PRACTICE PEARLS ON CANINE ACUTE HEMORRHAGIC DIARRHEAL SYNDROME

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Acute hemorrhagic diarrhea syndrome (AHDS) is an umbrella term that refers to hemorrhagic enteritis or colitis associated with several infectious and non-infectious causes, and that typically lasts < 1 week in duration. The term hemorrhagic gastroenteritis or "HGE," implies gastric involvement with consequent vomiting, and the author prefers using the term "acute hemorrhagic diarrheal syndrome" to describe dogs with the acute onset of hemorrhagic diarrhea with or without vomiting.

Acute hemorrhagic diarrheal syndrome in dogs has numerous potential causes, although an underlying cause for AHDS is often not identified. In a study of 61 dogs that were presented with AHDS to the Clinic of Small Animal Medicine of the LMU University of Munich between April 2006 and May 2007, it was found that dogs with AHDS were significantly younger (median age 4.2 years) and weighed less (median weight 12 kg) compared to the general hospital population.[1] Predisposed breeds were Yorkshire terrier, miniature Doberman pinscher, miniature Schnauzer, miniature poodle, and Maltese dogs. A fecal flotation was positive for intestinal parasites in 4/61 dogs with AHDS; fecal ELISA for *Giardia* was positive in 5/61 dogs with AHDS, canine Parvovirus (CPV) antigen was detected by ELISA in 2/58 dogs with AHDS; canine Coronavirus (CCV) was identified in 10/62 dogs with AHDS, and bacterial enteropathogens were cultured in 2/57 dogs (both *Salmonella* spp.)[1]

Clostridium perfringens enterotoxin (CPE) was significantly more frequently detected in dogs with AHDS (28/55) compared to a healthy control group of dogs (2/23). In addition, dogs with AHDS had a significantly increased hematocrit, white blood cell count, and banded neutrophil count compared to the control group. Primary intestinal pathogens were only detected in a small number of cases. However, CPE was far more commonly identified in dogs with AHDS than in control dogs.[1] It is difficult to determine whether *Clostridium perfringens* enterotoxin was the primary cause of AHDS in dogs, or whether the enterotoxin was elaborated in association with intestinal dysbiosis following dietary indiscretion, antimicrobial therapy, or an underlying enteropathy. Recent studies have documented an association between fecal PCR detection of *C. perfringens* netE/netF toxin genes and AHDS in dogs. The netE/netF toxin genes are pore-forming toxins that are related to the leucocidin/hemolysin superfamily, responsible for necrotic enteritis in dogs. *Dogs with canine Parvovirus enteritis were significantly younger, weighed less, had a lower hematocrit, total serum protein and serum albumin concentration, and higher alkaline phosphatase activity when compared to other dogs with AHDS*.[1] *Clostridium difficile* infection also been associated with AHDS in dogs, and the clinical signs and laboratory changes (hemoconcentration with low-normal plasma protein) in these dogs are very similar to those observed with *C. perfringens*.[2,3] Other primary bacterial enteropathogens commonly incriminated in canine AHDS include *Campylobacter* spp., *Salmonella* spp., and *Escherichia coli*.

Viral causes of AHDS include CPV, canine Coronavirus (CCV), and Circovirus. Canine Circovirus has been associated with severe hemorrhagic gastroenteritis, vasculitis, and granulomatous lymphadenitis in dogs recently. Circovirus was detected via PCR in fecal specimens from 19/168 (11.3%) dogs with diarrhea and in blood from 3.3% of dogs with thrombocytopenia, neutropenia, or fever of unknown origin. Co-infection with other canine pathogens was detected in 13/19 dogs (68%) infected with Circovirus.[4]

The need for performing fecal screening for putative enteropathogens, resting cortisol for Addison's disease, tests for pancreatitis (Spec cPL and ultrasound), or abdominal radiographs for GI foreign bodies should be based upon the patient's signalment, history (including vaccination history), and physical examination findings. Caution should be heeded in ruling out CPV in fully vaccinated dogs that are > 6 months old, including those lacking neutropenia on CBC, because "atypical" CPV, associated with CPV-2C has been well documented in these animals.[5] *A negative fecal ELISA test should never be used to rule out CPV.*

