis of mucosal and/or submucosal vessels, hemorrhage of muscularis and/or serosa, fibrinoid necrosis of blood vessels of mucosa and/or submucosa, presence of rarely sporulated gram-positive rods in the lumen and covering the denuded mucosa, presence of pseudomembrane covering the mucosa, and villus blunting (small intestine; Fig. 11). Regardless of the agent involved, the inflammatory exudate was mainly seen in the mucosa and submucosa, with rare cases in which a few inflammatory cells were observed in other layers of the intestine. There were no statistical differences between the different types of inflammatory cells among the 5 etiologies that we investigated (Fig. 10).

Extra-intestinal microscopic findings included pulmonary congestion and edema, pneumonia, myocardial necrosis, hepatic necrosis and/or hepatitis, congestion and hemorrhage of multiple organs, nephrosis, nephritis, ulcerative gastritis, splenitis, splenic lymphoid depletion, peritonitis, pododermatitis, laminitis, and polyarthritis. No statistical differences were observed between the presence of these lesions and any of the 5 etiologies that we investigated.

Regardless of the location, for *C. difficile* and *C. perfringens* type C infections, the lesions were severe in most cases, whereas for *S. enterica* ser. Typhimurium and *P. sordellii* the

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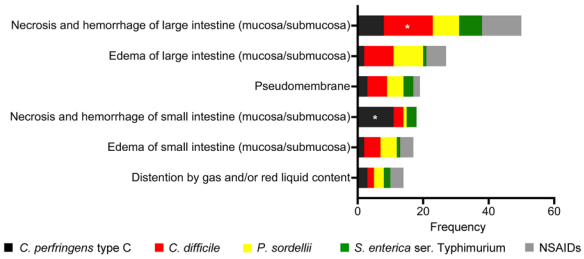

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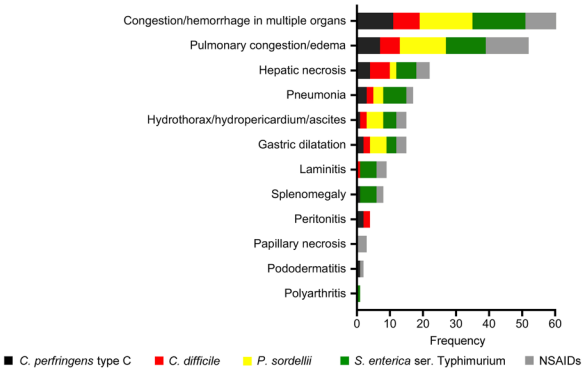

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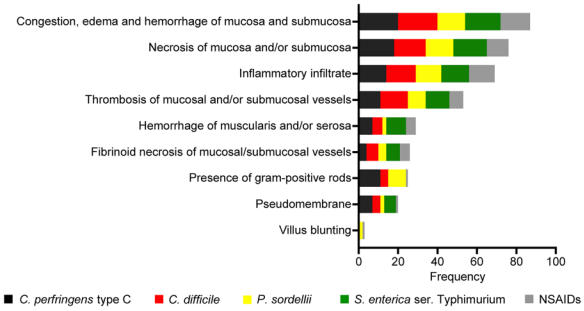


Figures 7–9. Distribution of gross intestinal and extra-intestinal lesions, and microscopic intestinal lesions in 90 horses that died as a result of enteric disease by 5 different causes. **Figure 7.** Distribution of gross lesions. The stars indicate statistical differences for that particular agent. **Figure 8.** Main extraintestinal lesions. **Figure 9.** Distribution of microscopic lesions in the intestine.

lesions were severe or extremely severe in most cases. The lesions in most cases of NSAID intoxication were moderate to severe (Fig. 12).

