

# Update on Canine Parvoviral Enteritis



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## KEYWORDS

• Parvovirus • Enteritis • Fluid therapy • Outbreak • Outpatient therapy

## KEY POINTS

- Canine parvoviral enteritis remains one of the most virulent and common enteric diseases of dogs worldwide.
- Canine parvovirus is endemic in many environments and can be carried by nonaffected hosts, contributing to spread of disease to domestic animals.
- Vaccination for canine parvovirus can effectively induce protective immunity in most dogs; however, vaccinations administered too early can interfere with maternal antibodies and result in a puppy being more susceptible to infection.
- Treatment currently involves administration of fluid to replenish hydration, early nutritional support, antiemetics, broad-spectrum antibiotics, and empiric deworming. Although inpatient therapy remains the gold standard, outpatient therapy protocols have been documented to have success rates of more than 80% survival.

## PARVOVIRAL ENTERITIS

### *Introduction*

Canine parvoviral enteritis is one of the most common causes of morbidity and mortality in young dogs worldwide.<sup>1</sup> Canine parvovirus belongs to the genus *Protoparvovirus*, family *Parvoviridae*, a single-stranded DNA virus that infects rapidly dividing cells of the gastrointestinal tract, bone marrow, lymphoid tissue, and cardiac myocytes.<sup>2</sup> The origin of canine parvovirus remains unknown. Because canine parvovirus (CPV) shares 98% structural homology with feline panleukopenia virus,<sup>3</sup> 1 theory is that CPV may have resulted from a genetic variant that later became capable of infecting dogs.<sup>4</sup> Because the family *Parvoviridae* is found in other wild mammals, including wild mink, genetic variation from other wildlife<sup>5</sup> may have also played a role in the evolution of CPV-1 and CPV-2.<sup>6,7</sup>

CPV-1, also known as minute virus of canines, was first discovered in the late 1960s as a cause of gastrointestinal and respiratory infection of dogs.<sup>8</sup> One decade later,

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mutation of CPV-1 resulted in a distinctly different variant, CPV-2, and caused the first pandemic outbreak in both adult and young dogs previously naive to CPV.<sup>8</sup> Since the first isolation of CPV-1 and CPV-2, genetic drift during the 1980s has resulted in 2 variants (CPV-2a and CPV-2b), followed by a third variant (CPV-2c) more recently recognized since early 2000. Since the first emergence of CPV-2c in Italy, this isolate has spread worldwide.<sup>9</sup> Despite development and administration of vaccination against CPV-2 strains, the disease is still one of considerable veterinary and economic importance.

### **PATHOPHYSIOLOGY**

CPV-2 strains are exquisitely robust in their strategies for infection in that they can infect mammalian hosts other than domestic dogs (raccoon, cat, coyote, wolves), are ubiquitous in the environment, and can remain viable for more than 1 year under favorable conditions.<sup>1,10</sup> Oronasal exposure and infection occurs in naive or poorly immunized dogs by ingestion of CPV-2 shed in the vomitus or feces of infected animals. The virus then replicates first in oropharyngeal and mesenteric lymph nodes and thymus, with infected animals becoming viremic within 1 to 5 days of exposure.<sup>2</sup> Next, CPV-2 targets rapidly dividing cells of the intestinal epithelial crypts, bone marrow, epithelium of the tongue, oral cavity, and cardiac myocytes, in addition to lung, spleen, liver, and kidneys.<sup>11</sup> Before widespread vaccination of dogs against CPV-2, myocarditis was a common cause of death in infected animals and can still rarely occur today.<sup>11-13</sup> Following exposure and an incubation period that can range from 4 to 14 days, virus shedding usually precedes the onset of clinical signs of vomiting and hemorrhagic diarrhea by several days.<sup>14-16</sup> The intestinal lining becomes denuded as enterocyte turnover is disrupted, resulting in blunting of the intestinal villi, which causes the clinical signs of vomiting and hemorrhagic diarrhea in addition to nutrient malabsorption and enteric bacterial translocation. Viral infection in the thymus results in destruction and collapse of thymic cortex. Along with destruction of leukocyte precursors in the bone marrow, this finding results in significant leukopenia in infected animals.<sup>17,18</sup> The lack of immunity, combined with bacteremia from translocation of gut bacteria, puts affected animals at high risk of developing septic shock, systemic inflammatory response syndrome, multiorgan failure, and death if left untreated.

Rare findings of erythema multiforme,<sup>19</sup> leukoencephalopathy,<sup>20</sup> and porencephaly with periventricular encephalitis<sup>21</sup> in puppies, as well as clinical disease and intracranial abscesses in cats,<sup>22-24</sup> infected with CPV-2 have been documented.

### **DIAGNOSTIC TESTING**

Within 3 days of infection with CPV-2, animals can shed virus in their feces,<sup>25</sup> with peak shedding occurring 4 to 7 days after infection.<sup>26</sup> Accurate detection of viral shedding and infection is paramount to helping decrease spread of disease in veterinary hospitals, shelters, and breeding kennels by isolating infectious animals, because clinical signs are similar in dogs that test positive or negative by fecal enzyme-linked immunoabsorbent assay (ELISA) methodology.<sup>18,27</sup> Methodology to detect CPV-2 infection must therefore be widely accessible and accurate.

Antemortem, CPV-2 can be detected in feces, oropharyngeal swab, or whole blood.<sup>15,28,29</sup> Definitive diagnosis depends on the detection of virus particles in feces or from oropharyngeal swabs using a variety of detection methods that include ELISA, polymerase chain reaction (PCR), electron microscopy, hemagglutination, and virus isolation.<sup>30,31</sup> At this time, DNA-based PCR methods for virus detection are considered the most sensitive and specific but are not immediately available in the clinical

setting.<sup>31</sup> Other methods, such as electron microscopy, hemagglutination, and virus isolation, are only available on a limited basis in specialized laboratories and are not as sensitive as more readily available cage-side ELISA or PCR methods.<sup>31</sup>

The most common method for initial screening and detection of canine parvovirus is the use of a cage-side, in-clinic immunochromatographic ELISA that has a high degree of sensitivity but intermediate to low specificity, compared with molecular methods such as PCR.<sup>18</sup> One study that compared PCR-positive CPV-2a, CPV-2b, and CPV-2c showed that a commonly used cage-side ELISA detected virus only 80.4%, 78.0%, and 77.0% for CPV 2a, CPV-2b, and CPV-2c, respectively.<sup>32</sup> Another study that compared the sensitivity and specificity of cage-side ELISA with PCR found a sensitivity of 81.8%.<sup>30</sup> The sensitivity of detection of both CPV-2b and CPV-2c was not statistically different, indicating that the cage-side ELISA, in addition to PCR, can detect the CPV-2c strain. The sensitivity and specificity of a second cage-side ELISA<sup>2</sup> compared with hemagglutination and PCR determine a sensitivity of 86.3% for ELISA and 65.3% for hemagglutination compared with PCR (100% sensitivity) for all CPV-2 strains.<sup>31</sup> A third cage-side ELISA test<sup>3</sup> was compared with PCR, and again showed lower sensitivity (76.5%) that seemed to decrease with storage time, but high specificity.<sup>33</sup> For all ELISA-positive animals with clinical signs of infection, the high specificity indicates that the animals should be considered true positive for means of isolation from other animals. Recent vaccination with modified live virus can result in false-positive results within 10 days; however, in puppies with clinical signs of vomiting and diarrhea who have been recently vaccinated, most cases are from true infection with field CPV strain or other gastrointestinal infection, rather than the vaccine itself.<sup>34</sup>

There are many reasons that fecal ELISA testing can be falsely negative. Investigation of fecal CPV viral load, serum antibody titers, and time of clinical signs to testing were compared, and dogs that had false-negative fecal ELISA characteristically were presented for evaluation earlier in the course of illness, had lower fecal virus loads, and had decreased frequency of defecation and higher serum antibody titers compared with dogs that tested CPV positive by fecal ELISA.<sup>27</sup> Fecal samples must contain a minimum of  $10^6$  copies of DNA per milligram of feces to test positive by ELISA methods.<sup>31</sup> CPV antibodies within the gastrointestinal tract can sequester virus particles and make them unavailable for detection by ELISA.<sup>35-37</sup> Fecal testing for parvovirus is warranted in any puppy with clinical signs of vomiting and diarrhea. If an animal tests negative by fecal ELISA and there is concern for infection of other animals in breeding kennels or shelters, additional testing by PCR should be considered.

