**Successful Management Strategies for Canine Parvovirus**

**Indiana Veterinary Medical Association Annual Meeting, 2014**

Karen M. Tefft, DVM, MVSc, DACVIM (SAIM)

Department of Veterinary Clinical Sciences, The Ohio State University, Columbus, OH

**Introduction**

Canine parvovirus (CPV)-2 is one of the most common infectious diseases of dogs and the most prevalent viral cause of diarrhea in dogs. CPV-2 initially emerged in 1978 to a naive canine population and spread rapidly with high morbidity and mortality.\(^1\) It is postulated to have arisen either from feline panleukopenia virus or a wild carnivore parvovirus. Over time, genetic mutations have led to different strains. Strains CPV-2b and CPV-2c are currently the most commonly identified strains in North America.\(^2\) Fortunately, strains differ in only a single amino acid substitution, so ELISA tests are cross-reactive and vaccination provides cross-protection.\(^3,4\)

Most affected dogs are under 6 months of age. Ten to twelve weeks of age is particularly vulnerable due to the waning protective effect of maternally-derived antibodies. Studies have reported a summer seasonality and increased prevalence in Rottweilers, Doberman pinschers, pit bulls, and German shepherds.\(^5\) While genetics appear to play a role in the breed-associated risk for Rottweilers and Doberman pinschers, other factors such as breed popularity and socioeconomic factors likely also contribute to breed associations.

**Diagnosis**

Sudden onset of hemorrhagic diarrhea, fever, and leukopenia in a young, unvaccinated dog is often considered indicative of CPV infection. However, not all dogs with CPV have bloody diarrhea or leukopenia, and other diseases such as parasitic or enteropathogenic bacterial infection can also cause these symptoms. Therefore, definitive diagnosis should be pursued.

Fortunately, practitioners have at their disposal a readily available, easy to use, in-office ELISA test to detect CPV in the feces of infected dogs. These tests are specific, but poorly sensitive for detecting CPV.\(^2\) Viral particles are readily detectable at the peak of shedding (4-7 days post-infection). False negative results may occur if tested early in the disease course, secondary to binding of serum-neutralizing antibodies with antigen in diarrhea or with decline of fecal viral shed (10-12 days post-infection). False positive results may occur after vaccination (3-10 days post-vaccination) with a modified live CPV vaccine.

While the ELISA test is sufficient for the majority of patients, fecal PCR for viral DNA may be performed in a dog with clinical signs and a negative ELISA test. The CPV PCR has a higher sensitivity and specificity than other methods of viral antigen determination in feces.\(^2\) Quantitative assays (real-time PCR) using blood can also provide an estimation of viral load, which can help distinguish vaccination from natural infection.\(^6\)

CPV-2b and 2c pose similar health risks for dogs; therefore, genetic sequencing of CPV to determine strain is not necessary for the clinical management of patients.\(^3\)
Prognostic Indicators
Treatment for CPV infection can be quite costly. This often places the practitioner and the owner in a difficult situation. The mostly likely reason the dog developed CPV infection was due to lack of vaccination. There was no vaccination likely due to financial constraints. Several biomarkers have been investigated to try to give some prognostic information, to help the practitioner and owner decide which patients are most likely to survive. Mortality without treatment is reportedly as high as 91%. However, survival rates with aggressive care can be as high as 64-92%. While some studies have identified leukocyte changes and signs of systemic inflammatory response syndrome (SIRS) at admission correlated with odds of survival, a number of more recent studies have suggested that the optimal time to prognosticate is at the 24 hour mark post-admission.

Hematology
The leukocyte count during CPV infection is classically depressed. This is attributable to destruction of hematopoietic precursor cells within the bone marrow and other lymphoproliferative tissue. This results in inadequate supply for the massive demand of leukocytes (specifically neutrophils) from the inflamed gastrointestinal tract. A lack of leukopenia, specifically the total leukocyte and lymphocyte counts, had a positive predictive value of 100% for survival 24 hours post admission in one study.

Biochemistry
Serum total cholesterol levels were lower in non-survival dogs than in survival dogs in one study evaluating CPV infected dogs with concurrent signs of severe sepsis.

Total and ionized magnesium concentrations were not associated with outcome in CPV infection. This relationship was investigated since total magnesium concentration has been found to be a prognostic indicator in critically ill humans.

