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CHAPTER 14

Canine Parvovirus Infections and Other Viral Enteritides

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Overview of Canine Parvoviral Enteritis

First Described: 1978, worldwide, Appel and others[1]

Cause: Canine parvovirus-2 variants (Family Parvoviridae, subfamily Parvovirinae, Genus *Parvovirus*)

Affected Hosts: Dogs and other Canidae such as coyotes, foxes, and wolves; cats

Geographic Distribution: Worldwide

Route of Transmission: Direct contact with virus in feces and vomitus as well as contact with contaminated fomites

Major Clinical Signs: Fever, lethargy, inappetence, vomiting, diarrhea, dehydration. Sudden death or tachypnea due to myocarditis occurs rarely.

Differential Diagnoses: Canine distemper virus infection, other canine viral enteritides, dietary indiscretion, toxins, gastrointestinal foreign body, enteric parasitic infections such as giardiasis and helminth infections, enteric bacterial infections such as salmonellosis, salmon poisoning disease, pancreatitis, hypoadrenocorticism, inflammatory bowel disease

Human Health Significance: CPV-2 variants do not infect humans

Etiology and Epidemiology

Canine parvovirus is the most widely recognized cause of transmissible viral diarrhea in dogs and one of the most common infectious diseases of dogs worldwide. It is caused by variants of canine parvovirus-2 (CPV-2), which are members of the genus *Parvovirus*. CPV-2 emerged in the early to mid-1970s and caused a worldwide pandemic of illness in dogs.[2] The spread of the virus worldwide occurred over a remarkable period of about 6 months. CPV-2 may have been derived from feline panleukopenia virus (FPV) or a closely related virus of wild carnivores. It has since mutated to CPV-2a in 1979, CPV-2b in 1984, and, most recently, CPV-2c, which was first detected in Italy in 2000 and has subsequently been found worldwide, with the exception of Australia. Separate lineages have been identified in different geographic locations worldwide.[3] The virus uses the transferrin receptor to enter host cells. With the mutation from CPV-2 to CPV-2a, the virus developed the ability to replicate readily in feline cells, and CPV-2a, CPV-2b, and CPV-2c are now responsible for some cases of feline viral enteritis.[4,5] Feline parvoviral enteritis is further discussed in Chapter 19. CPV-2 variants must be differentiated from CPV-1, also known as canine minute virus, which belongs to the genus *Bocavirus*. In general, CPV-1 is thought to have minimal pathogenic potential, but it has been associated with abortion in pregnant dogs; respiratory, cardiac, and gastrointestinal signs in neonatal dogs; severe gastroenteritis in adult dogs; and possibly neurologic signs in dogs.[6-8]

Parvoviruses are small, non-enveloped single-stranded DNA viruses (Figure 14-1, *A*) that can survive for long periods (over 1 year) in the environment. As a result, contact with virus that persists in the environment is an important means of transmission. Insects and rodents may also serve as mechanical vectors for the virus. Canine parvovirus requires the presence of mitotically active cells in order to replicate. Young animals (6 weeks to 6 months, and especially those less than 12 weeks of age) are more likely to develop severe illness; however, disease can also occur in unvaccinated or improperly vaccinated adult dogs. In North America, Rottweilers, American pit bull terriers, Doberman pinschers, English springer spaniels, and German shepherd dogs appear to be at increased risk for development of parvoviral enteritis,[9,10] but this has not been the case in other geographic locations. A seasonal distribution of disease has been reported in some geographic locations, which may reflect times when dogs access the outdoors and contact virus in the environment. For example, in Saskatoon, Canada, dogs were three times more likely to be admitted with parvoviral enteritis in July, August, and September, compared with the rest of the year.[9] In other locations, the seasonal pattern of disease has differed or been nonexistent.[11,12] For dogs older than 6 months of age, intact males were twice as likely as females to develop parvoviral enteritis.[9] A surveillance study from Australia found a correlation between clusters of parvoviral enteritis and regions of relative socioeconomic disadvantage.[12]

Other viral pathogens that have been associated with enteritis and diarrhea in dogs are canine distemper virus (CDV) (see Chapter 15), canine enteric coronavirus (Figure 14-1, *B*), rotaviruses, astroviruses, adenoviruses, caliciviruses, and novel viruses that include a norovirus, kobuvirus, sapovirus, and possibly also a circovirus.[13-17] Canine enteric coronavirus primarily causes mild diarrhea in puppies that are less than 6 weeks of age and may be found in co-infections with other viral causes of gastroenteritis, including CPV-2 variants. Rarely, it has been identified as a more significant cause of diarrhea in young dogs.[18] This chapter focuses on canine parvoviral enteritis, which is the most widely recognized and pathogenic viral enteritis of dogs.

Clinical Features

Signs and Their Pathogenesis

Transmission of parvovirus and other viral causes of gastroenteritis occurs by the fecal-oral route, after exposure to virus in feces or vomit, or importantly, virus that persists on fomites.

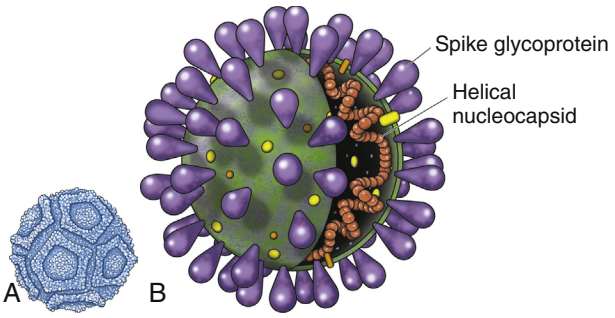

FIGURE 14-1 **A,** General structure of canine parvovirus. The virus is non-enveloped, is 25 nm in diameter, and has icosahedral symmetry. **B,** Structure of a coronavirus, which is an enveloped virus. Canine parvovirus is about one-quarter the size of a coronavirus.