Discussion

As expected, the most common clinical history was colic nonresponsive to treatment for all of the etiologies included in our study. This was followed by diarrhea, sudden death, and others. Diarrhea was reported most frequently in cases of *C. perfringens* type C infection. Given that this microorganism affects mostly neonates that do not have a fully developed intestinal microbiome,[29] this is likely the reason that diarrhea was most commonly seen in foals with *C. perfringens* type C infection.

Sudden death has been described in cases of *C. perfringens* type C and *C. difficile* enterocolitis.[8–10] These 2 agents can produce severe and acute lesions in the alimentary tract and elsewhere, and it is therefore possible that, at least in some cases, death occurred before clinical signs were observed. It is also possible that in some cases reported as sudden death, the horses were simply found dead, and the owner or veterinarian failed to observe clinical signs that occurred before death.

Not surprisingly, and consistent with previous reports,[7,8,25,26,28] enterocolitis caused by *C. perfringens* type C affected mostly neonatal animals and several foals. The reason for this age distribution is that CPB, the main virulence factor of *C. perfringens* type C,[18] is highly susceptible to the action of trypsin, which is the natural defense against this toxin. Neonatal animals have a low level of trypsin activity in the intestine because of the inhibitory action of colostrum.[19,28] A few cases of this infection occurred, however, in juvenile and adult animals. The predisposing factor for cases in these age groups has not been determined, but pancreatic disease and ingestion of trypsin inhibitors have been mentioned as possible inciting causes.[3,22,26]

S. enterica ser. Typhimurium affected mostly adult animals. This is probably because only horses with enteric lesions were included in our study. Salmonellosis in neonatal animals and foals usually appears as septicemia,[28] a form that was not included in our study. Cases of *P. sordellii* and NSAID intoxication were observed in foals, juveniles, and adult horses, with no cases detected in neonatal animals. The reason for the lack of cases of NSAID intoxication in neonatal animals is probably that there was insufficient time for these young animals to be treated with these drugs, or if they were treated, to develop lesions. The reason for the absence of cases of *P. sordellii* in neonatal horses remains undetermined.

C. difficile, *S. enterica* ser. Typhimurium, and NSAIDs affected the colon more frequently than the small intestine. This is consistent with previous reports,[6,10] but the reason is unknown. In pigs, it has been suggested that an earlier immune response of cytokines in the jejunum and ileum occurs and is maintained for a longer time than in the colon, permitting more efficient recruitment of phagocytes for clearance of infection.[5] It has also been suggested that specific intestinal segment lesion distribution may be attributed to the lower concentration of bile salts and beta-defensins in the cecum and colon.[2,4,5] The distribution of lesions in different parts of the intestine was similar in cases of *P. sordellii* and *C. perfringens* type C infection, which is also consistent with previous descriptions of these diseases.[8,20,27,28]

Not surprisingly, the right dorsal colon was the intestinal segment most frequently affected in cases of NSAID intoxication, a disease that is also known as right dorsal colitis. This, however, is considered a misnomer by some authors[28] because lesions produced by NSAIDs may be found in multiple segments of the alimentary canal, as demonstrated by our results. Although in some cases of NSAID intoxication, typical lesions were seen exclusively in the right dorsal colon, this cannot be used as a diagnostic criterion, because

