

CANINE PARVOVIRAL ENTERITIS: WHAT'S NEW?

Elisa M. Mazzaferro, MS, DVM, PhD, DACVECC

Cornell University Veterinary Specialists

Stamford, CT, USA

Parvoviridae are non-enveloped, single-stranded DNA viruses which replicate in rapidly dividing cells. Canine Parvovirus-1 (CPV-1) was first discovered in the early 1960's, and caused mild clinical signs of diarrhea in dogs. Since that time, evolution of the virus is thought to have occurred in Europe, and then spread worldwide. In the late 1970's and early 1980's, a new form of CPV, CPV-2, caused a widespread pandemic in adult domestic and wild dogs. In 1979, CPV-2a was discovered, then progressively worsened in virulence and pathogenicity to CPV-2b discovered in 1984. The CPV-2b caused vomiting, diarrhea, myocarditis, and congestive heart failure in naïve dogs. CPV-2b is now the most prevalent form of canine parvovirus worldwide, however a new genetic variant, CPV-2c, is being found in Europe and Asia, as well as North and South America.

CPV-2 is transmitted through oral-fecal contamination. Once ingested, the virus replicates in the oropharyngeal lymphoid tissue, mesenteric lymph nodes, and thymus, then is transferred through the blood plasma to rapidly dividing cells of the bone marrow and gastrointestinal crypt epithelium within 4 to 5 days of exposure. Viral replication within crypt cells causes collapse of the villi and villi necrosis, which leads to a break in the normal blood-epithelial barrier. Translocation of enteric bacteria and bacterial endotoxin into systemic circulation, combined with a lack of production of protective leukocytes (lymphocytes and neutrophils) from the infected bone marrow leads to systemic sepsis, septic shock, systemic inflammatory response syndrome (SIRS), and can lead to multiple organ dysfunction (MODS) and death if left untreated. Infected animals that are treated aggressively and early can survive, however, will shed parvovirus in their feces for up to 39 days following exposure. One gram of feces can contain up to 10 million infective doses of parvovirus.

Unvaccinated dogs of any age and breed can potentially become infected and develop clinical signs of disease following natural exposure to CPV. However, the majority of cases of clinical disease are observed in younger puppies from 6 to 20 weeks of age. Parvovirus does not appear to have a gender predilection until disease is observed in dogs greater than 6 months of age, in which intact male dogs seems to be over-represented. Clinical signs vary and often become progressively worse over time. Lethargy, inappetance, vomiting, diarrhea (often hemorrhagic) are cornerstones of disease. Weakness can be due to dehydration, or secondary to hypoglycemia from depletion of glycogen stores and sepsis. The most severely affected animals can develop seizures, thromboembolic disease, disseminated intravascular coagulation (DIC) and death if left untreated. Overall survival rates vary, and range from 64 – 95%. Due to the advent of widespread use of vaccination since the 1980s, and the presence of material derived antibodies, infection in utero and early myocarditis and congestive heart failure are rarely observed in recent times.

A fecal enzyme-linked chromatographic immunoabsorbent assay (ELISA) for detection of fecal antigen is an inexpensive and rapid cage-side test used to make a diagnosis of Parvovirus in affected animals. In some cases, false positive results can occur if a patient was vaccinated with a modified live vaccine within 5 to 15 days of testing. False negative results can occur early in the course of illness, or if maternal-derived antibody coats viral antigen in the feces and makes it unavailable to detection by ELISA testing. Clinically, however, the presence of a positive test with concomitant clinical signs of vomiting, diarrhea, lethargy and inappetance support a diagnosis of parvovirus in recently vaccinated animals. One study demonstrated that although vaccinated animals can shed vaccine strain of virus in their feces following vaccination, clinically ill dogs that developed parvovirus following vaccination were infected with field strains of virus, not reversion of the virus from modified live vaccination. Other diagnostic tests which are available, but take longer for results, include electron microscopy of feces, virus isolation, polymerase chain reaction or hemagglutination testing.