Virus is shed for a few days before the onset of clinical signs, and shedding declines considerably after 7 days.[19] The severity of clinical signs depends on factors such as virus strain and host immunity, which is affected by stressors such as weaning and overcrowding, maternal antibody, and the presence of concurrent infections such as other enteric viral and parasitic infections. Subclinical infections are probably widespread.

The incubation period for canine parvoviral enteritis is 7 to 14 days in the field, but shorter incubation periods (as short as 4 days) have been observed with experimental infections. The virus replicates in oropharyngeal lymphoid tissues, after which viremia occurs. Damage occurs to rapidly dividing cells in the gastrointestinal tract, thymus, lymph nodes, and bone marrow. Affected gastrointestinal tissues include the epithelium of the tongue, oral cavity, esophagus, and intestinal tract, and especially the germinal epithelial cells of the intestinal crypts. Neutropenia results not only from infection of the marrow but also sequestration of neutrophils in damaged gastrointestinal tissue. Malabsorption and increased intestinal permeability result. Secondary bacterial infections of the gastrointestinal tract, which may be followed by bacterial translocation, bacteremia, and endotoxemia, play a key role in the pathogenesis of the disease. Mucosal candidiasis has also been described in puppies with parvoviral enteritis (see Chapter 67). The outcome is clinical signs of fever, lethargy, inappetence, vomiting, diarrhea, rapid dehydration, and abdominal pain. Diarrhea is often liquid, foul-smelling, and may contain streaks of blood or frank blood. Ascarid nematodes may be identified in the vomitus of some dogs. Dogs with canine parvoviral enteritis have evidence of disordered coagulation, with decreased antithrombin activities, prolonged activated partial thromboplastin time, increased thromboelastography maximum amplitude, and increased fibrinogen concentrations. Catheter and organ thrombosis may occur.[20] Secondary bacteremia may be associated with multiple organ failure and death.

Infection of the dam by CPV-2 variants early in gestation can lead to infertility, resorption, or abortion. Puppies that are infected in utero or up to 2 weeks of age may develop viral myocarditis, which results in signs of sudden death or congestive heart failure.[21-23] Damage to the developing myocardium usually occurs up to the first 2 weeks of life, but clinical signs of myocardial damage may be delayed until up to 2 months of age. Cerebellar hypoplasia has been rarely reported in dogs after in utero infection[24] but is more common in kittens infected with FPV (see Chapter 19). Generalized infection has been reported in neonatal puppies, with hemorrhage and necrosis within the brain, liver, lungs, kidneys, lymphoid tissues, and gastrointestinal tract.[25] Because maternal antibody protects puppies during this period, the incidence of neonatal complications of parvovirus infection and myocarditis has declined dramatically since the virus first emerged, because of widespread vaccination and exposure of adult animals.

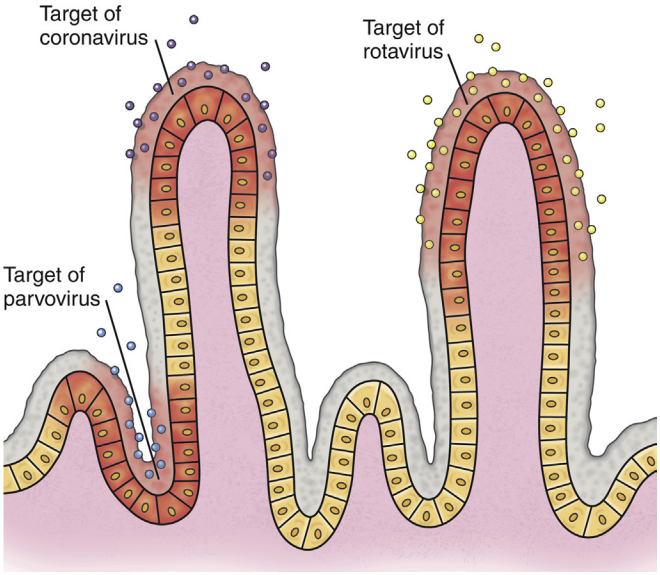

FIGURE 14-2 Target sites of replication of selected enteric viral pathogens. The most pathogenic enteric viruses, such as canine parvovirus, replicate and destroy crypt epithelial cells.

Neurologic signs in puppies with parvoviral enteritis may result from hypoxia secondary to myocarditis, hypoglycemia, or intracranial thrombosis or hemorrhage. The possibility of co-infection with CDV should also be considered. The DNA of CPV-2 variants has also been detected in the central nervous system,[26] and there have been rare reports of leukoencephalomalacia in association with infection.[27,28]

In contrast to canine CPV-2 variants, the replication of less pathogenic enteric viruses is restricted to the intestinal tract, and the crypt epithelial cells are generally spared (Figure 14-2). Canine enteric coronavirus, for example, infects the mature enterocytes at the tips of the villi. Crypt cell hyperplasia occurs to replace the damaged cells. The villi become shortened or distorted, which leads to malabsorption and diarrhea.

Physical Examination Findings

Physical examination of puppies with parvoviral enteritis often reveals fever (up to 41°C or 105°F), lethargy, weakness, dehydration, and abdominal tenderness and a fluid-filled intestinal tract on palpation (Figure 14-3). Vomiting or diarrhea may occur during the examination, or there may be evidence of diarrhea or frank blood on the perineum or the rectal thermometer. Occasionally abdominal palpation reveals a tubular mass as a result of intestinal intussusception. Ulcerative glossitis can occur in some puppies. Mucosal pallor, prolonged capillary refill time, or rarely hypothermia may be observed in some dogs.[29] Septic shock may be associated with tachycardia or bradycardia, mental obtundation, and poor pulse quality. Uncommonly, neurologic signs such as tremors and seizures are observed. Puppies with myocarditis may be tachypneic and have increased lung sounds as a result of congestive heart failure. Erythema multiforme has been reported in dogs with canine parvoviral enteritis; these dogs had generalized cutaneous and mucosal ulceration as well as swelling of the pinnae and paws.[30,31]

FIGURE 14-3 Obtundation in a 3-month-old intact male standard poodle puppy with canine parvovirus enteritis. The dog had been vaccinated for canine parvovirus at 8 and 10 weeks of age.