## CLINICAL SIGNS AND ADDITIONAL DIAGNOSTIC TESTING

In addition to fecal testing, physical examination findings, patient signalment, and clinician index of suspicion and other diagnostic testing can be supportive of but not pathognomonic for CPV infection. The most common clinical signs of parvoviral enteritis are lethargy, inappetence, vomiting, and diarrhea. The diarrhea can vary in appearance from soft to mucoid to liquid and hemorrhagic. Sloughing of the intestinal mucosal lining can give a red gelatinous appearance to the feces. With gastrointestinal fluid losses, interstitial dehydration that progresses to hypovolemic shock can occur quickly. Lack of enterocyte nutrient absorption, systemic bacteremia, and lack of sufficient hepatic and muscle glycogen stores also can result in significant hypoglycemia with neuroglycopenia and seizures. In addition, systemic inflammation and bacteremia can result in septic shock with hypotension and organ failure.

The severity of clinical signs can vary with age, protective antibody titer, and duration of illness. The diagnostic accuracy of using clinical signs and physical examination

alone to make a presumptive diagnose of parvovirus is only 58%. The index of suspicion can increase based on an individual patient's age and vaccination status. In addition to the clinical signs listed earlier, physical examination can reveal mucosal pallor, delayed capillary refill time, fever or hypothermia, and abdominal discomfort. Small intestinal intussusception can occur and create a painful, firm, tubular soft tissue mass effect found on abdominal palpation.<sup>38,39</sup> The presence and severity of clinical signs can be predictive of the length of time required in hospital.<sup>40</sup>

### COMPLETE BLOOD COUNT

Total white blood cell count and the presence of leukopenia have previously been considered to be a hallmark in patients with CPV because the virus attacks actively replicating cells of the bone marrow, thymus, and other lymphoid tissues. Lymphopenia can occur in puppies infected with CPV as well as puppies affected with canine coronavirus,<sup>41</sup> so is used along with other testing to further support a diagnosis of CPV in affected patients. The presence of cytopenia during the course of illness can be useful for predicting outcome in CPV. One study documented no significant difference in neutropenia between survivors and nonsurvivors with CPV.<sup>42</sup> The same study found that maintenance of total leukocyte count greater than 4500/ $\mu$ L and a lymphocyte count greater than 1000/ $\mu$ L at the time of admission and through 48 hours of hospitalization were strongly predictive of survival.<sup>42</sup>

### DIAGNOSTIC IMAGING

Diagnostic imaging is largely nonspecific for animals afflicted with CPV. Early in the course of illness, abdominal radiographs may appear normal, then develop radiographic signs of ileus with gas or fluid distension of the small intestine.<sup>43</sup> Findings of abdominal ultrasonography in 40 puppies with confirmed CPV infection were nonspecific, with signs of gas and fluid distension of all areas of the stomach and the small and large intestine, ileus with ineffective peristalsis, anechoic peritoneal effusion, in addition to a corrugated appearance to the duodenum with hyperechoic speckling.<sup>44</sup> However, ultrasonography is useful to rule out other causes of vomiting and diarrhea, such as gastrointestinal foreign body, obstruction, or intussusception, in animals with intractable discomfort or severe vomiting despite administration of antiemetic drugs. The degree of ultrasonographic abnormalities is positively correlated with the severity of illness in dogs with CPV.<sup>44</sup>

### ENDOCRINE AND OTHER BIOMARKERS IN CANINE PARVOVIRUS INFECTION

Other researchers have investigated a variety of clinicopathologic biomarkers in dogs infected with CPV. As observed with other critical illnesses, animals infected with CPV have augmented stress response and cortisol concentrations and develop euthyroid sick syndrome, which can be predictive of mortality at 24 and 48 hours of hospitalization.<sup>45,46</sup> In naturally occurring infection, endogenous canine granulocyte colony-stimulating factor (G-CSF) levels have been found to be increased during the period of time that the animal is neutropenic.<sup>47</sup> This finding was extrapolated to consideration for use of G-CSF as a treatment of neutropenia in affected animals and is discussed later. Serum magnesium levels are often decreased, as is found in other critical illness in dogs; however, this finding is not correlated with disease outcome.<sup>48</sup> C-reactive protein,<sup>49,50</sup> total cholesterol, high-density lipoprotein, serum triglyceride,<sup>51</sup> lipid peroxidase, zinc,<sup>52</sup> pancreatic lipase, and plasma citrulline levels<sup>53–55</sup> have also been documented to change in response to CPV infection. The tests are not useful

alone in predicting morbidity or mortality and are not easily available as cage-side tests; however, they may be predictive of the severity of infection.<sup>45,49,50</sup> In addition, the presence of inflammatory biomarkers as well as vascular endothelial damage, systemic inflammation, activation of coagulation, along with hypovolemia often predispose patients to a hypercoagulable state.<sup>56</sup> This possibility can be a factor in maintenance of intravenous (IV) catheters and the development of thrombophlebitis as well as contributing to end-organ damage in the most severe cases.

## TREATMENT

Treatment of parvoviral enteritis largely is supportive until clinical signs of vomiting and diarrhea resolve. In general, improvement in clinical signs often correspond with rebound in leukocyte count; however, development of adverse sequelae such as aspiration pneumonia, ongoing hypoglycemia, hypoalbuminemia with edema, or intussusception can result in higher morbidity and increased length of hospitalization. One of the primary challenges and limiting factors for client owners in the treatment of parvovirus is the cost of hospitalization and treatment. Clusters of cases of parvovirus have been documented in socioeconomic underprivileged areas,<sup>57–59</sup> highlighting perhaps a lack of education and financial opportunity for vaccination, making these puppies at higher risk of contracting the disease. The decision whether to admit an affected animal to the hospital to receive gold-standard versus outpatient therapy or euthanasia is largely based on the client's ability and willingness to pay for the cost of care.

## VASCULAR ACCESS AND FLUID THERAPY

The most aggressive therapy that involves administration of IV fluids to restore intravascular fluid volume status, replenish interstitial fluid losses, and maintain hydration is the gold standard of care for treatment of CPV. Ancillary therapies that minimize fluid loss in the form of antiemetics and gastroprotectant agents, provide analgesia and nutrition, and prevent secondary bacterial infection with antibiotics also are important factors for the best patient outcome. The mainstay of fluid therapy first involves establishing vascular access. In the most hypovolemic or interstitially dehydrated patients, this can sometimes be challenging, and may require placement of an intraosseous catheter or vascular cutdown. Because of the high risk of contamination of a catheter with vomitus and feces, placement of a jugular catheter is preferred. Jugular catheter placement not only provides a means of administration of IV fluids but can also allow for blood sample collection for glucose, acid-base, and electrolyte monitoring without the need for repeated percutaneous venipuncture. In the most hypovolemic patients, intraosseous access can be quicker with the same degree of success of jugular catheter placement,<sup>60</sup> and should be considered in the interest of time to start volume resuscitation strategies. When necessary, any fluid that can be administered intravenously can also be administered through an intraosseous catheter.<sup>61,62</sup>

Once vascular access is achieved, a balanced isotonic crystalloid fluid should be administered. The initial volume and rate of fluid administration largely depend on the degree of interstitial dehydration and whether hypovolemia is present. If a patient is showing clinical signs of hypovolemia (tachycardia or bradycardia, hypothermia, delayed capillary refill time, hypotension), IV fluid should be administered in incremental boluses (20 mL/kg) as quickly as possible while monitoring the perfusion parameters discussed earlier for normalization.