Leukopenia results from suppression of leukocyte precursors following viral infection of the bone marrow, as well as sequestration of leukocytes in intestinal crypt necrosis. Leukopenia, however, occurs in only 50% of affected dogs, therefore, is not a sensitive or specific indicator of parvovirus in infected animals. A total white blood cell count of greater than 4,500 WBC/uL, lymphocyte count > 1000/uL, monocyte count > 150/uL within 24 hours of admission for dogs infected with parvoviral enteritis is positively correlated with survival. While infected animals are often evaluated for neutropenia, the absolute lymphocyte value of less than 1000 lymphocytes/uL within 48 hours of admission has been correlated to be a negative prognostic indicator in affected animals. Daily blood smears evaluating both neutrophils and lymphocytes can be helpful

in gauging response to therapy and offer prognosis. Clinically, peripheral leukocyte numbers often increase at the same time that patients start appearing clinically better.

Other non-specific biochemical parameters which may be altered during parvoviral infection include hypoproteinemia and hypoalbuminemia (lack of albumin production and loss of protein in diarrhetic feces), anemia, extrahepatic cholestasis of sepsis (elevations in total bilirubin and alkaline phosphatase), pre-renal azotemia, coagulation defects including thrombocytopenia and prolonged coagulation times, hypoglycemia, and hypokalemia. Hypercoaguability as determined by thromboelastography and decreased antithrombin activity has been demonstrated in many dogs with parvoviral enteritis. More recently, plasma citrulline concentrations, an indicator of gastrointestinal cell mass have been found to be significantly decreased in dogs with parvovirus, however, does not appear to be a reliable predictive prognostic indicator for mortality versus survival. In addition, significantly higher plasma acute phase protein concentrations (C-reactive protein and ceroplasmin) has been found to be significantly increased in dogs with parvovirus, and can help predict mortality. Finally, serum total cholesterol and high-density lipoprotein levels have been significantly lower in dogs which succumb to parvovirus compared with survivors. Clearly, of the diagnostic tests that are available, not one is completely sensitive or specific. A combination of tests, along with response to therapy can aid the practitioner in speculating prognosis.

Treatment and monitoring of a patient with severe gastroenteritis of any cause can follow Kirby's Rule of Twenty.

- (1) Fluid Balance: Fluid balance is of paramount importance, as the majority of animals have significant fluid losses in vomitus and feces. Intravenous catheters should be placed in a vein that is less likely to become contaminated with feces or vomitus, however jugular catheters can have a tendency of becoming thrombosed over time. Calculation of estimated fluid deficits, combined with maintenance and ongoing losses is important. Frequent (Q8h) body weights can help guide fluid therapy, where acute losses in body weight are equivalent to fluid loss, where one gram is equal to one milliliter of water.
- (2) Blood pressure and perfusion: Patients can become so dehydrated that they become hypovolemic and hypoperfused. Therefore, careful regulation of fluid balance is of paramount importance. Serum lactate values can be used to guide fluid therapy and evaluate response to methods to improve perfusion. Lactate values are higher in puppies than adult dogs, so trends in lactate values, rather than one absolute number may be better reflective of response to therapy.
- (3) Heart rate, rhythm, and contractility: Due to circulating inflammatory cytokines, ventricular dysrhythmias and depressed myocardial contractility are possible, however are not common.
- (4) Blood glucose: As stated previously hypoglycemia is common, and should be monitored at least every 8 hours. Supplementation of dextrose in crystalloid fluids is often necessary.
- (5) Albumin and (6) Colloid Osmotic Pressure: Due to loss of protein in diarrhetic feces, hypoalbuminemia and decreased colloid osmotic pressure (COP) is common. Serum albumin concentrations less than 2.0 g/dL are associated with a negative prognostic outcome in many critical diseases. When available, daily monitoring of COP using a colloid osmometer can help direct colloid therapy. Albumin can be supplemented in very small patients using fresh frozen plasma at a dose of 15 – 20 ml/kg for each 0.5 g/dL increase in serum albumin concentration. For larger patients, fresh frozen plasma is a cost-prohibitive method of increasing serum albumin, and canine specific or concentrated human albumin infusion can be provided. To help maintain oncotic pressure, additional use of hydroxyethyl starches at doses of 20 – 30 ml/kg/day are often required.
- (7) Oxygenation and Ventilation: If a patient develops aspiration pneumonia, or pleural effusion, pulmonary edema or acute respiratory distress syndrome (ARDS), oxygenation can become impaired. Careful monitoring of a patient's respiratory rate and effort, as well as pulse oximetry may become necessary in the most severely affected patients. If a patient shows signs of increased respiratory effort or hypoxemia (SpO₂ < 94%), oxygen supplementation should be provided.
- (8) Acid-base, electrolyte: Frequently, patients can develop a metabolic acidosis from loss or sequestration of bicarbonate. Loss of chloride and bicarbonate from the gastrointestinal tract, in addition to hypomagnesemia and hypokalemia are common. When possible once to twice daily monitoring of venous blood gas with electrolytes can help guide necessary supplementation. If a patient has refractory hypokalemia, empiric addition of magnesium in the form of magnesium chloride (0.75 mEq/kg/day IV CRI) should be considered.