Diagnosis

Laboratory Abnormalities

Complete Blood Count

The most common abnormalities found on the CBC are leukopenia, neutropenia, and lymphopenia (Table 14-1). Toxic neutrophils and monocytopenia may also be present. Only around one third of dogs had leukopenia in one study.[29] Leukopenia can develop after the onset of gastrointestinal signs, when puppies are first brought for examination. Some dogs have leukocytosis due to a neutrophilia and monocytosis. Although the presence of leukopenia supports a diagnosis of parvoviral enteritis, other severe gastrointestinal infections such as salmonellosis can also cause leukopenia and diarrhea, so it is not specific for diagnosis of the disease. Thrombocytosis or, less commonly, thrombocytopenia may also occur.[29] Some puppies develop anemia as a result of gastrointestinal blood loss, which may be non regenerative or become regenerative.

Serum Biochemical Tests

The serum biochemistry panel in dogs with parvoviral enteritis often shows hypoproteinemia, hypoalbuminemia, and hypoglycemia. Mild hyperglycemia has also been reported. Electrolyte abnormalities such as hyponatremia, hypochloremia, and hypokalemia may occur (Table 14-2). Occasionally severe dehydration results in prerenal azotemia. Puppies with bacterial sepsis may develop increased liver enzyme activities and hyperbilirubinemia.

Coagulation Profile

Coagulation abnormalities have been reported in a small number of dogs with parvoviral enteritis. When abnormalities occur, findings include prolonged activated partial thromboplastin time, decreased antithrombin activity, increased fibrinogen

TABLE 14-1

Complete Blood Count Findings at Admission in 45 Dogs Diagnosed with Canine Parvoviral Enteritis at the UC Davis VMTH

Test	Reference Range	Percent below the Reference Range	Percent within the Reference Range	Percent above the Reference Range	Range for Dogs with CPV Enteritis	Number Tested
Hematocrit (%)	40-55	71	29	0	21-53	45
MCV (fL)	65-75	29	71	0	54-74	45
MCHC (g/dL)	33-36	24	69	7	30-37	45
Neutrophils (cells/μL)	3000-10,500	56	31	13	8-22,453	45
Band neutrophils (cells/μL)	0-rare	0	31	69	0-1582	45
Monocytes (cells/μL)	150-1200	20	60	20	11-2475	45
Lymphocytes (cells/μL)	1000-4000	49	22	0	165-3698	45
Eosinophils (cells/μL)	0-1500	0	100	0	0-1236	45
Platelets (cells/μL)	150,000-400,000	5	60	35	103,000-639,000	43

Note: Adult reference ranges were used by the laboratory.
CPV, Canine parvovirus.

TABLE 14-2

Findings on Serum Biochemistry Analysis in 27 Dogs with Canine Parvoviral Enteritis at the UC Davis VMTH

Test	Reference Range	Percent below the Reference Range	Percent within the Reference Range	Percent above the Reference Range	Range for Dogs with Parvoviral Enteritis	Number of Dogs Tested
Sodium (mmol/L)	145-154	85	15	0	132-147	26
Potassium (mmol/L)	3.6-5.3	4	92	4	3.4-5.9	26
Chloride (mmol/L)	108-118	65	31	4	94-120	26
Bicarbonate (mmol/L)	16-26	8	92	0	14-25	26
Calcium (mg/dL)	9.7-11.5	30	70	0	7.4-11.5	27
Phosphorus (mg/dL)	3.0-6.2	0	52	48	3.1-12.3	27
Creatinine (mg/dL)	0.3-1.2	37	59	4	<0.2-1.6	27
BUN (mg/dL)	5-21	0	85	15	5-48	27
Albumin (g/dL)	3.0-4.4	70	30	0	0.9-3.8	27
Globulin (g/dL)	1.8-3.9	26	67	7	1.4-4.5	27
Cholesterol (mg/dL)	135-361	4	89	8	108-460	26
Total bilirubin (mg/dL)	0-0.2	0	89	12	0-1.7	26
ALT (U/L)	19-67	15	62	23	10-165	26
ALP (U/L)	21-170	0	42	58	56-397	26

Note: Adult reference ranges were used by the laboratory.

concentrations, and increased thromboelastography maximum amplitude.[20] An increase in D-dimers or fibrin degradation products has not been reported. More research is warranted to understand the range of coagulation abnormalities that can occur in parvoviral enteritis.

Diagnostic Imaging

Plain Radiography

Plain abdominal radiography in dogs with parvoviral enteritis may show poor serosal detail (often due to lack of intra-abdominal fat in puppies) and a fluid- and gas-filled gastrointestinal tract. Abdominal radiography is usually performed to assess for the presence of a gastrointestinal foreign body.

Sonographic Findings

Findings on abdominal ultrasonography in canine parvoviral enteritis are nonspecific but can include a thickened gastrointestinal mucosa, mild peritoneal effusion, fluid distention of the gastrointestinal tract, and decreased gastrointestinal motility. Mild mesenteric lymphadenopathy may be present. Abdominal ultrasound is useful to confirm a diagnosis of secondary intestinal intussusception.

Microbiologic Tests

Diagnostic assays for canine parvoviral enteritis in dogs are listed in Table 14-3.