Once intravascular volume status has been restored, interstitial fluid losses can then be replenished. Despite some veterinarians' practice of multiplying a patient's maintenance fluid requirements by an arbitrary factor of 1.5 or 2 to replace interstitial fluid

deficits, this practice often underestimates the needs of individual patients, particularly when ongoing losses are present. A more accurate and recommended approach is to calculate the patient's interstitial hydration deficit and replace that over the next 12 to 24 hours, taking care to also consider the maintenance fluid requirements and ongoing losses. A simple method of monitoring fluid loss is to weigh the patient frequently, because 1 g of body weight is equal to 1 mL of fluid lost. Once intravascular and interstitial volume have been restored, ongoing fluid gain or loss is equal to the patient's body weight, provided that third spacing of fluid is not occurring.

In addition to provision of fluid, crystalloid fluids can be used to help restore acid-base and electrolyte derangements observed in patients with CPV enteritis. Although most patients have normal acid-base status, the degree of hydrochloric acid loss in the vomitus can cause a hypochloremic metabolic alkalosis to develop.<sup>34</sup> Potassium<sup>63</sup> can be supplemented based on the individual patient's serum potassium concentration.<sup>64</sup> Hypoglycemia is common. Serum glucose concentration should be monitored frequently and supplemented as needed. If serum glucose level decreases to less than 60 mg/dL, administration of an IV (or intraosseous) dextrose (VetOne Dextrose 50%, Nova-Tech, Inc., Grand Island, NE) bolus (1–2 mL/kg 25% dextrose) should be administered, followed by addition of 2.5% to 5% dextrose in the crystalloid fluids.

### ONCOTIC SUPPORT

Fluid loss in diarrheic feces, along with lack of enteral intake of nutrients and production of acute phase proteins in preference to albumin synthesis, all can result in significant hypoproteinemia in patients with CPV enteritis. The decision to provide oncotic support in the form of either natural or synthetic colloids usually depends on clinician preference, product availability, and patient size and need. Patient morbidity and mortality can increase when serum albumin concentration decreases to less than 2.0 g/dL.<sup>65</sup> Albumin also contributes to free radical scavenging and drug transport, making albumin replacement essential in puppies with CPV. Albumin can be restored by administration of either fresh or fresh-frozen plasma or concentrated albumin products. Roughly 20 mL/kg of plasma must be administered to increase serum albumin concentration by 0.5 g/dL. Anecdotal reports suggest that administration of fresh-frozen plasma (6.6–11 mL/kg IV or intraperitoneal, 3 doses administered 12 hours apart) may be prophylactic at preventing severe infection in exposed dogs.<sup>66</sup> Canine-specific albumin concentrate (Virbagen Omega, feline omega-interferon, Virbac Animal Health, Carros, France) is also available for administration and is a cost-effective method of restoring serum albumin without significant risk of immune stimulation observed with administration of concentrated human albumin products.<sup>67–69</sup> If further oncotic support is required, hydroxyethyl starch (20–30 mL/kg/d) can be administered, depending on clinician preference.

### ANTIEMETICS

In addition to fluid therapy and enteral nutrition, the use of antiemetics is important in decreasing vomiting in patients with CPV. One prospective study that investigated antiemetic use in puppies with CPV enteritis documented an increased length of hospital stay in patients who did not receive antiemetics.<sup>70</sup> A randomized, prospective study that compared the use of metoclopramide (0.5 mg/kg IV every 8 hours), ondansetron (0.5 mg/kg IV every 8 hours), and maropitant (1 mg/kg subcutaneously every 24 hours) showed that all antiemetics were equally successful at reducing the number of vomiting events.<sup>71</sup> In contrast with the first study,<sup>70</sup> the second study<sup>71</sup> documented that the use of antiemetics decreased the number of vomiting events on day 1 and

from day 3 onward. Another study<sup>72</sup> showed no difference in the duration of hospitalization, need for rescue antiemetics, duration of vomiting, or days to voluntary food consumption in puppies with CPV treated with ondansetron (0.5 mg/kg IV every 8 hours) or maropitant (1 mg/kg IV every 24 hours).

## ANTIMICROBIAL USE

Patients with CPV enteritis are at high risk of bacterial translocation from intestinal villous collapse and lack of protective immune function. A variety of bacteria (*Escherichia coli*, *Clostridium difficile*, *Salmonella* spp) have been documented in septic patients with CPV enteritis.<sup>73–77</sup> Broad-spectrum antibiotics are recommended in all CPV-affected patients (Table 1). Ongoing fluid losses from vomiting and diarrhea, combined with the potential for hypotension and sepsis, make dogs with CPV enteritis at high risk of developing acute kidney injury (AKI). A study that investigated routine use of blood urea nitrogen (BUN), creatinine, urine specific gravity (SpGr), and urine protein/creatinine ratio (UPC) in dogs with CPV enteritis showed no change in BUN and creatinine; however, UPC and SpGr were higher compared with healthy controls. Other biomarkers of glomerular injury and renal tubular injury were significantly increased, showing occult AKI in dogs with CPV.<sup>78</sup> Because there are numerous other broad-spectrum antimicrobial combinations for use in patients with CPV enteritis, aminoglycoside antibiotics that have the inherent risk of nephrotoxicity are not recommended.

Puppies with CPV enteritis often have comorbidities, including gastrointestinal parasitism. With this in mind, antiparasite therapy should be initiated as soon as the puppy can tolerate oral therapies<sup>79</sup> (Table 2).

## ENTERAL NUTRITION

Enteral nutrition is essential to help prevent enterocyte atrophy and to provide nutrients required for healing. Early provision of enteral nutrition in puppies with CPV enteritis was found to decrease patient morbidity and length of hospital stay.<sup>80</sup> A variety of formulae exist for calculation of resting energy expenditure (REE). A simple, linear formula for calculation of an individual patient's energy needs is  $REE = \text{Kcal/d} = (30 \times BW_{\text{kg}}) + 70$ , where  $BW_{\text{kg}}$  is body weight in kilograms. Because individual patients' REEs can vary from day to day during the course of hospitalization,<sup>81</sup> multiplication of arbitrary illness, injury, and infection factors is not accurate and is not generally recommended. Placement of a nasogastric tube in patients with CPV can be a means of provision of enteral nutrition as well as allowing for gastric suctioning

**Table 1**  
Antibiotic choices for use in inpatient and outpatient treatment protocols for canine parvoviral enteritis

Antibiotic	Dose (mg/kg)/Route/Frequency	In/Outpatient
Ampicillin	20–40/IV/Q 8 h	Inpatient
Ampicillin-sulbactam	30–50/IV/Q 6–8 h	Inpatient
Cefovecin	8/SQ/once	Outpatient
Cefoxitin	20–30/IV/Q 8 h	Inpatient
Enrofloxacin	10/IV/Q 24 h	Inpatient
Metronidazole	10/IV/Q 8 h	Inpatient

Abbreviations: Q, every; SQ, subcutaneous.



<b>Drug</b>	<b>Dosage</b>	<b>Efficacy Against</b>
Pyrantel pamoate	5–10 mg/kg PO Q 24 h Repeat in 7–10 d	<i>Toxocara canis</i> <i>Ancylostoma spp</i>
Fenbendazole	50 mg/kg PO Q 24 h for 3–5 d	<i>Giardia duodenalis</i> <i>Ancylostoma spp</i> <i>Trichuris vulpis</i> <sup>a</sup> <i>T canis</i>
Sulfadimethoxine	50–60 mg/kg PO Q 24 h for 5–20 d	<i>Isospora spp</i>
Metronidazole	10–30 mg/kg PO Q 12 h for 5–7 d	<i>G duodenalis</i>

Abbreviation: PO, by mouth.