- (9) Coagulation: As stated previously, many patients with parvoviral enteritis are hypercoagulable. If hypercoagulability can be demonstrated through use of thromboelastography, vascular thrombosis, or changes in platelet count, APTT or PT, replenishment of coagulation factors in the form of fresh frozen plasma or cryoprecipitate may be warranted.
- (10) Red blood cell count and hemoglobin concentration: Oxygen delivery requires hemoglobin. If red cell mass becomes so diminished from loss in hemorrhagic feces, packed red blood cell or whole blood transfusions may become necessary. In general daily to twice daily monitoring of a patient's packed cell volume is recommended.
- (11) Mentation: Mentation changes secondary to depression, hypoglycemia, pain, and thromboembolic disease should be monitored. If acute changes such as seizures occur in the most critically ill patients, rapid assessment of blood glucose should be performed, and if blood glucose is low, supplementation in the form of a bolus followed by constant rate infusion recommended.
- (12) Renal function and urine output: Renal function and urine output is an end-organ indicator of perfusion as well as fluid balance. Often, patients with parvoviral enteritis have a pre-renal azotemia. Until adequate volume resuscitation and replenishment of dehydration deficits have been performed, renal values will not decline, and the patient will not begin to produce urine. Frequent urination in a patient with normal renal function, combined with appropriate weight gain, supports that fluid therapy is effective at maintaining hydration and perfusion in the face of gastrointestinal losses.
- (13) WBC, immune status, antibiotic dose and selection: Immune status is often severely impaired in patients with parvoviral enteritis. Careful selection of broad spectrum or "four-quadrant" bactericidal antibiotics that will affect gram-positive and -negative, as well as aerobic and anaerobic bacteria should be considered. Common choices include Ampicillin (22 mg/kg IV Q8h), Cefazolin (22 mg/kg IV Q8h) or Unasyn (ampicillin-sulbactam 30 mg/kg IV Q8h) in combination with enrofloxacin (5 – 10 mg/kg IV once daily) are used. Although enrofloxacin has been reported to cause cartilage defects in young dogs, clinically the benefit of covering for gram negative bacterial organisms and gram negative bacterial endotoxin is superior to the perceived low risk of causing cartilage defects in affected patients. In the most severe cases, metronidazole (10 – 15 mg/kg IV Q8- Q12h) can also be added for improved anaerobic coverage. Nephrotoxic aminoglycoside antibiotics are often good choices for gram negative coverage, however, should never be used in a dehydrated or hypovolemic patient. Once rehydrated, if aminoglycoside antibiotics are chosen, daily evaluation of a urinalysis for glycosuria, urinary GGT, and a urine sediment for renal tubular casts should be performed to evaluate for renal tubular damage.
- (14) Drug doses and metabolism: Many patients with parvoviral enteritis are on a large number of drugs. The dose, selection, and route of administration should be evaluated on a daily basis, taking care in particular to avoid administration of drugs that can potentially interfere with each other's mechanism of action or metabolism.
- (15) GI motility and integrity: Gastrointestinal motility and integrity is severely compromised in the patient with parvoviral enteritis. As a result of villous atrophy and necrosis, bacterial translocation into the bloodstream often occurs. In addition, the combination of enterocyte atrophy, blunting of intestinal villi, hypoalbuminemia, vomiting, and ileus leads to nutrient malassimilation. The combination of broad spectrum antibiotics, antiemetic drugs (ondansetron 1 mg/kg IV Q12h, dolasetron 0.6 mg/kg IV Q24h, metoclopramide 1 – 2 mg/kg/day IV CRI, lidocaine 30 mcg/kg/minute, cisapride 0.2 mg/kg PO Q8h, and maropitant 1 mg/kg IV or SQ Q24h) are all used alone and in combination to decrease emesis. Placing a naso-gastric tube can allow for both enteral nutrition, as well as gastric decompression as necessary to help prevent additional vomiting. The presence of gastrointestinal parasites can worsen patient morbidity and response to therapy, so careful evaluation of fecal flotation, smears and with ELISA for giardia, coccidia and other gastrointestinal parasites is necessary. Empiric deworming is recommended in severely affected cases.
- (16) Nutrition: Research has documented that trickle feeding enteral nutrition will decrease enterocyte atrophy and improve patient morbidity and decrease mortality in puppies with parvoviral enteritis, even in the face of vomiting. Calculation of resting energy expenditure (30 x body weight in kilograms + 70 = Kcal/day) and administering a partial or full dose as tolerated is preferable over parenteral nutrition. Parenteral nutrition or partial parenteral nutrition can be administered if the gastrointestinal tract cannot tolerate any form of enteral feeding, or can be used to provide calories in combination to