Fecal Parvovirus Antigen ELISA

The most widely used assay for diagnosis of canine parvoviral enteritis is an in-house fecal antigen ELISA, which is performed on a rectal swab specimen. Several assays are available, and although they detect all variants of CPV-2 including CPV-2c, their sensitivities and specificities vary.[32,33] Sensitivity is particularly problematic, because viral shedding is transient, and antibody present may bind viral antigen so that it is unavailable for reaction with the assay. The sensitivities of three commercially available fecal antigen assays (SNAP Parvo antigen, IDEXX Laboratories GmbH; FASTest Parvo Strip, Scil Animal Care Company GmbH; Witness Parvo Card, Selectavet GmbH) were 50%, 40%, and 60%, respectively, when compared to immunoelectron microscopy, and 18%, 16%, and 26%, respectively, when compared with results of a fecal PCR assay.[33] Because some dogs that lack evidence of gastrointestinal signs can be positive using PCR assay, immunoelectron microscopy may be a more appropriate gold standard for disease (although it is not widely available for routine diagnosis). In another study, the sensitivity of a fecal antigen test for detection of CPV-2a, CPV-2b, and CPV-2c, on specimens that contained high CPV DNA loads (>10^5 copies/mg of feces as determined with real-time PCR) was 80%, 78%, and 77%, respectively.[32]

When compared with PCR and immunoelectron microscopy of stool, the specificities of the three commercially available antigen assays above were 98%, 98%, and 92%, respectively,[33] so false positives were uncommon. It has been suggested that false-positive antigen tests can occur 4 to 8 days after vaccination with attenuated live CPV-2 vaccines.[34] In kittens, false-positive test results did occur after vaccination for FPV, but they were more likely to occur with some assays as opposed to others, were generally weak positives, and occurred even after vaccination with inactivated vaccines.[35] Similar studies have not been reported for CPV.

TABLE 14-3

Diagnostic Assays Available for Canine Parvoviral Enteritis in Dogs

Assay	Specimen type	Target	Performance
Fecal antigen ELISA	Feces	CPV antigen	Specificity for detection of virus nears 100%, but weak false positives have the potential to occur after immunization with attenuated live vaccines. False negatives are common (low sensitivity).
Hemagglutination assay	Feces	CPV antigen	Inexpensive and rapid. Sensitivity and specificity in naturally infected dogs has not been well established.
Histopathology	Usually necropsy specimens, especially gastrointestinal tissues	Crypt necrosis with intranuclear inclusions; parvovirus antigen with IHC or parvovirus DNA with in situ hybridization	Can be used for diagnosis at necropsy. In situ hybridization may be most sensitive for detection of virus in tissues.
Polymerase chain reaction (PCR)	Feces, tissue species	CPV DNA	Sensitivity and specificity may vary depending on assay design. Attenuated live vaccine virus may be detected in feces for days to weeks after vaccination, but some assays differentiate between vaccine and field virus. Because of the high sensitivity of some assays, the significance of a positive result may be difficult to interpret. False negative results may occur as a result of inhibition of PCR by components of feces. Degradation of nucleic acid during specimen transport is more problematic for RNA viruses such as canine coronavirus.
Fecal electron microscopy	Feces	Virus particles	Not widely available, turnaround time can be slow, and may be expensive. Requires the presence of large amounts of virus.
Virus isolation	Feces, tissues	CPV	Difficult, not widely available. Used as a research tool.

CPV, Canine parvovirus (refers to CPV-2 variants); IHC, immunohistochemistry.

Hemagglutination Testing

Canine parvovirus agglutinates erythrocytes, and so the presence of the virus in stool can be detected with a simple hemagglutination test that involves mixing a suspension of feces with porcine erythrocytes. Agglutination of erythrocytes in a microwell plate or on a slide indicates the presence of parvovirus in the feces.[36] The sensitivity and specificity of these assays in dogs with and without natural parvoviral infections in the field require further investigation.

Molecular Diagnosis Using the Polymerase Chain Reaction

Several commercial veterinary diagnostic laboratories now offer real-time PCR assays for detection of CPV-2 variants and other enteric viral pathogens (such as canine coronavirus). Assays may detect as few as 1000 copies of viral DNA per milligram of stool. Turnaround times are less than 24 hours in some laboratories. PCR assays are useful when fecal antigen tests are negative but parvoviral enteritis is still suspected as a diagnosis, or when canine enteric coronavirus infection is a potential cause of illness (because PCR panels that assay for parvovirus DNA also often include an assay for canine enteric coronavirus RNA). Unfortunately, although infrequent, positive PCR assay results for CPV can occur in dogs without signs of gastroenteritis or in dogs with chronic diarrhea, and so it may be difficult to ascertain whether a positive parvovirus PCR result indicates that CPV is the cause of a dog's illness. Attenuated live vaccine virus can also be detected in the feces with PCR assays after vaccination, although assays have been designed that can differentiate between vaccine and wild-type virus.[37] It is not yet clear for how long after vaccination false-positive PCR results might occur, and this could vary based on the design of the PCR assay used. Both vaccine and field virus have been detected simultaneously in some dogs using these assays. In the future, quantitation of virus loads in feces using real-time PCR may be helpful for interpretation of the significance of a positive PCR assay result.

Fecal Electron Microscopy

Fecal electron microscopy is still offered by some institutions for diagnosis of viral enteritis. It is generally used on a research basis when viral enteritis is suspected but a diagnosis cannot be made with antigen tests or PCR assays. Fecal electron microscopy may facilitate diagnosis of other viral infections such as rotavirus, norovirus, and coronavirus infections. Turnaround time may be slow. Generally speaking, large amounts of virus must be present for results to be positive, and technical expertise is required to accurately identify virus in the stool.

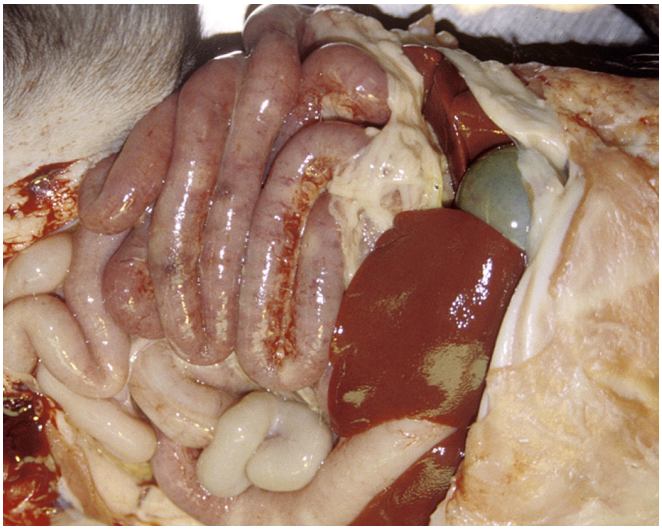

FIGURE 14-4 Discoloration of the small intestinal wall and serosal hemorrhage in a puppy that died of canine parvoviral enteritis. (Courtesy University of California, Davis Veterinary Anatomic Pathology Service.)