The clinical significance of isolation of enteropathogenic bacteria causing diarrhea in dogs is clouded by the existence of many of these organisms as normal constituents of the indigenous intestinal flora. Fecal cultures and toxin analysis should be reserved for dogs with an acute onset of bloody diarrhea (with or without concurrent evidence of sepsis), and in diarrhea outbreaks occurring in multiple animals in a densely populated shelter or kennel environment. In addition, screening for *C. difficile*, *Campylobacter* spp., or *Salmonella* spp. is indicated when zoonotic implications are present. A prospective study including 87 dogs with AHDS and 21 healthy dogs showed for the first time that the incidence of bacteremia in dogs with AHDS is low and not different from those of healthy control dogs.[6] In a prospective placebo-controlled treatment study, antibiotics did not change outcome or time to recovery in dogs with aseptic AHDS.[7] Antibiotics should thus be used judiciously in dogs with AHDS, and are typically warranted in febrile patients, patients that exhibit neutropenia or neutrophilia (< 4 or > 25 x 10^9/l), increased band neutrophils, and/or evidence of immunosuppression (dog receiving chemotherapy, poorly controlled diabetic patient, etc).

IS THERE A PLACE FOR ANTIMICROBIAL THERAPY IN DOGS WITH ACUTE DIARRHEA, AND IF SO, WHEN AND WHAT TYPE OF ANTIMICROBIAL(S) SHOULD BE ADMINISTERED?

There is no published consensus on the management of acute diarrhea in cats and dogs, and most veterinarians implement a variety of supportive therapies, including dietary modification (typically a highly digestible diet), antibiotics (typically metronidazole), empiric deworming, probiotics, motility modifiers (eg., loperamide), and various clays to resolve the diarrhea. The mechanism of action of metronidazole's antidiarrheal effects are incompletely understood, although it has been proposed that the drug has immunomodulatory and anti-inflammatory effects. Metronidazole also increases thickness of the intestinal mucus layer, increases *Bifidobacterium* populations, and reduces the colonic oxidative damage to proteins. Its efficacy against *Giardia* and *Clostridium* spp. is well-described. Interestingly, investigations into the role of metronidazole in treating other causes of canine diarrhea have yielded mixed results. No therapeutic benefit was demonstrated when metronidazole administration was compared to probiotic or placebo administration in 60

dogs with acute onset, non-specific diarrhea in a randomized, double-blinded clinical trial. Additionally, no benefit was observed with the addition of metronidazole to amoxicillin/clavulanic acid in the treatment of canine hemorrhagic diarrhea (AHD), or to prednisone for induction therapy of canine inflammatory bowel disease (IBD). In contrast, a recently published prospective trial comparing metronidazole treatment to placebo in a cohort of dogs with acute diarrhea demonstrated a significant reduction in time to resolution of diarrhea of 1.5 days in the dogs treated with metronidazole. Importantly, this study did not conclude that metronidazole should be utilized as a first-line drug for management of acute diarrhea because 88% of cases resolved within 7 days even in the absence of treatment. Injudicious antibiotic use can have a significant impact on the individual patient. Administration of metronidazole also causes significant changes to the microbiome, including decreased microbial diversity which can persist for weeks to months past discontinuation of the drug.

Antimicrobial therapy is typically warranted in canine or feline patients with acute hemorrhagic diarrhea syndrome (AHDS) patients that manifest systemic signs of sepsis or severe decompensation (fever, degenerative or regenerative left shift with toxicity, breakdown of intestinal mucosal barrier in immunocompromised patients, etc.). Broad-spectrum bactericidal therapy including a combination of a fluoroquinolone with a penicillin-based antibiotic (e.g., Unasyn) reflect reasonable choices in the latter situation. Most dogs with AHDS do not warrant antibiotic therapy, and there is compelling evidence documenting similar outcomes in non-septic dogs with AHDS managed with placebo or probiotics compared to dogs receiving clavamox therapy. There is also provocative evidence documenting the benefit of fecal microbiota transplantation (FMT) for the management of dogs with parvovirus, and this relatively cost-effective treatment was associated with a significant shortening in the duration of hospitalization (3 days vs. 6 dogs) compared to dogs receiving standard medical therapy without FMT. Probiotics have also been demonstrated to shorten the duration of acute diarrhea in dogs and cats compared to placebo.

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