<sup>a</sup> For *T vulpis*, repeat dose of fenbendazole 3 weeks then 3 months after first therapy.

to prevent abdominal discomfort and vomiting or regurgitation. A recent article<sup>82</sup> documented little to no change in acid-base status in patients whose treatment protocols included gastric suctioning. Liquid enteral diets can be started at 25% of a patient's REE and administered either in intermittent boluses or as constant-rate infusions, depending on clinician preference and hospital resources. Other studies have documented that the use of an (Hydroyte Advanced Nutritional Support, Hormel Health Labs, Austin, MN.) or commercially available enteral nutrition product (Viyo Recuperation, Viyo International, Antwerp, Belgium.) is palatable and can be voluntarily consumed by some puppies during their recovery period, and this may be beneficial in increasing caloric intake and influence the return of appetite.<sup>83,84</sup> Because aggressive early interventional nutrition is beneficial and the preferred method of providing calories and nutrients to patients infected with CPV, parenteral nutritional strategies are no longer needed.<sup>1</sup>

## ANALGESIA

Many patients with CPV infection show abdominal discomfort caused by vomiting, ileus, and possible intussusception.<sup>1</sup> Opioid analgesics can promote ileus and vomiting. Partial agonists such as buprenorphine (0.01–0.02 mg/kg IV every 8 hours) or an agonist-antagonist such as butorphanol (0.1–0.2 mg/kg/h) may be preferred to pure mu agonists such as methadone (0.1–0.2 mg/kg IV every 6 hours), morphine (0.1–0.2 mg/kg IV, intramuscularly [IM], or subcutaneously every 8 hours), hydromorphone (0.1 mg/kg IV or IM every 8 hours), or fentanyl (1–5 µg/kg/h IV continuous-rate infusion [CRI]). Lidocaine (15–30 µg/kg/min IV CRI) can promote gastrointestinal motility and also provide some degree of analgesia. In addition to its actions as a centrally acting antiemetic, maropitant, a neurokinin-1 receptor antagonist, functions to provide visceral analgesia in puppies with CPV enteritis.<sup>85</sup> Alpha-2 agonists, which can promote extreme vasoconstriction and limit gastrointestinal perfusion, and nonsteroidal antiinflammatory drugs, which can impair gastrointestinal and renal perfusion, are both contraindicated.

## MONITORING

Monitoring of patients with CPV involves careful and frequent assessment of their interstitial and intravascular volume status, blood pressure, blood glucose levels,



acid-base and electrolyte status, level of comfort, and degree of nausea. By using Kirby's Rule of 20 monitoring,<sup>86</sup> clinicians can use a checklist to monitor the patient's status without overlooking important consideration of aspects of care (**Box 1**).

## OUTPATIENT TREATMENT

The prognosis for animals infected with CPV is dismal without treatment. Because cost of hospitalization and therapy is a limiting factor that can influence patients' outcomes, recent prospective and retrospective studies have documented a 75% to 80% survival using outpatient strategies for CPV infection.<sup>87,88</sup> The similarities for both studies include the need for hydration in the form of subcutaneous fluids, use of an antiemetic, and essential need for enteral nutrition. The prospective study<sup>88</sup> recommends placement of an IV catheter, then to administer IV crystalloid fluid (15–45 mL/kg) until perfusion parameters (heart rate, capillary refill time, pulse quality, mentation, serum lactate concentration, and body temperature) normalize. When present, hypoglycemia was corrected using IV dextrose (25%, 1–2 mL/kg). Once intravascular volume status and perfusion had been restored, affected puppies received 1 dose of cefovecin (8 mg/kg subcutaneously), maropitant (1 mg/kg subcutaneously every 24 hours), buprenorphine (0.02 mg/kg subcutaneously), high-fructose corn

### Box 1

#### Kirby's Rule of 20

1. Fluid balance
2. Oxygenation and ventilation
3. Blood pressure and perfusion
4. Heart rate, rhythm, and contractility
5. Glucose
6. Body temperature
7. Albumin/oncotic pressure
8. Electrolytes
9. Mentation
10. Hemoglobin/red blood cell mass
11. Gastrointestinal integrity and motility
12. Nutrition
13. Renal function
14. Coagulation
15. Immune status, antibiotic dose and selection
16. Drug doses and metabolism
17. Wound care and bandages
18. Pain control
19. Nursing care
20. Tender loving care

A checklist to use for treatment and monitoring of critical animals, including those with parvoviral enteritis.

syrup, a commercially available diet<sup>89</sup> (1 mL/kg by mouth every 6 hours), oral potassium supplementation, and subcutaneous fluids (30 mL/kg crystalloid every 6 hours). Dedicated owners whose financial limitations preclude inpatient therapy can be instructed how to administer subcutaneous fluids and other medications at home with a moderately good chance of success.

### ANCILLARY THERAPIES

Discovery of viral replication strategies, immunosuppression, failure of protective immunity, presence of biomarkers and inflammatory cytokines, bacterial endotoxin, and disruption of the fecal microbiome have led to investigative strategies to improve outcomes in patients with CPV enteritis.

### ANTIVIRAL STRATEGIES

Oseltamivir, an antiviral drug used primarily for the treatment of human influenza, is a neuraminidase inhibitor that has been studied in puppies with CPV enteritis.<sup>90,91</sup> Although 1 study documented increased body weight and maintenance of white blood cell counts in oseltamivir-treated animals,<sup>90</sup> neither study documented a decrease in morbidity, length of hospitalization, or mortality.<sup>90,91</sup> The role of interferons as a possible antiviral therapy has been investigated for dogs with CPV enteritis. Recombinant feline omega-interferon ( $1-5 \times 10^6$  IU/kg/d IV for 3 days) has been shown to decrease the incidence of fever, vomiting, diarrhea, and mortality and to improve appetite.<sup>92-95</sup> The drug is not currently approved for use in the United States, but is available for use in Europe and Australia.

### IMMUNE PLASMA

The decline in circulating antibodies derived from maternal passive immunity is a significant contributing factor in the risk of contracting CPV infection. Antibodies that bind with and attack cells, effectively decreasing infection and ability to replicate.<sup>96</sup> Strategies to increase circulating antiparvovirus antibodies have been investigated as a potential therapy.<sup>96-99</sup> Administration of canine CPV-hyperimmune plasma immediately after CPV inoculation to experimentally infected dogs effectively decreased the incidence of vomiting and diarrhea and improved survival.<sup>97,98</sup> In a randomized prospective study, a single dose of 12 mL of immune plasma obtained from dogs that survived natural infection with CPV was not successful at improving white blood cell count or weight, or decreasing viremia or length of hospital stay.<sup>96</sup> Feline antiparvovirus antibodies, too, failed to decrease gastrointestinal signs, fecal viral load and shedding, duration of hospitalization, morbidity, or mortality.<sup>100</sup> Lyophilized immunoglobulin G has been documented in 1 study to decrease clinical signs and length of hospital stay in naturally occurring CPV enteritis.<sup>99</sup> Despite inconclusive findings of parenteral administration of immune plasma, early enteral administration of CPV antibodies has been shown to be effective at reducing clinical signs in puppies with experimental CPV infection, suggesting that early administration of antibodies may be effective at reducing the risk of infection in exposed animals before the onset of clinical signs.<sup>101</sup>