Virus Isolation

Canine parvovirus variants can be isolated in canine and feline cells, but isolation is difficult, and the virus shows minimal cytopathic effects. As a result, virus isolation is rarely used for diagnosis and is not widely available. It remains important as a research tool.[38]

Serology

Antibodies to CPV-2 can be measured in the laboratory using hemagglutination inhibition (see Chapter 2). In addition, an in-clinic ELISA assay is available for semiquantitative measurement of antibodies to CPV-2. These assays are generally used to assess the need for vaccination, rather than for diagnosis of CPV-2 enteritis, because affected dogs are either seronegative or previous vaccination or material antibodies confound early serodiagnosis.

Pathologic Findings

Gross Pathologic Findings

Gross pathologic findings in dogs with CPV enteritis include thickening and discoloration of the intestinal wall with serosal hemorrhage (Figure 14-4) and enlarged, edematous abdominal lymph nodes. The intestine may contain bloody liquid contents, and mucosal hemorrhage may be identified. Pale areas may be seen within the myocardium of dogs with parvoviral myocarditis.

Histopathologic Findings

The major histopathologic finding is necrosis of the crypt epithelium in the small intestine, with widespread systemic lymphoid depletion and necrosis. The crypts can be dilated and distended with cellular debris and mucus (Figure 14-5). Proliferation of crypt enterocytes may be observed as part of the recovery response. Intestinal villi are collapsed, shortened, and fused, with attenuation of the epithelial lining, and there may be mild to severe fibrinous inflammation and hemorrhage. Myeloid depletion may be found in the bone marrow. Parvoviral myocarditis is characterized by myocardial degeneration and necrosis, with a lymphocytic inflammatory infiltrate. Myocardial fibrosis can also be present. Rarely, central nervous system lesions consisting of leukoencephalomalacia have been described.[27] Viral intranuclear inclusions may be visible in some cells, especially the intestinal crypt epithelium. Immunohistochemistry can be used to detect viral antigen in the gastrointestinal tract, marrow, lymphoid tissues, and rarely in the myocardium. In situ hybridization (see Chapter 5) can also be used to detect virus in histopathology specimens and may have greater sensitivity than immunohistochemistry.[39,40]

Treatment and Prognosis

Antimicrobial Treatment and Supportive Care

Treatment of CPV enteritis involves supportive care and treatment of secondary bacterial infections with antimicrobial drugs (Table 14-4). Whenever possible, the patient should be hospitalized in isolation. Appropriate fluid therapy and maintenance of adequate blood glucose concentrations are the most critical aspect of treatment. Whenever possible, fluids should be given intravenously and supplemented as needed with potassium chloride and dextrose. Blood glucose concentrations should be monitored at least twice daily, and more frequent monitoring may be indicated if hypoglycemia is present. Although not generally recommended for puppies that are vomiting or dehydrated, administration of subcutaneous fluids and antimicrobial drugs in the home can sometimes result in recovery when client finances do not permit treatment in hospital. Fluids administered subcutaneously should never be supplemented with dextrose, because dextrose is hyperosmotic and can cause further dehydration, as well as injection-site reactions. Unfortunately, the owners of many dogs with parvoviral enteritis lack financial resources for treatment. In these situations, the inability to afford vaccination may have been a reason the puppy develops parvoviral enteritis in the first place.

An antimicrobial drug or drug combination with activity against gram-negative and anaerobic bacteria should be administered parenterally. Injectable ampicillin or cefazolin alone may be sufficient for many dogs, but puppies that have hemorrhagic diarrhea or evidence of the systemic inflammatory response syndrome (SIRS) should probably be treated with a combination of a penicillin and a fluoroquinolone, or a combination of a penicillin and an aminoglycoside. Use of fluoroquinolones in young, rapidly growing animals has been associated with cartilage damage (see Chapter 8), but when used for the short periods of time required to treat parvoviral enteritis, this may not be of significant concern. Proper hydration is critical before aminoglycosides are used because of their potential for nephrotoxicity.

Treatment with antiemetics (such as a constant rate infusion of metoclopramide or parenteral ondansetron), H2 blockers such as famotidine, whole blood or plasma transfusions, colloids such as hetastarch, or partial or total parenteral nutrition may be indicated in some dogs. Placement of a central line or multilumen catheter may be necessary in severely ill puppies, but strict sterile technique must be adhered to because of the potential for hospital-associated infection. In general, unless absolutely necessary, invasive surgical procedures and the use of parenteral nutrition solutions should be avoided in puppies with severe neutropenia. Whether plasma or hetastarch is the treatment of choice for dogs with low colloid oncotic pressure requires further study. Plasma may offer benefit over hetastarch in that it contains antibodies from immune dogs, but titers may not be sufficient to be beneficial, and most puppies