Acute Phase Proteins
Acute phase proteins are considered a sensitive biomarker of inflammation. C-reactive protein (CRP) is a major positive acute phase protein, which means its levels increase with inflammation. One study found that serum CRP concentrations greater than 92.4 mg/L at admission had a sensitivity of 91% to predict mortality. A second study evaluated the association of serum CRP concentrations over the course of hospitalization. Their results indicated that higher serum CRP concentrations at 12 and 24 hours after admission were associated with shorter survival times. A CRP concentration cutoff value of 97.3 mg/L at 24 hours after admission had a sensitivity of 86.7% and a specificity of 78.7% to predict death.

Endocrinology
The response of the adrenal and thyroid glands to critical illness is essential for survival. Cortisol is the signature hormone involved in the body's response to inflammation. High serum cortisol and low serum thyroxine concentrations at 24 and 48 hours after admission were associated with death in CPV infection in one study.
**Treatment**

There is no antiviral treatment specific for CPV, therefore the mainstay of treatment is supportive care. The primary goals of supportive care are to restore fluid and electrolyte balance, prevent secondary bacterial infections, and palliate the symptoms of infection.

**Fluid Therapy**

The vast majority of dogs with symptomatic CPV infection are dehydrated. Accurately assessing the degree of dehydration in puppies can be challenging, due to their elastic skin. Intravenous or intraosseous routes for rehydration are most effective. Subcutaneous fluids are only appropriate for the mildest of cases. Subcutaneous fluids are contraindicated in the face of shock as there is inadequate distribution secondary to peripheral vasoconstriction.

A balanced electrolyte solution such as Plasmalyte-148 or Normosol-R is the best initial fluid choice. The rate of administration depends on the status of patient. Patients presenting in shock should receive “shock dosages” of fluids (i.e. 90 ml/kg/hr). Patients not in shock should have their dehydration corrected over the initial 6-12 hours of hospitalization. After dehydration is corrected, ongoing fluid therapy should be calculated based on maintenance rates plus replacement of ongoing losses due to diarrhea or vomiting. Because of their skewed body surface area to body mass ratio compared to adult dogs and their immature nephrons, the maintenance rate fluid for young puppies is greater than that for older puppies or adult dogs. A minimum of 60 ml/kg/day should be considered maintenance in a young puppy; values can exceed 100 ml/kg/day for maintenance in neonates.\(^\text{15}\)

Place the intravenous catheter aseptically and practice good catheter care, examining the catheterization site daily for phlebitis and changing the bandaging as frequently as needed to keep it clean of vomitus and feces. One study found bacteria colonized 22% of catheters placed in young dogs suspected of having CPV.\(^\text{16}\) Most of the bacteria was enteric in origin. Bacterial colonization of indwelling IV catheters is considered a potential precursor of catheter-related infection. Only 1 of the dogs in the study was suspected to have a catheter-related infection. However, given the profound immunosuppression of CPV infected dogs, fastidious catheter care appears to be prudent.

If the patient is anorexic or if hypokalemia is present, potassium chloride should be added to the balanced electrolyte solution after the initial dehydration has been corrected. The following chart gives suggested potassium chloride supplementation rates based on the degree of hypokalemia:

<table>
<thead>
<tr>
<th>Serum K⁺ (mEq/L)</th>
<th>2.0 - 2.5</th>
<th>2.6 - 3.0</th>
<th>3.1 - 3.5</th>
<th>3.6 - 5.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>mEq/L KCl</td>
<td>80</td>
<td>60</td>
<td>40</td>
<td>30</td>
</tr>
</tbody>
</table>

Since fluid rates can be quite high in these patients, ensure that the rate of potassium supplementation does not exceed 0.5 mEq/kg/hr, as rates in excess of this may negatively affect cardiac function.
Hypoglycemia, secondary to sepsis, hypermetabolism, and/or decreased glycogen stores, is commonly observed with CPV infection. After rehydration, 2.5–5% dextrose may be added to the balanced electrolyte solution. Supplementation of concentrations greater than 5% will require placement of a central line, as delivering such a hyperosmolar solution peripherally will lead to phlebitis. Practitioners should be aware of the fact the administration of dextrose supplementation in intravenous fluids does not constitute nutritional support. See discussion of “Nutritional Support” below.

Puppies suffering from CPV often develop a severe protein-losing enteropathy due to the destruction of intestinal villi. Colloidal support (e.g. Hetastarch, Dextrans) should be considered when total protein drops below 35 g/L or if the patient shows evidence of third space loss of fluid (e.g. ascites, edema). Overzealous colloidal therapy should be avoided to prevent blunting of endogenous hepatic albumin production. Dosage of colloidal fluids is 10-20 mL/kg/day. Boluses of 5 mL/kg may be used to treat shock refractory to crystalloid boluses. When administering colloids, the rate of crystalloids administered should be decreased by 30-40%.

