

Recurrent diarrhea associated with enterotoxigenic *Clostridium perfringens* in 2 dogs

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Abstract — Two dogs were diagnosed with enterotoxigenic *Clostridium perfringens*-associated diarrhea. Diarrhea was responsive to antimicrobial therapy, but recurred after treatment was ceased. *Clostridium perfringens* enterotoxin was present in feces during diarrheic episodes but not when feces were normal. Both dogs responded to a prolonged course of oral cephalixin and dietary modification.

Résumé — Diarrhée récurrente associée à un *Clostridium perfringens* entérotoxigène chez 2 chiens. Un diagnostic de diarrhée associée à un *Clostridium perfringens* entérotoxigène a été posé sur 2 chiens. La diarrhée répondait à l'antibiothérapie mais revenait à la fin du traitement. L'entérotoxine de *Clostridium perfringens* était présente dans les fèces au cours des épisodes diarrhéiques mais non lorsque les fèces étaient normales. Les 2 chiens ont répondu à un traitement prolongé à la céphalexine par voie orale associée à une modification du régime alimentaire.

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An 11-month-old, 22-kg, castrated male vizsla-cross was presented to the Guelph Animal Hospital with a 2-day history of intermittent vomiting and a 1-day history of diarrhea. The dog had not been hospitalized recently or treated with antimicrobials; however, it had been kenneled for 2 d, commencing 4 d prior to presentation. A normal appetite was maintained. The diarrhea was reported to be semiformal with no blood or mucus. At approximately 2 m of age, the dog was diarrheic and giardiasis was diagnosed. Treatment with metronidazole had been prescribed; however, metronidazole administration was associated with vomiting and treatment was changed to albendazole. Diarrhea resolved following treatment and no problems were reported in the interim.

On presentation, the dog was bright and alert with normal vital parameters and no abnormalities on physical examination. Zinc sulfate flotation and a saline wet mount of a fecal sample were negative for the presence of gastrointestinal parasites. Food was withheld for 24 h and treatment with fenbendazole (Panacur; Hoechst Canada, Regina, Saskatchewan), 25 mg/kg BW, PO, q12h, for 7 d, was prescribed. Normal feces were passed following completion of this treatment regimen.

Fourteen days following completion of the above treatment, the dog was presented for evaluation of profuse, bloody diarrhea of 24 hours' duration. Mild pain on abdominal palpation was the only remarkable abnormality present on physical examination. Occasional *Isoospora canis* oocytes were detected on fecal flotation. While awaiting the results of further testing, it was recommended that the dog be fasted for 24 h and

then fed a bland diet consisting of cooked, drained, ground beef and cooked rice for 48 h. A herbal dietary supplement (D'Ayu Relief; Ayuvet, India), 7.5 mL, PO, q8h, for 4 d, was also administered. Sulfadimethoxine (S-250; Rhône-Mérieux, Victoriaville, Quebec), 27.5 mg/kg BW, PO, for 1 d and then 13.5 mg/kg BW, PO, q24h, for 4 d, was prescribed for the treatment of coccidiosis. Fecal samples were also submitted for bacterial culture and testing for clostridial toxins. Moderate numbers of *Campylobacter jejuni* were present, as was heavy growth of *Clostridium perfringens*. *Clostridium perfringens* enterotoxin (CPE) was detected in the fecal sample using an ELISA (*Clostridium perfringens* enterotoxin ELISA; Tech Lab, Blacksburg, Virginia, USA). *Clostridium difficile* toxins were not detected (*C. difficile* TOX A/B Test; Tech Lab). Due to the previous adverse reaction to metronidazole, treatment with amoxicillin (Novamoxin; Novopharm, Toronto, Ontario), 22 mg/kg BW, PO, q12h, for 14 d, was prescribed. Normal feces were passed by day 10. A fecal sample obtained 1 d following completion of the treatment was negative for gastrointestinal parasites, *C. difficile*, and CPE. Moderate growth of *C. perfringens* was still present.

Twenty-three days after completion of amoxicillin treatment, the dog was presented with diarrhea of 3 days' duration. No abnormalities were present on physical examination. No gastrointestinal parasites were detected. The dog was again fasted for 24 h and then fed a bland diet consisting of cooked, drained, ground beef and cooked rice for 48 h. Amoxicillin, 22 mg/kg BW, PO, q12h, for 21 d, was prescribed. Feces were semiformal within 3 d and normal feces were passed by day 8 of treatment.