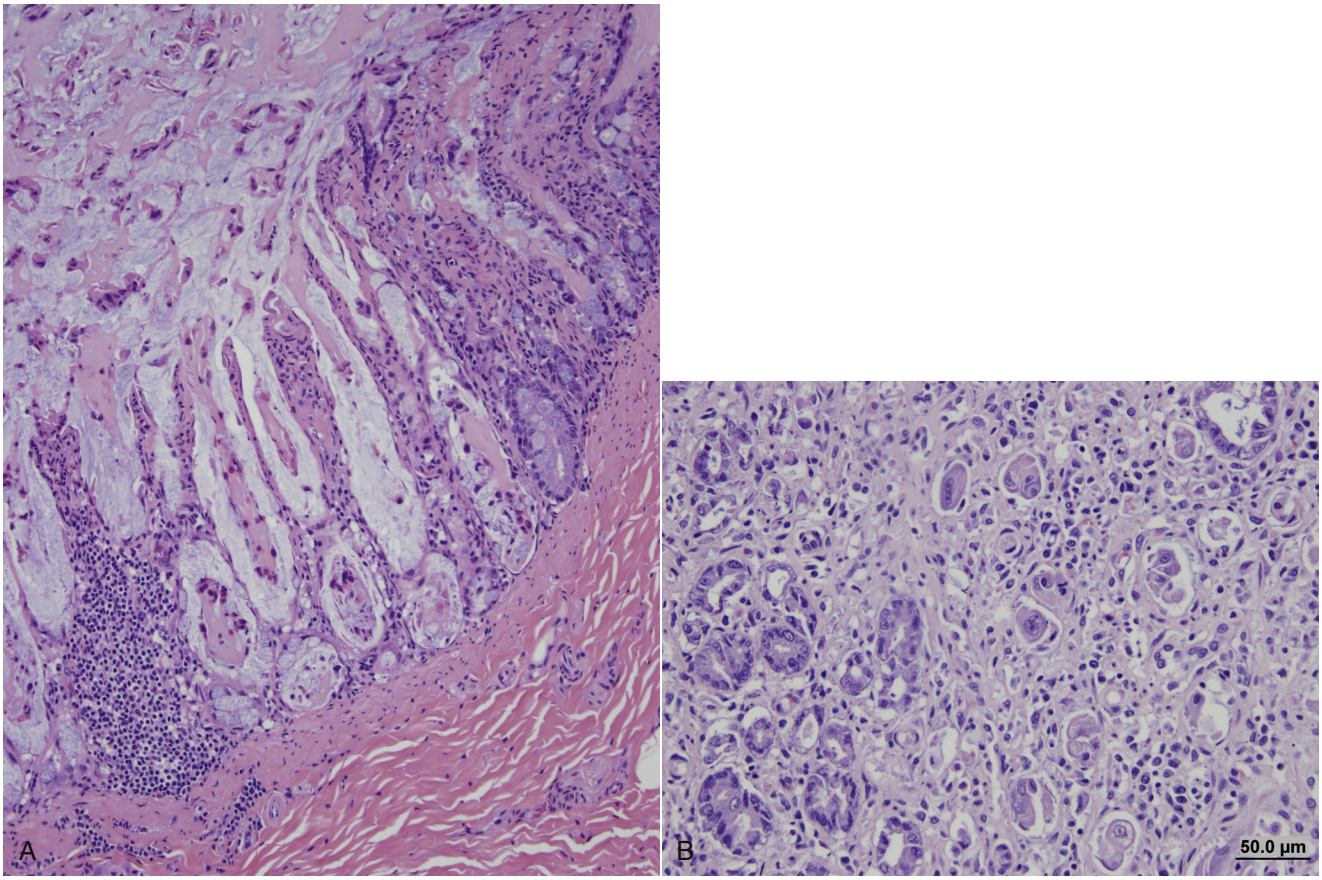

FIGURE 14-5 **A,** Segmental crypt necrosis in the ileum of a dog infected with a CPV-2 variant. There is severe loss of crypt epithelial cells. Hematoxylin and eosin (H&E) stain. **B,** Jejunum of a dog after infection by a CPV-2 variant. Regenerating epithelial cells, which here are nested in an inflamed jejunal lamina, have a large and bizarre appearance and resemble adenoma cells. As a result, the disease has been termed *adenomatosis*. Parvovirus antigen was no longer detectable by immunohistochemistry at this stage. The crypts in the bottom left corner have a more normal appearance. H&E stain. (Courtesy Dr. Patricia Pesavento, University of California, Davis Veterinary Anatomic Pathology Service.)

TABLE 14-4

Medications That May Be Used in Conjunction with Fluid Therapy to Treat Canine Parvoviral Enteritis

Drug	Dose (mg/kg)	Route	Interval (hours)
Ampicillin sodium	20	IV	6
Cefazolin sodium	20	IV	8
Enrofloxacin*	5	IV	24
Ondansetron	0.5 to 1	IV	12
Maropitant citrate	1	SC	24
Metoclopramide	1-2 mg/kg/d	IV	CRI
Famotidine	0.5	IV	12 to 24

CRI, Constant-rate infusion.
*Has been associated with cartilage injury in growing animals. Prolonged use (>7 days) is not recommended. See Chapter 8.

show evidence of an antibody response within 3 days after onset of clinical signs. Hetastarch has anticoagulant properties that could be beneficial in light of the hypercoagulable state that has been documented in canine parvoviral enteritis, but these effects also have the potential to increase mortality, and hetastarch has been associated with acute kidney injury in critically ill human patients.[41] Early enteral nutrition with a nasogastric feeding tube was associated with reduced hospitalization times in one study, as compared to withholding food until vomiting had ceased (Figure 14-6).[42] Gastric suction should be performed through the tube before food is administered.

Other treatments that have been investigated include anti-endotoxin sera, recombinant bactericidal permeability-increasing (BPI) protein, recombinant granulocyte colony-stimulating factor (G-CSF), recombinant feline interferon-omega (rfIFN-ω, Virbagen omega), and oseltamivir. Anti-endotoxin sera, recombinant BPI protein, and human recombinant G-CSF were not found to be beneficial. Although neutrophil counts were higher and hospital times were shorter in dogs treated with recombinant canine G-CSF, survival times in these dogs were decreased.[43] Treatment of parvovirus infections with G-CSF might cause harm, because the increased cell turnover induced by the drug might promote parvovirus replication. Treatment of puppies with parvoviral enteritis with rfIFN-ω in a number of placebo-controlled trials has been associated with reduced disease severity and, in some studies, significantly reduced mortality, but it has not been beneficial for treatment of FPV infections (see Chapter 19).