### GRANULOCYTE COLONY-STIMULATING FACTOR

Leukopenia is an important contributor to impaired immune function and morbidity associated with bacteremia in dogs with CPV infection. Increases in endogenous concentrations of canine G-CSF (cG-CSF) have been documented to improve neutrophil

counts in puppies with experimental parvoviral infection.<sup>47,102–106</sup> Human G-CSF (hG-CSF)<sup>102–104</sup> and cG-CSF<sup>105,106</sup> have been investigated to promote bone marrow stimulation and release of neutrophils. Although 1 study<sup>102</sup> did show that the use of recombinant hG-CSF improved neutrophil counts in a small population of puppies infected with parvovirus, other studies showed no improvement in neutrophil count, length of hospitalization, or survival.<sup>104,105</sup> Two studies have shown that canine-specific G-CSF (5 µg/kg recombinant cG-CSF [recombinant canine Granulocyte-Colony Stimulating Factor] once daily) is effective at statistically increasing white blood cell and neutrophil count,<sup>105</sup> as well as monocyte and lymphocyte counts.<sup>106</sup> Despite these findings, the use of rcG-CSF may not necessarily improve survival.<sup>105</sup>

## FECAL TRANSFAUNATION

The fecal microbiota has multipurpose benefits for the host, including enterocyte nutrition, protective barrier function, immune regulation, and gastrointestinal motility.<sup>107</sup> Disruption of host fecal bacteria and the microbiota occurs in acute gastroenteritis, including that observed with CPV enteritis.<sup>108</sup> Administration of probiotics to puppies with CPV has shown improved clinical scoring with respect to degree of dehydration, incidence of vomiting and diarrhea, fecal scoring, and appetite,<sup>109</sup> although a second study showed no benefit with respect to length of hospital stay or case fatality.<sup>110</sup> Other methods of restoring fecal microbiota include transfaunation, or administration of fecal transplants from a healthy host to animals with acute hemorrhagic diarrhea. A recent study that investigated rectal administration of 10 g of feces from a healthy canine donor, diluted in 10 mL of sterile 0.9% saline, to puppies with CPV enteritis showed earlier onset of resolution of diarrhea, decreased length of hospital stay, and improved survival in the fecal transplant group.<sup>107</sup>

## PREVENTION

Subclinical infection in both wild and domestic dogs that shed virus in their feces can represent a significant potential source of infection to other dogs, particularly in crowded or unsanitary conditions such as shelters or some breeding kennels.<sup>75</sup> Dilute 0.75% sodium hypochlorite solution on environmental surfaces is effective at significantly reducing spread of CPV within crowded areas such as veterinary hospitals and shelters.<sup>111</sup> The only method of preventing infection is to isolate at-risk puppies from exposure to CPV. Client education to avoid exposure of at-risk puppies to other dogs until the puppy has received its full series of vaccinations is of paramount importance, because well-vaccinated adults with normal feces can still shed CPV virus and be a potential source of exposure. Within shelters and veterinary hospitals, personnel should adhere to careful handwashing and wearing of new gloves between each patient. Clothing, instrumentation, and environment such as thermometers, stethoscopes, fluid pumps, tables, cages, and bedding should be carefully cleaned and disinfected on a regular basis with a detergent and virucidal solutions that are effective at deactivating CPV. In any diarrheic patient, even with a negative fecal ELISA, barrier methods with disposable gloves, cap, gown, and booties should be worn when handling the patient to prevent cross-contamination and spread of infection.

## VACCINATIONS

In addition to strict hygiene strategies, the most effective method of preventing CPV infection and disease is through careful and strategic inoculation with the development of protective antibodies. Dogs of any age and breed can be infected

with parvovirus, but puppies between the ages of 6 and 16 weeks seem to be the most susceptible.<sup>1</sup> Young puppies that are born to and allowed to nurse colostrum from vaccinated bitches have maternally derived passive immunity.<sup>112</sup> As maternally derived antibody levels start to decrease at 8 to 12 weeks of age, neonates are at a higher risk of infection.<sup>8,26</sup> Earlier decreases in maternally derived antibodies can occur if maternal antibody dose is low. Vaccination strategies are therefore directed at stimulating innate immunity by administration of a series of vaccinations during the time period that maternal antibody is waning. In young animals, maternally derived antibodies can interfere with vaccine-induced protective antibodies,<sup>6</sup> particularly between 49 and 69 days of age. For this reason, the timing of vaccinations is important when considering a protocol to help prevent infection in puppies. Current vaccination guidelines recommend vaccination using a high-titer, low-passage, modified live vaccination starting at 6 weeks of age and repeated every 3 to 4 weeks through 16 weeks of age. For dogs with significantly increased risk of exposure (eg, those in shelters), vaccination as early as 4 weeks through 18 to 20 weeks of age may be recommended.<sup>113</sup> One study documented that even 1 vaccination can decrease the risk of developing CPV enteritis by 2.3 times.<sup>40</sup> Current vaccinations impart protective immunity against CPV-2, CPV-2b, and CPV-2c strains.<sup>114–117</sup> A booster vaccination is recommended at 1 year of age, then every 3 years.

Vaccination failure has been documented in both young and adult dogs. A recent study documented a high prevalence of CPV-seronegative dogs admitted to a veterinary critical care unit, despite receiving recent vaccination according to standard guidelines.<sup>118</sup> Others have reported lack of protective immunity in dogs that received the recommended series of vaccinations through adulthood but developed infection and were able to shed virus in their feces, posing a risk to other dogs.<sup>119,120</sup> Despite vaccination, animals with rare contact with other dogs also may have inadequate CPV antibodies, although this does not necessarily reflect an increased risk of infection.<sup>121</sup> CPV should be considered as a possible differential diagnosis in adult animals with clinical signs of gastroenteritis with no other cause. Dogs that test positive may lack the ability to develop protective immunity from routine vaccination or exposure and should be culled from breeding populations.

## PROGNOSIS

The prognosis for survival often depends on the severity of clinical signs at the time that therapy is initiated. Clinical signs indicating hypovolemia and poor perfusion and fever, along with low protein C level, increased cortisol level, low thyroxine level, lymphocyte count less than 1000/ $\mu$ L, and hypoalbuminemia have been associated with increased mortality.<sup>40</sup> Lymphopenia and hypoalbuminemia at the time of admission have been associated with increased length of hospitalization.<sup>40</sup> Overall, the prognosis for survival ranges from 60% to 90%, depending on the study, type of therapy, and individual patient response to treatment.<sup>36,40,122,123</sup> Comorbidities such as canine coronavirus and gastrointestinal parasitism also increased patient morbidity and mortality. Recent outpatient strategies<sup>88</sup> have improved outcomes when client financial limitations prevent hospitalization and aggressive care. Without therapy, prognosis is grim, with death occurring in more than 90% of patients.<sup>36</sup>

## DISCLOSURE

The author has nothing to disclose.