One week later, the dog was presented again with a 1-day history of semiformal, bloody diarrhea. No abnormal findings were present on physical examination. A fecal sample was obtained and was negative for the presence of gastrointestinal parasites and *C. difficile* toxins but positive for CPE. Heavy growth of *C. perfringens* was present on anaerobic culture. Based on antimicrobial susceptibility testing, treatment with cephalixin

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(Novalexin; Novopharm), 22 mg/kg BW, PO, q12h, for 14 d, was instituted. The diet was also changed to a highly digestible diet (Medi-Cal Gastro; Veterinary Medical Diets, Guelph, Ontario), supplemented with a commercial probiotic preparation (Nutrigest; Rx Vitamins, Larchmont, New York, USA), 2 capsules, q12h. The diarrhea resolved within 2 d and did not recur following termination of the antimicrobial therapy. At last report, the dog had been asymptomatic for approximately 10 mo. A fecal sample was obtained approximately 4 mo after treatment: *C. perfringens* was present in the sample; however CPE was not detected.

A 6-month-old, 3.4 kg, female shih tzu was presented with a 1-day history of intermittent vomiting and diarrhea. The dog had a normal appetite but was lethargic. There was no history of inappropriate ingestion or change in diet. Defecation frequency was increased with some evidence of straining. Diarrhea was semi-formed with no observable blood. On presentation, the dog was bright and alert. Mild resistance to abdominal palpation and increased borborygmi were the only abnormalities present on physical examination. *Isospora canis* oocytes were detected in a fecal sample. The dog was treated with sulfadimethoxine (S-125; Rhône-Mérieux), 27.5 mg/kg BW, PO, for 1 d and 13.5 mg/kg BW, PO, q24h, for the following 4 d. Diarrhea resolved during the treatment period.

The dog was presented for reevaluation of diarrhea 6 d after cessation of treatment. Semiformed feces were passed and it was reported that the frequency of defecation was increased. Four zinc sulfate fecal flotations were completed over 2 d, but no gastrointestinal parasites were detected. Following a 24-hour fast, the dog was fed a bland diet consisting of cooked, drained, ground beef and cooked white rice. A herbal dietary supplement (D'Ayu Relief; Ayuvet), 2.5 mL, PO, q8h, for 4 d, was also administered. A fecal sample was then submitted for bacterial culture and testing for *C. difficile* toxins and CPE. *Clostridium perfringens* and CPE were detected in the sample. A delay of 96 h from sample collection until reporting of results occurred at this time and normal feces were passed by the time the owner was contacted. As a result, no further treatment was recommended. However, 20 d later the dog was presented with a complaint of acute onset of vomiting and diarrhea. The history and clinical signs were identical to those noted at the initial presentation. No gastrointestinal parasites were detected in feces. *Clostridium perfringens* enterotoxin was again present in the sample, as was moderate growth of *C. perfringens*. The isolated strain of *C. perfringens* was resistant to metronidazole but sensitive to cephalosporins, so treatment with cephalexin, 22 mg/kg BW, PO, q12h, for 14 d was prescribed. A dietary change to a highly digestible diet (Medi-Cal Gastro; Veterinary Medical Diets) was instituted. The diarrhea resolved within approximately 7 d and did not recur following cessation of treatment. A fecal sample was obtained 4 mo after resolution of clinical signs. *Clostridium perfringens* enterotoxin was not detected in the sample. At last report, the dog had been asymptomatic for approximately 8 mo.

Clostridium perfringens is an anaerobic, gram-positive, spore-forming bacterium that is widespread within animal populations and the environment (1). Toxigenic strains of *C. perfringens* are classified into 5 types, A

through E, based on the production of 4 major toxins. In addition, isolates may produce a variety of other toxins, including one designated as CPE. Production of CPE is most commonly associated with type A strains but can occur with other types (1). *Clostridium perfringens* production is co-regulated with, but not necessary for, sporulation and is released upon lysis of vegetative cells (1). This toxin is a cytotoxic enterotoxin that causes tissue damage (2), but the exact method by which CPE causes diarrhea is still unclear. In rat and rabbit ileal loop models, CPE causes structural damage and secretion in the small intestine, particularly the ileum, but has little effect in the rabbit colon (2).