Fresh frozen plasma (FFP) transfusion has been recommended in the treatment of CPV for its ability to provide albumin, immunoglobulins, and serum protease inhibitors, which may help to neutralize circulating virus and control the systemic inflammatory response. However, FFP alone is a poor means of supporting patient albumin concentrations; very large volumes of plasma are required to achieve a small increase in plasma albumin. See “Controversial Therapies” below for more discussion regarding the use of FFP in CPV.

**Antimicrobial Therapy**
CPV disrupts the gastrointestinal mucosal barrier, allowing for increased translocation of enteric bacteria. Coupled with the neutropenia experienced by patients with severe CPV infection, the risk of sepsis is high. Mildly affected, afebrile dogs with normal white blood cell counts do not require aggressive combination antibiotic therapy, but dogs with evidence of sepsis should receive bacteriocidal coverage for gram-negative and anaerobic bacteria. The parenteral route is preferred over enteral as CPV-2 infection is often associated with vomiting and delayed gastric emptying which may result in poor absorption of oral medications. A combination of a β-lactam antibiotic (e.g. ampicillin 20 mg/kg IV q 8 hr) with an aminoglycoside antibiotic (e.g. amikacin 20 mg/kg IV q 24 hr) or fluorquinolone antibiotic (e.g. enrofloxacin 5 mg/kg IV q 24 hr) would cover this spectrum. If using an aminoglycoside, do not begin its use until the patient is rehydrated because of the risk of nephrotoxicity with this class of antibiotics. Enrofloxacin has been associated with cartilage abnormalities in growing dogs, so it should be avoided in large and giant breed puppies and owners should be warned of the risk.

**Antiemetic Therapy**
Persistent vomiting leads to fluid and electrolyte loss, interferes with nutritional support, precludes oral administration of medications, and puts the patient at risk for the development of pneumonia and esophagitis. The most commonly used classes of antiemetics for CPV infection are α2-adrenergic antagonists (e.g. chlorpromazine, prochlorperazine), D2-dopaminergic antagonist (e.g. metoclopramide), 5-HT3-serotonergic
antagonists (dolasetron, ondansetron) and NK\textsubscript{1} receptor antagonist (e.g. maropitant). It is not uncommon for multimodal antiemetic therapy to be required for severe cases of CPV enteritis.

The α\textsubscript{2}-adrenergic antagonists (Chlorpromazine: 0.2–0.4 mg/kg SQ, IM q 6-8 hr; Prochlorperazine: 0.1–0.5 mg/kg SQ, IM q 6-8 hr) are phenothiazine derivatives. They limit stimulation of the chemoreceptor trigger zone and emetic center. Their antiemetic effect is potent, however they also can cause sedation and hypotension. They should not be used in dehydrated patients.

Metoclopramide (0.2-0.4 kg/kg SQ, IM q 6-8 hr; 1–2 mg/kg/day IV CRI) blocks the chemoreceptor trigger zone, stimulates and coordinates motility of the upper intestinal tract, and increases pressure in the lower esophageal sphincter. The motility effects of metoclopramide are beneficial to counteract the gastroparesis frequently found in CPV infection; however, it does increase the risk of intussusception. It can also cause extrapyramidal signs (e.g. involuntary muscle spasms, restlessness, aggression). The antiemetic effect of metoclopramide is relatively weak compared to other antiemetics although it appears to perform better as a CRI rather than intermittent injections.

The 5-HT\textsubscript{3}-serotonergic antagonists (dolasetron: 0.5-0.6 mg/kg IV q 24 hr; ondansetron: 0.1–0.3 mg/kg IV q 8-12 hr) limit stimulation of the chemoreceptor trigger zone and vagal afferents. Their antiemetic effect is potent. They appear to be fairly well tolerated by dogs, however they are more expensive than the α\textsubscript{2}-adrenergic antagonists and metoclopramide.

Maropitant (1 mg/kg SQ, IV q 24 hr) limits stimulation of the chemoreceptor trigger zone and emetic center. In addition, it may have some visceral analgesic effects. Its antiemetic effect is potent. It is labeled for dogs older than 8 weeks of age. Other than stinging on SQ injection (which can be decreased by keeping the drug refrigerated), it appears to be fairly well tolerated by dogs. While off label, it can be diluted and given slowly IV. In a study comparing maropitant to ondansetron in dogs infected with CPV, maropitant appeared to be equally as effective in controlling vomiting as compared to ondansetron. In addition, dogs treated with maropitant demonstrated improved ability to maintain body weight.