Oseltamivir inhibits the neuraminidase of influenza viruses and does not have specific anti-parvoviral activity, but it has been widely used for treatment of canine parvoviral enteritis. As canine parvovirus does not possess a neuraminidase, it has been

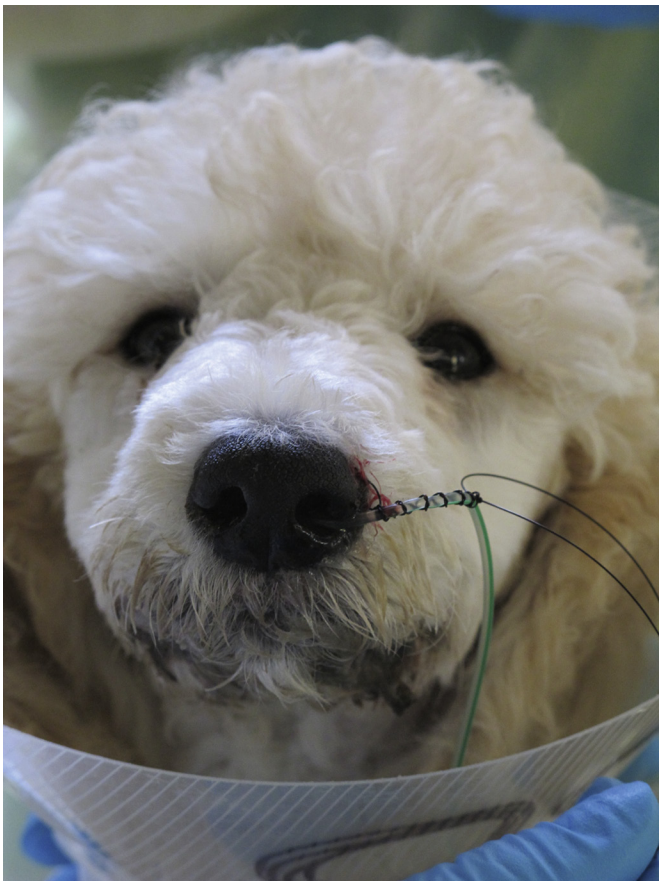

FIGURE 14-6 Puppy in Figure 14-2 after placement of a nasogastric feeding tube.

hypothesized that oseltamivir instead may act on the neuraminidases of bacteria that are normally responsible for secondary bacterial infections in parvovirus enteritis, primarily those of the gastrointestinal tract. A single prospective, randomized, masked, placebo-controlled trial of 35 dogs with parvovirus enteritis showed that dogs treated with oseltamivir (2 mg/kg PO q12h) had no significant drop in their leukocyte count, whereas untreated dogs had a significant drop in their leukocyte count in the first 5 days of hospitalization.[44] Treated dogs also gained weight during hospitalization, whereas untreated dogs lost weight. However, there was no difference in hospitalization time, clinical scores, morbidity, or mortality between the two groups, and the number of dogs in each group was small. The authors acknowledged the potential concerns that relate to administration of an oral medication to dogs with enteritis, with possible variability in drug absorption. A major concern that relates to treatment of canine parvoviral enteritis with oseltamivir is the possibility of selection for resistant mutants among influenza viruses if widespread use of the drug occurs in veterinary clinics. Given the restrictions on the use of this drug for treatment of human influenza virus infections, further investigation is required before the widespread use of oseltamivir can be recommended for treatment of CPV enteritis. More information on canine G-CSF, rfIFN-ω, and oseltamivir can be found in Chapter 7 of this book.

After recovery from viral enteritis, intestinal parasites should be treated with a broad-spectrum anthelmintic such as fenbendazole.

Prognosis

The prognosis for viral enteritis in puppies varies with the severity of illness and the owners' ability to afford appropriate treatment. Survival rates for puppies with CPV-2 enteritis have ranged from 9% in untreated puppies to greater than 90% with aggressive treatment in tertiary referral hospitals.[10,45-47] Factors that have been related to mortality include the presence of initial leukopenia or lymphopenia, monocytopenia, neutropenia, and evidence of SIRS.[29,48,49] SIRS was defined as the presence of at least three of the following four criteria: heart rate greater than 140 beats/min, temperature above 102.5°F or below 100°F, and white blood cell counts greater than 17,000 or less than 6000 cells/μL (see Chapter 86). Survival may also be lower in Rottweilers when compared to other breeds and in young puppies (less than 7 to 12 weeks of age).[50] In Australia, euthanasia was more likely to occur in summer; among pedigree dogs, in hounds, gundogs, and non-sporting breed dogs; and in puppies less than 6 months of age.[47] Vomiting and lethargy at admission as well as lymphopenia and hypoalbuminemia have been associated with prolongation of hospitalization times by approximately 2 days.[29] Positive changes in leukocyte counts (and especially lymphocyte counts) as early as 24 hours after admission have also been associated with survival.[48] In general, puppies that survive the first 3 to 4 days of treatment make complete recoveries. Complications of infection include bacteremia and septic shock, intestinal intussusception, aspiration pneumonia, and esophageal strictures.

Immunity and Vaccination

Immunity that follows natural infection by CPV-2 variants is probably lifelong. Immunization with attenuated live viral vaccines also provides sterile immunity that may even be lifelong. Both attenuated live and inactivated CPV vaccines are available. With the possible exception of shelter environments, attenuated live vaccines should never be administered to pregnant bitches because they may cause disease in the developing fetus. If possible, pregnant bitches introduced into shelter environments should be tested for antibody to CPV before vaccination with attenuated live vaccines, and these dogs should only be vaccinated if they test negative. The use of inactivated vaccines is not recommended in contaminated environments, because the window of vulnerability and the time to onset of protection is too long. The *window of vulnerability* is the period when maternal antibody interferes with the vaccine's ability to stimulate an effective immune response, but does not prevent infection with virulent field virus (see Chapter 12 for a discussion of this concept). Small quantities of attenuated live vaccine virus are shed from the intestinal tract after immunization, but this should not be relied on to immunize other in-contact animals. Protection against challenge with field virus occurs for at least 3 years and possibly for life after the initial puppy series is administered (see Chapter 12). Exposure of dogs to virus in the environment may also serve to booster immunity after vaccination.