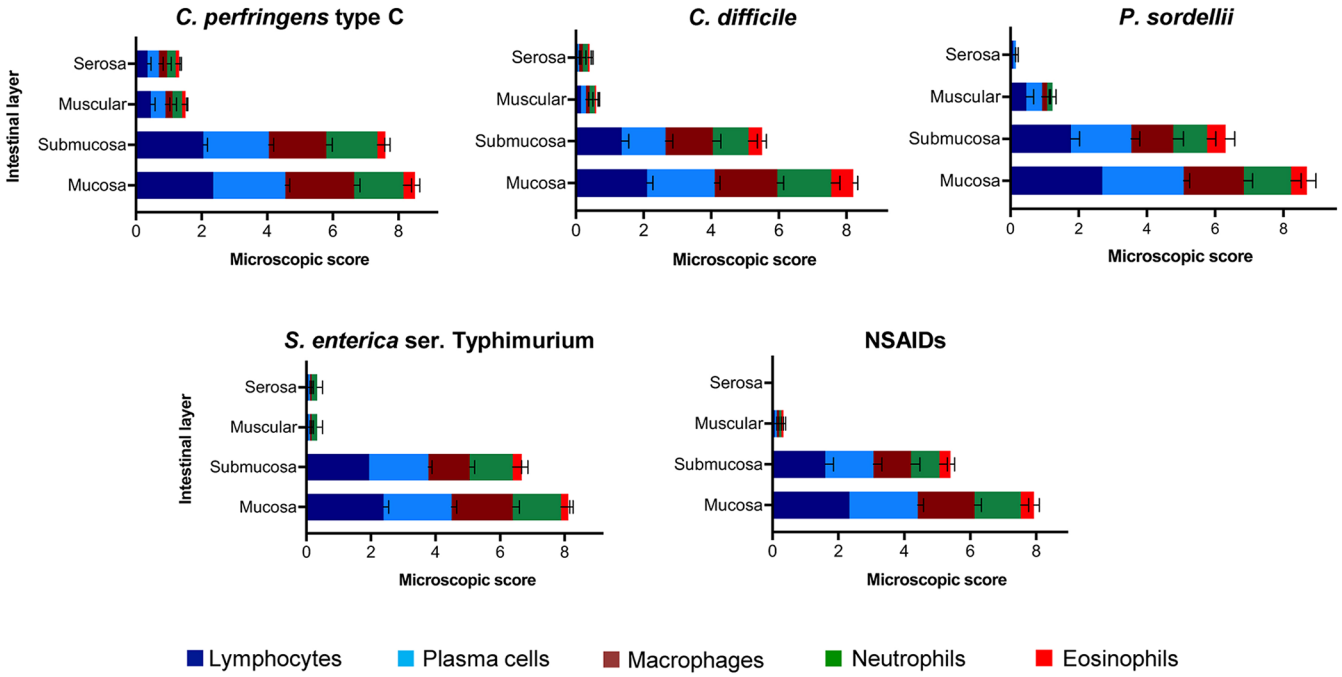
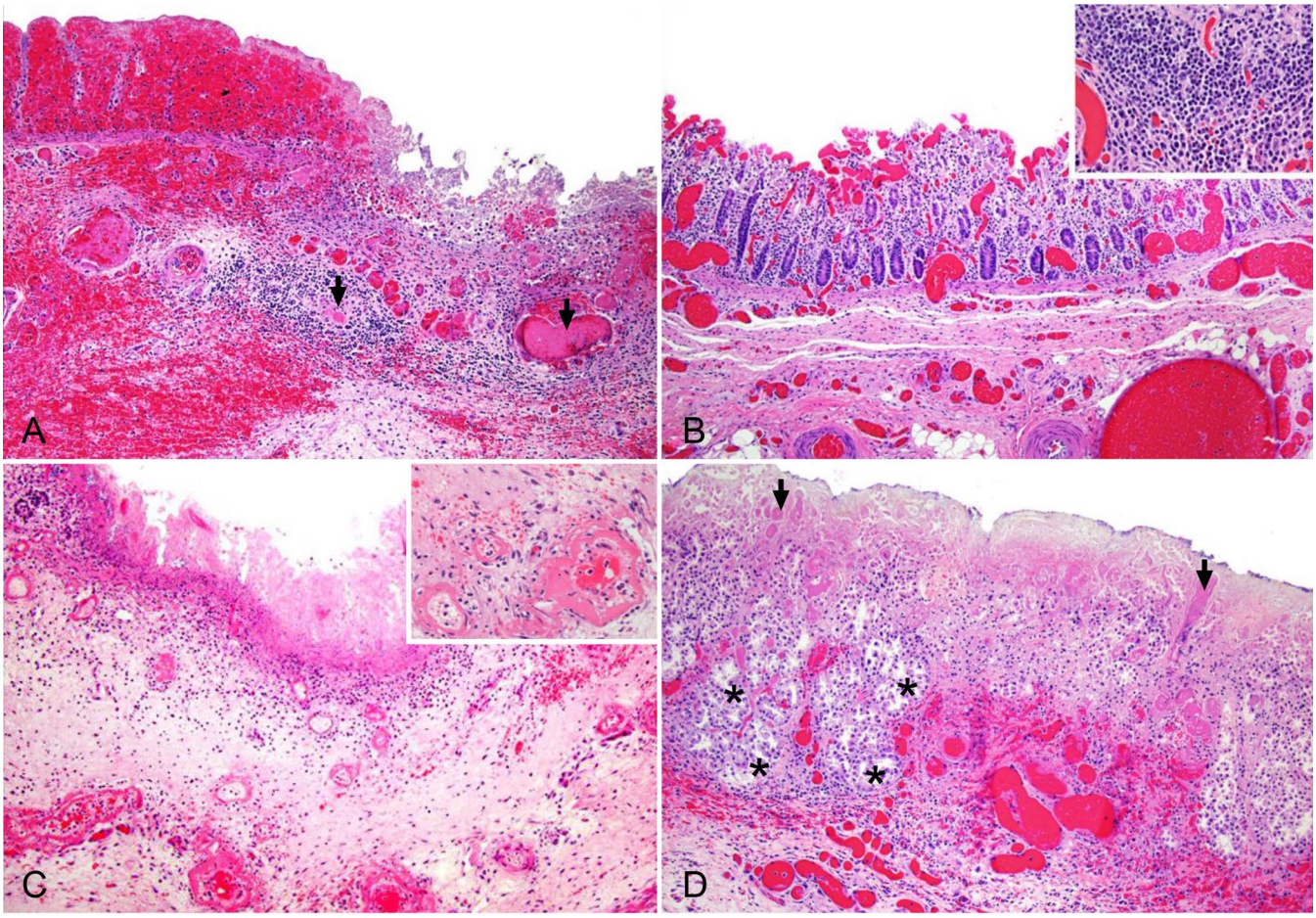