Gastroprotectant Therapy
Antacids and sucralfate (0.25-0.5 g PO q 8 hr) can be used to treat the gastritis and esophagitis that occurs secondary to CPV infection. While H\textsubscript{2}-receptor antagonists (e.g. famotidine 0.5-1 mg/kg PO, SQ, IV q 12 hr) are less expensive than proton pump inhibitors (e.g. pantoprazole: 0.7–1 mg/kg IV q 24 hr; omeprazole: 0.7–1 mg/kg PO q 24 hr), they are less efficacious. Enteral gastroprotectants should only be used once vomiting is under control.

Analgesic Therapy
Ileus can cause significant visceral pain in CPV patients. NSAIDs are contraindicated for pain management in CPV patients because of their ulcerogenic potential. Also, using NSAIDs in a dehydrated patient increases the risk of acute renal injury. Opioids (e.g. buprenorphine: 0.005–0.02 mg/kg IV q6–12hr; butorphanol: 0.1–0.4 mg/kg/hr IV CRI) are
the preferred class of analgesic, but remain mindful that higher doses may worsen ileus and cause sedation.

**Anthelminthic Therapy**
The presence of intestinal parasites can worsen the disease process by enhancing intestinal cell turnover. Therefore once the patient can tolerate oral medications, deworming (e.g. fenbendazole: 50 mg/kg PO q24hr for 3 doses) is recommended.

**Nutrition**
Early enteral feeding has been shown to help maintain mucosal integrity, which decreases the risk of bacterial translocation. In turn, this leads to faster clinical improvement in patients, significant weight gain, and decreased hospitalization times. Therefore, the old recommendations to keep a CPV patient NPO for 24-48 hours beyond the last instance of vomiting are no longer recommended. Administration of dextrose supplementation in intravenous fluids does not constitute nutritional support. Total or partial parenteral nutrition may be used if a patient absolutely does not tolerate enteral feeding, but meticulous catheter care and monitoring should be performed because of the high risk of sepsis in CPV patients.

To perform enteral nutrition, a nasoesophageal (NE) and nasogastric (NG) tube can be placed with minimal sedation. The benefit of NE tubes is that they do not cross the lower esophageal sphincter, so may cause less gastroesophageal reflux. The benefit of NG tubes is that they allow the practitioner to intermittently measure gastric residual volume. If large residual gastric volumes are consistently measured, a promotility agent (e.g. metoclopramide) should be started. Large residual volumes are defined as greater than 50% of the last volume fed if intermittent bolus feeding or volumes greater than twice what is fed in an hour of CRI feeding. The removal of large residual gastric volumes will also improve patient comfort and nausea.

As the patient recovers, there may be temporary intestinal malabsorption and protein-losing enteropathy until intestinal villi are repaired. Initial feeding should consist of small amounts of an easily digestible low fat diet fed frequently. The normal diet is gradually reintroduced after appetite and stool have returned to normal.

**Controversial Therapies**
Granulocyte colony-stimulating factor (G-CSF) is a cytokine produced by the bone marrow, whose actions include release of granulocytes from the storage pool of the bone marrow, shortened neutrophil maturation time, and enhanced granulopoiesis. Recombinant human G-CSF (rhG-CSF) has been investigated in the treatment of severe neutropenia associated with CPV infection. Results have been mixed. One study demonstrated an increase in the neutrophil count in puppies treated with rhG-CSF during hospitalization. Other investigators have found neither an increase in white blood cell count nor improved survival.

In addition to lack of proven efficacy, one complication associated with the rhG-CSF is the development of neutralizing antibodies, resulting in a decline in leukocyte counts within 3
weeks of treatment. To avoid this issue, a recombinant canine G-CSF (rcG-CSF) has been developed, but it is not commercially available. One study investigating rcG-CSF in CPV patients found significantly higher neutrophil counts in treated dogs and decreased hospitalization time. However, survival times were also decreased in treated dogs. Given the conflicting efficacy reports, expense, and sometimes difficulty in obtaining G-CSF, the speaker does not recommend the use of rhG-CSF or rcG-CSF in the treatment of CPV.

Equine-origin anti-endotoxin serum has also been suggested for treatment of the endotoxia associated with CPV infection. Because this product is of equine origin, it can cause anaphylaxis. Studies investigating its use are conflicting. One study showed a decrease in the mortality rate by 31%. However, another study found an increase in mortality rate when puppies 16 weeks of age or younger were treated with anti-endotoxin serum. Given the conflicting efficacy reports, the speaker does not recommend the use of anti-endotoxin in the treatment of CPV.