Toxigenic strains of *C. perfringens* have been associated with enteric disease in a number of species including humans (3), horses (1,4), and cattle (1). In humans, enterotoxigenic *C. perfringens* has been associated with sporadic diarrhea, food poisoning, and antibiotic-associated diarrhea (3). *Clostridium perfringens* has also been implicated in nosocomial and sporadic diarrhea in dogs (5–7), although there are few reports evaluating CPE in diarrheic dogs. Kruth et al, using an ELISA, reported an association between CPE and diarrhea in a study of nosocomial diarrhea (7). In contrast, Marks et al reported no association between CPE and diarrhea in dogs, by using a reverse passive latex agglutination assay (RPLAA) (8). The RPLAA is a sensitive test for CPE but is not very specific (9), which may have resulted in a large number of false positive results. The CPE ELISA used in the present case studies is thought to be more specific than the RPLAA (8), reducing the number of false positive results. When this ELISA was used, preliminary results of a recent study indicated an association between detection of CPE and diarrhea in dogs (10).

Diagnosis of CPE-associated disease requires more than bacterial culture, since *C. perfringens* is commonly isolated from the feces of normal dogs (1). *Clostridium perfringens* proliferates rapidly following disruption of the normal gastrointestinal flora. As a result, *C. perfringens* is commonly present in large numbers in the feces of dogs with diarrhea of any etiology (10). Quantitation of *C. perfringens* in fecal samples or evaluation of fecal smears for endospores has been recommended (9); however, spore counts and fecal smears must be interpreted with caution, since many studies have reported no correlation with the presence of CPE in humans and dogs (3,8). As a result, diagnosis of CPE-associated disease is dependent on detection of CPE in fecal samples.

Both dogs in this report were initially diagnosed with gastrointestinal parasitism. The association of this diagnosis to the CPE-associated disease is unclear. Testing for CPE was not performed at the time the dogs were diagnosed with gastrointestinal parasitism, so it is possible that CPE, and not parasites, was responsible for the initial diarrheic episode. Alternatively, gastrointestinal parasitism and CPE-associated disease could have occurred simultaneously, or enterotoxigenic *C. perfringens* could have proliferated secondary to disruption of the gastrointestinal microflora by intestinal parasites or sulfonamide treatment.

The role of dietary modification in the response to treatment in these dogs is not clear. Dietary change may have modified the gastrointestinal flora and assisted recovery, although this cannot be proven. Both dogs have

been maintained on a highly digestible diet. Because resolution of diarrhea also corresponded with the dietary change, food allergy cannot be ruled out in these cases. Reversion to the previous diet could help determine whether food allergy was, indeed, involved; however, the owners of both dogs have been reluctant to change the diet now that diarrhea has been eliminated.

The presence of CPE in fecal samples of these dogs during diarrheic episodes, but not during periods with normal feces, suggests the involvement of enterotoxigenic *C. perfringens*. The recognized role of enterotoxigenic *C. perfringens* in enteric disease in other species, known pathogenic effects of CPE, and lack of identification of another cause of diarrhea support this hypothesis. However, it cannot be ruled out that *C. perfringens* proliferated and produced CPE secondary to disruption of the intestinal microflora from the gastrointestinal tract by other pathogens. Further study of the role of enterotoxigenic *C. perfringens* is required to better understand the role of this pathogen in canine enteric disease.

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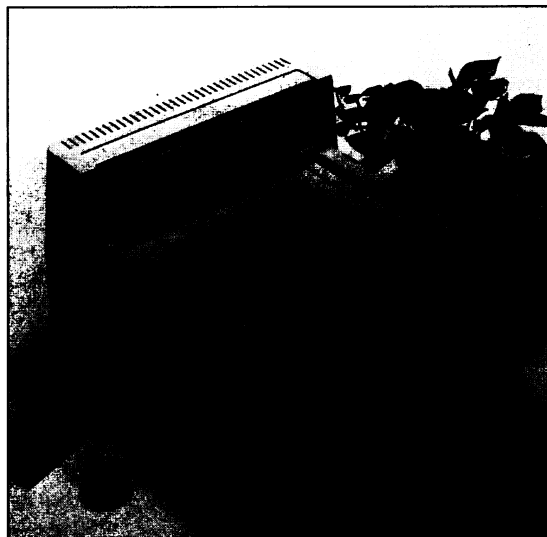
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