Figure 10. Inflammatory infiltrate in the alimentary tract of 90 horses that died as a result of enteric disease by 5 different causes.



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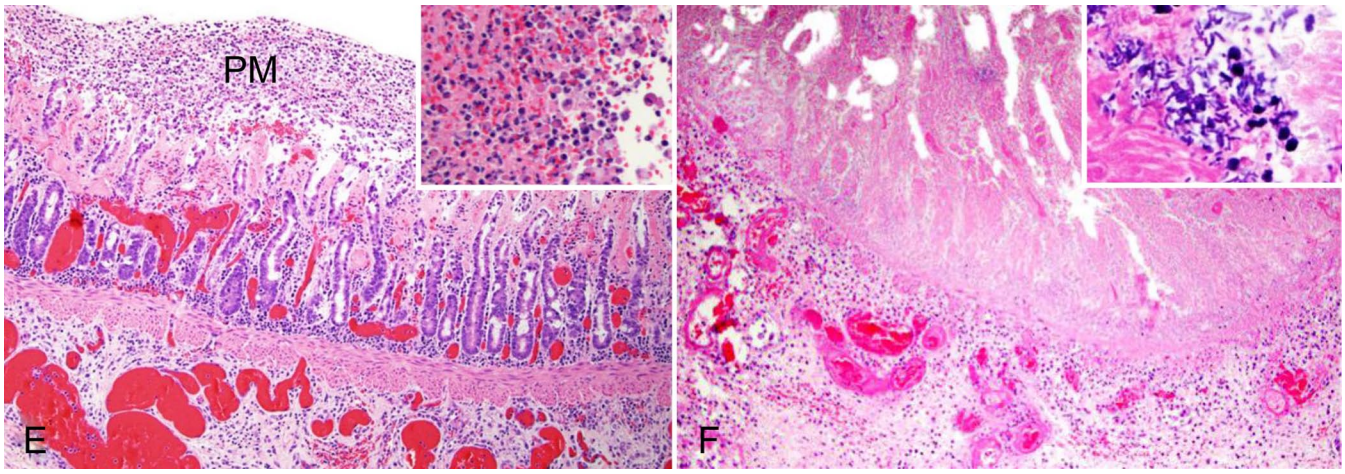