## REFERENCES

1. Mylonakis ME, Kalli I, Rallis TS. Canine parvoviral enteritis: an update on the clinical diagnosis, treatment and prevention. *Vet Med* 2016;11(7):91–100.
2. Goddard A, Leisewitz AL. Canine parvovirus. *Vet Clin North Am Small Anim Pract* 2010;40(6):1041–53.
3. Chang SF, Sgro JY, Parrish CR. Multiple amino acids in the structure of canine parvovirus coordinately determine the canine host range and specific antigenic and hemagglutination properties. *J Virol* 1992;66:6858–67.
4. Ohshima T, Mochizuki M. Evidence for recombination between feline panleukopenia virus and canine parvovirus Type 2. *J Vet Med Sci* 2009;71(4):403–8.
5. Wang J, Cheng S, Yi L, et al. Evidence for natural recombination between mink enteritis virus and canine parvovirus. *Virol J* 2012;30(9):252.
6. Pollack RV, Carmichael LE. Canine viral enteritis. In: Barlough JE, editor. *Manual of small animal infectious diseases*. London: Churchill Livingstone; 1988. p. 101–7.
7. Kramer JM, Meunier PC, Pollack RV. Canine parvovirus: update. *Vet Med Small Anim Clin* 1980;75(10):1541–55.
8. Lamm CG, Rezabek GB. Parvovirus infection in domestic companion animals. *Vet Clin North Am Small Anim Pract* 2008;38:837–50.
9. Decaro N, Desario C, Addie DD. The study of molecular epidemiology of canine parvovirus Europe. *Emerg Infect Dis J* 2007;13:1222–4.
10. Sykes JE. Canine parvovirus infections and other viral enteritides. In: Sykes JE, editor. *Canine and feline infectious disease*. 1st edition. St Louis (MO): Elsevier; 2014. p. 141–51.
11. Ford J, McEndaffer L, Renshaw R, et al. Parvovirus infection is associated with myocarditis and myocardial fibrosis in young dogs. *Vet Pathol* 2017;54(6):964–71.
12. Strom LM, Reis JC, Brown CC. Parvoviral myocarditis in a dog. *J Am Vet Med Assoc* 2015;246(8):853–5.
13. Sime TA, Powell LL, Schildt JC, et al. Parvoviral myocarditis in a 5-week-old dachshund. *J Vet Emerg Crit Care (San Antonio)* 2015;25(6):765–9.
14. Decaro N, Desario C, Campolo M, et al. Clinical and virological findings in pups naturally infected with canine parvovirus type 2 Gluc-426 mutant. *J Vet Diagn Invest* 2005;17(2):133–8.
15. Smith-Carr S, Macintire DK, Swango LJ. Canine parvovirus: Part I Pathogenesis and vaccination. *Comp Cont Educ Pract* 1997;19(2):125–33.
16. McCaw DM, Hoskins JD. Canine viral enteritis. In: Green CE, editor. *Infectious diseases of the dog and cat*. 4th edition. St Louis (MO): Saunders; 2006. p. 63–73.
17. Pollack RV. Experimental canine parvovirus infection in dogs. *Cornell Vet* 1982;72:103–19.
18. Decaro N, Buonavoglia C. Canine parvovirus – a review of the epidemiological and diagnostic aspects, with emphasis on type 2c. *Vet Microbiol* 2012;155:1–12.
19. Woldemskel M, Liggett A, Ilha M, et al. Canine parvovirus-2b associated erythema multiforme in a litter of English setter puppies. *J Vet Diagn Invest* 2011;23(3):576–80.
20. Schaudien D, Polizopoulou Z, Koutinas A, et al. Leukoencephalopathy associated with parvovirus infection in Cretan hound puppies. *J Clin Microbiol* 2010;48(9):3169–75.

21. Marenzoni ML, Calo P, Foiani G, et al. Porencephaly and periventricular encephalitis in a 4 month old puppy: detection of canine parvovirus type 2 and potential role in brain lesions. *J Comp Pathol* 2019;169:20–4.
22. Decaro N, Desario C, Amorisco F, et al. Canine parvovirus type 2c infection in a kitten with intracranial abscess and convulsions. *J Feline Med Surg* 2011;13(4):231–6.
23. Gamoh K, Shimazaki Y, Macki H, et al. The pathogenicity of canine parvovirus type 2-b, FP84 strain isolated from a domestic cat. *J Vet Med Sci* 2003;65(9):1027–9.
24. Miranda C, Parrish CR, Thompson G. Canine parvovirus 2c infection in a cat with severe clinical disease. *J Vet Diagn Invest* 2014;26(3):462–4.
25. Johnson RH, Smith JR. Epidemiology and pathogenesis of canine parvovirus. *Aust Vet Pract* 1983;13(1):31.
26. Pollack RV, Carmichael LE. Maternally derived immunity to canine parvovirus infection: transfer, decline, and interference with vaccination. *J Am Vet Med Assoc* 1982;204(8):37–42.
27. Proksch AL, Unterer S, Speck S, et al. Influence of clinical and laboratory variables on faecal antigen ELISA results in dogs with canine parvovirus infection. *Vet J* 2015;204(3):304–8.
28. Meunier PC, Cooper BJ, Appel MJ, et al. Pathogenesis of canine parvovirus: the importance of viremia. *Vet Pathol* 1985;22(1):60–71.
29. Decaro N, Campolo M, Desario C, et al. Maternally derived antibodies in pups and protection from canine parvovirus infection. *Biologicals* 2005;33:259–65.
30. Maarkovich JE, Stucker KM, Carr AH, et al. Effects of canine parvovirus strain variations on diagnostic test results and clinical management of enteritis in dogs. *J Am Vet Med Assoc* 2012;241(11):66–72.
31. Decaro N, Desario C, Billi M, et al. Evaluation of an in-clinic assay for the diagnosis of canine parvovirus. *Vet J* 2013;198:504–7.
32. Decaro N, Desario C, Beall MJ, et al. Detection of canine parvovirus type 2c by a commercially available in-house rapid test. *Vet J* 2010;184(3):373–5.
33. Kantere MC, Athanasiou LV, Spyrou V, et al. Diagnostic performance of a rapid in-clinic test for the detection of canine parvovirus under different storage conditions and vaccination status. *J Virol Methods* 2015;215-216:52–5.
34. Decaro N, Dessario C, Elia G, et al. Occurrence of severe gastroenteritis in pups after canine parvovirus vaccination administration: a clinical and laboratory diagnostic dilemma. *Vaccine* 2007;25(7):1161–6.
35. Pollack RV, Coyne MJ. Canine parvovirus. *Vet Clin North Am Small Anim Pract* 1993;23(3):555–68.
36. Prittie J. Canine parvoviral enteritis a review of diagnostic, management and prevention. *J Vet Emerg Crit Care (San Antonio)* 2004;13:167–76.
37. Macintire DK, Smith-Carr S. Canine parvovirus. II. Clinical signs, diagnosis and treatment. *Comp Cont Educ Pract* 1996;19(3):291–302.
38. Faz M, Martinez JS, Gomez LB, et al. Origin and genetic diversity of canine parvovirus 2c circulating in Mexico. *Arch Virol* 2019;164(2):371–9.
39. Rallis TS, Papazoglou LG, Adamama-Moraitou KK, et al. Acute enteritis or gastroenteritis in young dogs as a predisposing factor for intestinal intussusception: a retrospective study. *J Vet Med A Physiol Pathol Clin Med* 2000;47(8):507–11.
40. Kalli I, Leontides LS, Mylonakis ME, et al. Factors affecting the occurrence, duration of hospitalization and final outcome in canine parvoviral enteritis. *Res Vet Sci* 2010;89:174–8.