Oseltamivir (Tamiflu®) is a neuraminidase (NA) inhibitor originally designed to treat human influenza virus. NA is necessary for liberation of newly formed virions from the host cell and allows virus penetration through the mucin layer covering the respiratory epithelium. Unlike the influenza virus, CPV does not rely on NA for replication. Any beneficial effects oseltamivir may have in CPV infection would not be due to a direct antiviral effect. Some have proposed that NA inhibition could block bacterial penetration through the mucin layer covering the gut endothelium, thus decreasing bacterial translocation. One study did not find a significant improvement in the days hospitalized or outcome; however the oseltamivir treated group did not lose as much weight or have as significant neutropenia as the control group. Given the lack of improvement in outcome, expense, and shortages of the drug during influenza season, the speaker does not recommend the use of oseltamivir in the treatment of CPV.

Plasma from dogs who recovered from CPV infection has been recommended anecdotally to provide passive immunization in affected dogs. In theory, the infused antibodies would neutralize free virus in plasma, impede viral spread by blocking entry into new target cells, and suppress the release of new infectious virions from infected cells. One study did show that passive immunotherapy, performed 24 hours after experimental inoculation with CPV protected from the development of clinical disease. However, a recent study, which evaluated a fixed dose of immune plasma in dogs with naturally occurring CPV infection did not find that it improved clinical signs, reduced viremia or improved hematologic recovery. However, this study had a small sample size, the dose of plasma may have been too low, and the dose may have been administered too late in the disease process. Plasma administration is certainly indicated in CPV puppies with documented hypocoagulability associated with disseminated intravascular coagulation. While the role of plasma for immunoglobulin delivery and serum protease inhibitor replenishment is less well defined, the speaker prefers to use FFP in moderate-to-severe cases of CPV enteritis if finances allow.

Emerging Therapies
Interferons modulate immune function and have antiviral effects. In 2 experimental models of CPV infection, administration of recombinant feline interferon-ω (rFeIFN-ω), for 3 successive days after inoculation with CPV, resulted in a significant reduction in the severity of clinical signs in affected dogs and decreased morbidity and mortality. More recently, administration of rFeIFN-ω (2.5 MU/kg intravenously for 3 consecutive days) to a group of dogs with naturally acquired CPV enteritis resulted in a 4.4-fold overall reduction in mortality. Unfortunately, this promising treatment is not licensed for use in the United States.

**Monitoring**

Monitoring should be performed frequently and treatments (e.g. fluid rate) constantly re-evaluated in light of changing parameters. Complications to be vigilant for in CPV infected patients include intussusception, esophagitis, and aspiration pneumonia. Until the patient begins eating on their own, it is recommended to monitor the following on at least a daily basis: body weight, abdominal palpation, packed cell volume and total solids, white blood cell count (or review of a blood smear for a subjective quantification of leukocyte numbers), blood glucose, serum potassium, and urine specific gravity (which should range from 1.015-1.020 if euhydrated). In small patients such as young toy breeds, you may want to consider using pediatric sampling tubes (aka “avian tubes”) for blood sampling so as to not iatrogenically contribute to anemia.

**Infection Control**

CPV is a non-enveloped virus, which makes it hardy in the environment and resistant to many disinfectants. It can survive in the environment for at least 6 months at room temperature and even longer in the cold. 5% bleach diluted 1:32 or a quaternary ammonium disinfectant (e.g. Parvosol®, Roccal-D®) are effective disinfectants. Soiling with bodily fluids should be cleaned prior to disinfecting a cage or exam table as the presence of organic material diminishes the effectiveness of disinfectants. Disinfectants should have contact for a minimum of 10 minutes to properly kill CPV.

In your hospital, patients with CPV should be isolated and barrier procedures employed. This is to both prevent the spread of CPV in your hospital, but to also protect the patient who is immune-compromised. If you do not have a separate isolation room, tape an isolation perimeter around the cage. Keep a separate trash and laundry stream for the patient. Wear disposable protective clothing (e.g. gloves, apron, overshoes) whenever working with the patient. Remove soiled bedding promptly from the patient’s cage to minimizing the presence of infectious agents and keeping the patient clean, warm and comfortable. Use an antiseptic hand wash and a footbath as you leave the isolation area. Bathe the patient immediately prior to discharge.

**References**