Figure 11. Main microscopic lesions in the intestines of 90 horses that died as a result of enteric disease by 5 different causes. **A.** Colitis caused by *Salmonella enterica* subspecies *enterica* serovar Typhimurium with severe mucosal and submucosal hemorrhage, mucosal necrosis and edema, and thrombosis of submucosal vessels (arrows). H&E. **B.** Colitis caused by nonsteroidal anti-inflammatory drug intoxication with necrosis of surface epithelium, mucosal and submucosal congestion, and infiltration of lamina propria by numerous lymphocytes, plasma cells, and fewer histiocytes and neutrophils (inset). H&E. **C.** Enteritis caused by *Clostridium perfringens* type C. There is diffuse mucosal necrosis, and the submucosa is expanded by edema and fibrin deposition. Vascular fibrinoid necrosis (inset). H&E. **D.** Colitis caused by *Paeniclostridium sordellii* with necrotic mucosa, thrombosis of lamina propria vessels (arrows), dilated and degenerate crypts (asterisks), and severe mucosal and submucosal congestion and hemorrhage. H&E. **E.** Colitis caused by *Clostridioides difficile* with a pseudomembrane (PM) composed of fibrin, desquamated necrotic cells, cell debris, and leukocytes (inset). H&E. **F.** Enteritis caused by *C. perfringens* type C, with necrotic mucosa and villus blunting. Clusters of rod-shaped bacilli are present in the necrotic areas (inset). H&E.

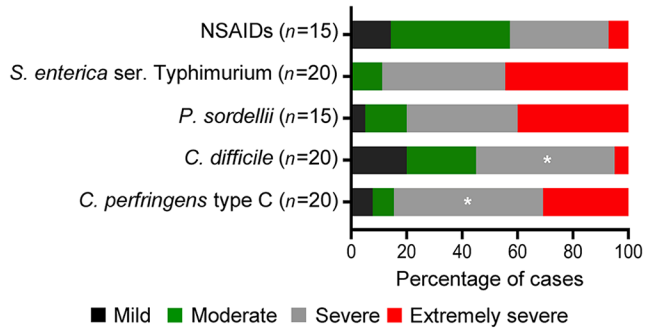

Figure 12. Severity of microscopic lesions in the intestine of 90 horses that died as a result of enteric disease by 5 different causes. The stars indicate statistical differences for that particular agent.

in a significant percentage of cases, lesions were observed in other parts of the intestine.

A variety of extra-intestinal lesions were observed in horses affected by all of the etiologies investigated in our study. Traditionally, the majority of those lesions are considered to be the result of endotoxemia, which ensues once the intestinal epithelial barrier is breached as a consequence of the direct action of toxins and/or the inflammatory process occurring in the intestine.[28] It is possible, however, that at least some of those lesions were associated with the direct effect of some of the bacterial toxins or NSAIDs, which were absorbed into the systemic circulation.

The gross and microscopic enteric lesions found in all horses in our study, regardless of etiology, were similar, with any case differences being related to intestinal location and the age of affected animals rather than to lesion morphology. These findings suggest that, although age and site of intestinal lesions may assist in formulating a presumptive causation, the changes are largely nonspecific, and additional ancillary tests are required to make an accurate etiologic diagnosis.

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Declaration of conflicting interests

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