41. Castro TX, Cubel Garcia Rde C, Goncalves LP, et al. Clinical, hematological and biochemical findings in puppies with coronavirus and parvovirus enteritis. *Can Vet J* 2013;54(9):885–8.
42. Goddard A, Leisewitz AL, Christopher MM, et al. Prognostic usefulness of blood leukocyte changes in canine parvoviral enteritis. *J Vet Intern Med* 2008;22:309–16.
43. Farro CS. Radiographic appearance of canine parvoviral enteritis. *J Am Vet Med Assoc* 1982;180(1):43–7.
44. Stander N, Wagner WM, Goddard A, et al. Ultrasonographic appearance of canine parvoviral enteritis in puppies. *Vet Radiol Ultrasound* 2010;51(1):69–74.
45. Schoeman JP, Goddard A, Herrtage ME. Serum cortisol and thyroxine concentrations as predictors of death in critically ill puppies with parvoviral diarrhea. *J Am Vet Med Assoc* 2007;231:1534–9.
46. Schoeman JP, Herrtage ME. Serum thyrotropin, thyroxine and free thyroxine concentrations as predictors of mortality in critically ill puppies with parvovirus infection: a model for human paediatric illness? *Microbes Infect* 2008;10:203–7.
47. Cohn LA, Rewerts RM, McCaw D, et al. Plasma granulocyte-colony stimulating factor concentrations in neutropenic, parvoviral-enteritis infected puppies. *J Vet Intern Med* 1999;13:581–6.
48. Mann FA, Boon GD, Wagner-Mann CC, et al. Ionized and total magnesium concentrations in blood from dogs with naturally acquired parvovirus. *J Am Vet Med Assoc* 1998;212:1398–401.
49. Kocaturk M, Martinez S, Eralp O, et al. Prognostic value of serum acute-phase proteins in dogs with parvoviral enteritis. *J Small Anim Pract* 2010;51:478–83.
50. McClure V, van Schoor M, Goddard A, et al. Serial C-reactive protein measurements as a predictor of outcome in puppies infected with parvovirus. *J Am Vet Med Assoc* 2013;243(3):361–6.
51. Yilmaz Z, Senturk S. Characterisation of lipid profiles in dogs with parvoviral enteritis. *J Small Anim Pract* 2007;48:643–50.
52. Panda D, Patra R, Nandi S, et al. Oxidative stress indices in gastroenteritis in dogs with canine parvoviral infection. *Res Vet Sci* 2009;86:36–42.
53. Kalli IV, Adamama-Moraitou KK, Patsika MN. Prevalence of increased canine pancreas-specific lipase concentrations in young dogs with parvovirus enteritis. *Vet Clin Pathol* 2017;46(1):111–9.
54. Dossin O, Rupassara S, Weng HY, et al. Effect of parvoviral enteritis on plasma citrulline concentration in dogs. *J Vet Intern Med* 2011;25:215–21.
55. Otto CM, Drobatz KJ, Soter C. Endotoxemia and tumor necrosis factor activity in dogs with naturally occurring parvoviral enteritis. *J Vet Intern Med* 1997;11:65–70.
56. Otto CM, Rieser TM, Brooks MB, et al. Evidence of hypercoagulability in dogs with parvoviral enteritis. *J Am Vet Med Assoc* 2000;217:1500–4.
57. Brady S, Norris JM, Kelman M, et al. Canine parvovirus in Australia: the role of socio-economic factors. *Vet J* 2012;193(2):522–8.
58. Zourkas E, Ward MP, Kelman M. Canine parvovirus in Australia: a comparative study of reported rural and urban cases. *Vet Microbiol* 2015;181(3–4):198–203.
59. Kelman M, Ward MP, Barrs VR, et al. The geographic distribution and financial impact of canine parvovirus in Australia. *Transbound Emerg Dis* 2019;66:299–311.
60. Allukian AR, Abelson AL, Babyak J, et al. Comparison of time to obtain intraosseous versus jugular catheterization in canine cadavers. *J Vet Emerg Crit Care (San Antonio)* 2017;27(5):506–11.



61. Hughes D, Beal MW. Emergency vascular access. *Vet Clin North Am Small Anim Pract* 2000;30(3):491–507.
62. Macintire DK. Pediatric fluid therapy. *Vet Clin North Am Small Anim Pract* 2008;38(3):621–7.
63. Ford RB, Larson LJ, McClure KD, et al. 2017 AAHA Canine Vaccination Guidelines. American Animal Hospital Association.
64. Heald RD, Jones BD, Schmidt DA. Blood gas and electrolyte concentrations in canine parvoviral enteritis. *J Am Anim Hosp Assoc* 1986;22:745–8.
65. Mazzaferro EM, Rudloff E, Kirby R. The role of albumin replacement in the critically ill veterinary patient. *J Vet Emerg Crit Care (San Antonio)* 2002;12(2):113–24.
66. Dodd WJ. Immune plasma for treatment of parvoviral gastroenteritis. *J Am Vet Med Assoc* 2012;240(9):1056.
67. Cohn LA, Kerl ME, Lenox CE, et al. Response of healthy dogs to infusions of human serum albumin. *Am J Vet Res* 2007;68(6):657–63.
68. Martin LG, Luther TY, Alperin AC, et al. Serum antibodies against human albumin in critically ill dogs and cats. *J Am Vet Med Assoc* 2008;232(7):1004–9.
69. Mazzaferro EM, Balakrishnan A, Hackner SG, et al. Delayed Type-III hypersensitivity reaction with acute kidney injury in two dogs following administration of concentrated human albumin during treatment for hypoalbuminemia secondary to septic peritonitis. *J Vet Emerg Crit Care (San Antonio)* 2020. <https://doi.org/10.1111/vec.12976>.
70. Mantione NL, Otto CM. Characterization of the use of antiemetic agents in dogs with parvoviral enteritis treated at a veterinary teaching hospital: 77 cases (1997-2000). *J Am Vet Med Assoc* 2005;227(11):1787–93.
71. Yalcin E, Keser GO. Comparative efficacy of metoclopramide, ondansetron and maropitant in preventing parvoviral enteritis-induced emesis in dogs. *J Vet Pharmacol Ther* 2017;40(6):599–603.
72. Sullivan LA, Lenberg JP, Boscan P, et al. Assessing the efficacy of maropitant versus ondansetron in the treatment of dogs with parvoviral enteritis. *J Am Anim Hosp Assoc* 2018;54(6):338–43.
73. Sykes JE. Immunodeficiencies caused by infectious diseases. *Vet Clin North Am Small Anim Pract* 2010;40:409–23.
74. Silva ROS, Dorella FA, Figueriedo HCP, et al. Clostridium perfringens and C. difficile in parvovirus positive dogs. *Anaerobe* 2017;48:66–9.
75. Tupler T, Levy JK, Sabshin SJ, et al. Enteropathogens identified in dogs entering a Florida animal shelter with normal feces or diarrhea. *J Am Vet Med Assoc* 2012;241(3):338–43.
76. Duijvestijn M, Mughini-Gras L, Schuurman N, et al. Enteropathogen infections in canine puppies (co)occurrence, clinical relevance and risk factors. *Vet Microbiol* 2016;195:115–22.
77. Botha WJ, Schoeman JP, Marks SL, et al. Prevalence of salmonella in juvenile dogs affected with parvoviral enteritis. *J S Afr Vet Assoc* 2018;89:e1–6.
78. Van den Berg MF, Schoeman JP, Defauw P, et al. Assessment of acute kidney injury in canine parvovirus infection: comparison of kidney injury biomarkers with routine renal function parameters. *Vet J* 2018;242:8–14.
79. Brunner CJ, Swango LJ. Canine parvovirus infection: effects on the immune system and factors that predispose to severe disease. *Comp Cont Educ Pract* 1985;7(12):979–88.