- trickle feeding small amounts of amino acids and glucose in the patient. As vomiting is controlled, oral feeding of a bland diet is preferable.
- (17) Analgesia and pain control: Cramping and ileus can decrease feeding tolerance. As opioids often can promote ileus at doses necessary to provide analgesia, lidocaine (30 mcg/kg/min) in combination with low doses of a partial mu agonist such as buprenorphine (0.01 mg/kg IV Q8h) may be beneficial in improving patient comfort.
 - (18) Nursing care and patient mobilization: Nursing care and patient mobilization is of paramount importance in maintaining patient cleanliness.
 - (19) Bandage and wound care: Catheter sites should be monitored closely and changed daily to evaluate for catheter thrombosis and contamination.
 - (20) TLC: Is a given, for any critically ill patient

Alternative therapies that have been investigated for use in patients with parvoviral enteritis include the use of anti-endotoxin, hyperimmune serum, antiviral drugs such as oseltamivir, and recombinant human granulocyte colony stimulating factor. In addition to increasing the cost of therapy, none of the aforementioned alternative therapies have been associated with proven benefit in survival or decreasing patient morbidity. More recently, the use of canine specific granulocyte colony stimulating factor was documented to improve neutrophil count and decrease length of hospital stay in puppies with naturally acquired parvoviral enteritis. In addition, feline interferon omega, licensed for use on continents other than North America, has been shown to significantly decrease clinical signs and mortality in naturally infected patients (2.2 units/kg IV once daily for 3 consecutive days). At this time, this drug is not available or approved for use in the United States.

Outpatient therapy for parvoviral enteritis has been described, when client financial constraints prevent hospitalization for standard care. Members of the Small Animal Center for Companion Animal Studies at Colorado State University have developed an outpatient protocol to be used when longer-term hospitalization is not possible. The protocol first administers intravenous crystalloid fluids as boluses to stabilize cardiovascular stability and hypoglycemia. Once more stable, subcutaneous fluids (Normosol-R) is administered three times daily (40 ml/kg/dose), along with analgesia (buprenorphine (0.02 mg/kg SQ Q6-8h), one dose of Cefovacin (8 mg/kg SQ), maropitant (1 mg/kg/day SQ), and rescue antiemetic as needed. Provision of enteral nutrition every 2 – 6 hours has been shown to be effective at further improving outcome.

PREVENTION

Prevention of exposure to parvovirus by decreasing environmental contamination and inducing immunity to infection through use of a low-passage, high titer modified live vaccination is the cornerstone of prevention. Vaccination earlier in life before 6 weeks of age can be counterproductive as maternal antibodies in circulation can interfere with development of an immune response. Starting at 6 to 8 weeks of age, then every 3 weeks through 12 weeks of age, or through 16 weeks of age in predisposed breeds (Rottweiler, Doberman pinscher, pit bull terrier) is recommended. For pregnant, unvaccinated bitches, vaccination with a killed vaccine is recommended. Repeat vaccination should occur at 1 year, then at 3 year intervals in combination with other vaccinations. Although the low-passage, high titer vaccinations with CPV-2b appear to be cross-protective against the newly emerging CPV-2c strain, there have been isolated reports of clinical infection in highly vaccinated dogs. For this reason, CPV-2c infection should remain on the list of differential diagnoses in adult dogs that have been previously vaccinated, with clinical signs of vomiting and diarrhea.

As parvovirus can remain in the environment for up to one year, any infected area should be cleansed thoroughly with soapy water to remove debris, then disinfected with 1 part sodium hypochlorite (bleach) solution to 32 parts water. No new unvaccinated dogs should be allowed into the environment for 1 year after contamination of an area.