80. Mohr AJ, Leisewitz AL, Jacobson LS, et al. Effect of early enteral nutrition on intestinal permeability, intestinal protein loss and outcome in dogs with severe parvoviral enteritis. *J Vet Intern Med* 2003;17:791–8.
81. O'Toole E, Miller CW, Wilson BA, et al. Comparison of the standard predictive equation for calculation of resting energy expenditure with indirect calorimetry in hospitalized and healthy dogs. *J Am Vet Med Assoc* 2004;225(1):58–64.
82. Chih A, Rudloff E, Waldner C, et al. Incidence of hypochloremic metabolic alkalosis in dogs and cats with and without nasogastric tubes over a period of up to 36 hours in the intensive care unit. *J Vet Emerg Crit Care (San Antonio)* 2018;28(3):244–51.
83. Tenne R, Sullivan LA, Contreras ET, et al. Palatability and clinical effects of an oral recuperation fluid during recovery of dogs with suspected parvoviral enteritis. *Top Companion Anim Med* 2016;31(2):68–72.
84. Reineke EL, Walton K, Otto CM. Evaluation of an oral electrolyte solution for treatment of mild to moderate dehydration in dogs with hemorrhagic diarrhea. *J Am Vet Med Assoc* 2013;243(6):851–7.
85. Marquez M, Boscan P, Weir J, et al. Comparison of NK-1 receptor antagonist (maropitant) to morphine as a preanesthetic agent for canine ovariohysterectomy. *PLoS One* 2015;10(10):e0140734.
86. Purvis D, Kirby R. Systemic inflammatory response syndrome: septic shock. *Vet Clin North Am Small Anim Pract* 1994;24(6):1225–47.
87. Sarpong KJ, Lukowski JM, Knapp CG. Evaluation of mortality rate and predictors of outcome in dogs receiving outpatient treatment for parvoviral enteritis. *J Am Vet Med Assoc* 2017;251(9):1035–41.
88. Venn EC, Presinder K, Boscan PL, et al. Evaluation of an outpatient protocol in the treatment of canine parvoviral enteritis. *J Vet Emerg Crit Care (San Antonio)* 2017;27(1):52–65.
89. Hill's AD. Hill's Pet Nutrition. Topeka(KS).
90. Savigny MR, Macintire DK. Use of oseltamivir in the treatment of canine parvoviral enteritis. *J Vet Emerg Crit Care (San Antonio)* 2010;20(1):132–42.
91. Papaioannou E, Soubais N, Theodorou K, et al. The potential role of oseltamivir in the management of canine parvoviral enteritis in 50 natural cases. Abstract BSAVA Congress April 4–7, 20-13 Birmingham, UK.
92. Ishiwata K, Minagawa T, Kajimoto T. Clinical effects of feline interferon-omega on experimental parvovirus infection in beagle dogs. *J Vet Med Sci* 1998;72:1145–51.
93. Minagawa T, Ishiwata K, Kajimoto T. Feline interferon-omega treatment on canine parvovirus infection. *Vet Microbiol* 1999;69:51–3.
94. Martin V, Najbar W, Gueguen S, et al. Treatment of canine parvoviral enteritis with interferon-omega in a placebo-controlled challenge trial. *Vet Microbiol* 2002;89:115–27.
95. De Mari K, Maynard L, Eun HM, et al. Treatment of canine parvoviral enteritis with interferon-omega in a placebo-controlled field trial. *Vet Rec* 2003;152:105–8.
96. Bragg RF, Duffy AL, DeCecco FA, et al. Clinical evaluation of a single dose of immune plasma for treatment of canine parvovirus infection. *J Am Vet Med Assoc* 2012;240(6):700–4.
97. Meunier PC, Cooper BJ, Appel MJ, et al. Pathogenesis of canine parvoviral enteritis sequestration, virus distribution and passive immunization studies. *Vet Pathol* 1985;22:617–24.

98. Ishibashi K, Maede Y, Ohsugi T, et al. Serotherapy for dogs infected with canine parvovirus. *Nippon Juigaku Zasshi* 1983;45:59–66.
99. Macintire D, Smith-Carr S, Jones R, et al. Treatment of dogs naturally infected with canine parvovirus with lyophilized canine IgG. Proceedings 17th Annual Conference of the American College of Veterinary Internal Medicine, Chicago, USA, June 10–13, 1999, p 721.
100. Gerlach M, Proksch AL, Unterer S, et al. Efficacy of feline anti-parvovirus antibodies in the treatment of canine parvovirus infection. *J Small Anim Pract* 2017;58:408–15.
101. Van Nguyen S, Umeda K, Yokoyama H, et al. Passive protection of dogs against clinical disease due to canine parvovirus-2 specific antibody from chicken egg yolk. *Can J Vet Res* 2006;70:62–4.
102. Kraft W, Kuffer M. Treatment of severe neutropenia in dogs and cats with filgrastim. *Tierarztl Prax* 1995;23:609–13.
103. Rewerts JM, McCaw DL, Cohn LA, et al. Recombinant human granulocyte-colony stimulating factor for treatment of puppies with neutropenia secondary to canine parvovirus infection. *J Am Vet Med Assoc* 1998;213:991–2.
104. Mischke R, Barth T, Wohlsein P, et al. Effect of recombinant human granulocyte colony-stimulating factor (rhG-CSF) on leukocyte count and survival rate in dogs with parvoviral enteritis. *Res Vet Sci* 2001;70:221–5.
105. Duffy A, Dow S, Ogilvie G, et al. Hematologic improvement in dogs with parvovirus infection treated with recombinant canine granulocyte-colony stimulating factor. *J Vet Pharmacol Ther* 2010;33:352–6.
106. Armenise A, Trerotoli P, Cirone F, et al. Use of recombinant canine granulocyte-colony stimulating factor to increase leukocyte count in dogs naturally infected by canine parvovirus. *Vet Microbiol* 2019;231:177–82.
107. Pereira GQ, Gomes LA, Santos IS, et al. Fecal microbiota transplantation in puppies with canine parvovirus infection. *J Vet Intern Med* 2018;32:707–11.
108. Honneffer JB, Minamoto Y, Suchodolski JS. Microbiota alterations in acute and chronic gastrointestinal inflammation of cats and dogs. *WJG* 2014;20:16489–97.
109. Arslan HH, Saripinar AD, Terzi G, et al. Therapeutic effects of probiotic bacteria in parvoviral enteritis in dogs. *Rev Med Vet* 2012;163:55–9.
110. DeCamargo P, Ortolani M, Uenaka S, et al. Evaluation of the therapeutic supplementation with commercial powder probiotic to puppies with hemorrhagic gastroenteritis. *Semin Cienc Agrar* 2006;27:453–61.
111. Cavalli A, Marinaro M, Desario C, et al. In vitro virucidal activity of sodium hypochlorite against canine parvovirus type 2. *Epidemiol Infect* 2018;146(15):2010–3.
112. Mila H, Grellet A, Desario C, et al. Protection against canine parvovirus type 2 infection in puppies by colostrum-derived antibodies. *J Nutr Sci* 2014;3:e54.
113. De Cramer KG, Stylianides E, van Vuuren M. Efficacy of vaccination at 4 and 6 weeks in the control of canine parvovirus. *Vet Microbiol* 2011;149(1–2):126–32.
114. Larson LJ, Schulz RD. Do current canine parvovirus Type 2 and type 2b vaccinations provide protection against the new type 2c variant? *Vet Ther* 2008;9(2):94–101.
115. Wilson S, Stirling C, Borowski S, et al. Vaccination of dogs with duramune DAPPi-LC protects against pathogenic parvovirus type 2c challenge. *Vet Rec* 2013;172(25):662.

116. Wilson S, Illambas J, Siedek E, et al. Vaccination of dogs with canine parvovirus type 2b (CPV-2b) induces neutralizing antibody responses to CPV-2a and CPV-2c. *Vaccine* 2014;32(42):5420–4.
117. Siedek EM, Schmidt H, Sture GH, et al. Vaccination with canine parvovirus type 2 (CPV-2) protects against challenge with virulent CPV-2b and CPV-2c. *Berl Munch Tierarztl Wochenschr* 2011;124(1–2):58–64.
118. Mahon JL, Rozanski EA, Paul AL. Prevalence of serum antibody titers against canine distemper virus and canine parvovirus in dogs hospitalized in an intensive care unit. *J Am Vet Med Assoc* 2017;250(12):1413–8.
119. Miranda C, Thompson G. Canine parvovirus in vaccinated dogs: a field study. *Vet Rec* 2016;178(16):397–402.
120. Decaro N, Cirone F, Desario C, et al. Severe parvovirus in a 12 year old dog that had been repeatedly vaccinated. *Vet Rec* 2009;164:593–5.
121. Riedl M, Truyen U, Reese S, et al. Prevalence of antibodies to canine parvovirus and reaction to vaccination in client-owned healthy dogs. *Vet Rec* 2015;177(23):597.
122. Miranda C, Carvalheira J, Parrish CR, et al. Factors affecting the occurrence of canine parvovirus in dogs. *Vet Microbiol* 2015;180:59–64.
123. Ling M, Norris JM, Kelman M, et al. Risk factors for death from canine parvoviral-related disease in Australia. *Vet Microbiol* 2012;158(3–4):280–90.