The initial immunization series should be given every 3 to 4 weeks from 6 to 8 weeks of age, until no sooner than 14 to 16 weeks (16 to 20 weeks in breeding kennels), because of persistence of sufficient titers of maternal antibody in some puppies until this age. After that, a booster should be given at 1 year of age, and every 3 years thereafter (see Appendix). Puppies should be isolated in the home environment until 7 to 10 days after the last booster. Attendance at organized puppy classes has been advocated as a way to promote socialization in this period,

and currently there is no evidence that such activities increase risk for parvoviral enteritis. Serum antibody titers of at least 1:80 as determined with hemagglutination-inhibition correlate well with protection.

Concern has been raised that currently available CPV vaccines may not provide adequate protection against CPV-2c infection, because of reports of CPV-2c enteritis in vaccinated dogs.[51] Furthermore, the serum of animals immunized against CPV-2, CPV-2a, and CPV-2b poorly recognized CPV-2c.[52] However, experimental challenge studies have demonstrated strong protection against CPV-2c challenge when dogs are immunized with vaccines that contain CPV-2.[53,54] The extent to which maternal antibody against non-CPV-2c strains protects against infection with CPV-2c requires investigation.

Both inactivated and attenuated live vaccines are available for prevention or reduction of canine enteric coronavirus infection, but because the disease is generally mild or inapparent and primarily occurs in puppies younger than 6 weeks of age, their use has not been generally recommended.[55]

Prevention

Prevention of CPV-2 enteritis requires immunization and appropriate quarantine, isolation, cleaning, and disinfection procedures. Proper immunization is the most effective method. Puppies that are incompletely vaccinated should not be introduced into environments where there has been a history of parvoviral enteritis and adequate environmental disinfection cannot be guaranteed. Although extremely resistant to disinfectants, parvoviruses can be inactivated with a 1 in 30 dilution of household bleach; potassium peroxymonosulfate (Trifectant, Virkon S); accelerated hydrogen peroxide; or high-level chemical disinfectants such as glutaraldehyde and *ortho*-phthalaldehyde, when contact times of at least 10 minutes are used (see Chapter 11 for more information on disinfection). These disinfectants will also inactivate other enteric viruses. Steam cleaning should be used on surfaces that cannot be otherwise disinfected, and dishwashers that attain temperatures of at least 75°C should be used to wash dishes. For shelters, quarantine periods of 2 weeks have been recommended before introduction of puppies that might be shedding virus, because shedding rarely continues for longer than 10 days.[56] The bathing of recovered puppies can help to remove virus that persists on the haircoat. Rodent and insect vector control can also be used to prevent spread of the virus in the environment. Outdoor grassy areas and dirt are difficult or impossible to adequately disinfect, and so only immunized animals should be allowed on these areas. The use of bleach on these areas is not recommended because of adverse environmental effects from runoff.

The prevalence and impact of enteric viral infections can also be reduced through regular removal of fecal contamination, prolonged exposure of contaminated surfaces to sunlight and drying, and elimination of stressors such as overcrowding, transport, poor nutrition, and concurrent infections such as intestinal parasites.

Public Health Aspects

Enteric viral pathogens of dogs, including CPV-2 variants, do not infect humans. However, other infectious causes of gastroenteritis in puppies have the potential to be zoonotic, and coinfections with these pathogens can occur, so caution should be maintained when handling puppies with diarrhea. Precautions used in isolation should be sufficient to prevent enteric zoonoses (see Chapter 11).

CASE EXAMPLE

Signalment: "Sam", an 8-week old intact male Hungarian vizsla puppy from northern California.

History: Sam was acquired 6 days ago from a breeder, and at that time was eating and active. The next day Sam was examined at a local veterinary clinic, and a routine fecal examination revealed infection with *Giardia* and *Isospora* spp. Treatment with sulfamethoxazole was initiated, but 1 day later the puppy developed diarrhea. The next day, lethargy and vomiting were noted. Vomiting and diarrhea occurred every few hours. The diarrhea contained fresh blood and the vomitus consisted of clear, frothy fluid. Inappetence and intermittent vomiting continued for the next 2 days.

Current Medications: None

Other Medical History: Vaccination with an attenuated live CDV, CPV-2, and canine parainfluenza vaccine was performed when Sam was 6 weeks of age. There were no other dogs in the household, only one adult cat.

Physical Examination:

Body weight: 4.2 kg

General: Quiet, alert, responsive. Estimated to be 7% to 8% dehydrated, T = 103.4°F (39.7°C), HR = 240 beats/min, RR = 36 breaths/min, mucous membranes pale pink and tacky, CRT = 2 seconds.

Integument: Full, shiny haircoat. No ectoparasites were seen.

Eyes, ears, nose, and throat: Enophthalmos and a dry nasal planum were present.

Musculoskeletal: Body condition score 2/9. The dog was ambulatory, but emaciated and weak.

Cardiovascular: Weak but synchronous femoral pulses. No murmurs or arrhythmias ausculted.

Respiratory: No clinically significant findings.

Gastrointestinal: No evidence of abdominal pain on palpation. Fluid-filled intestinal tract. Full urinary bladder noted.

Rectal examination: Bloody diarrhea was present on the thermometer. Rectal examination was not performed.

Lymph nodes: All lymph nodes were within normal limits.

Laboratory Findings:

CBC:

HCT 31.5% (40-55%)
MCV 62.6 fL (65-75 fL)
MCHC 35.6 g/dL (33-36 g/dL)
WBC 530 cells/µL (6000-13,000 cells/µL)
Neutrophils 16 cells/µL (3000-10,500 cells/µL)
Lymphocytes 504 cells/µL (1000-4000 cells/µL)
Monocytes 11 cells/µL (150-1,200 cells/µL)
Platelets clumped but appeared adequate.

Serum Chemistry Profile:

Sodium 143 mmol/L (145-154 mmol/L)
Potassium 3.8 mmol/L (3.6-5.3 mmol/L)

Continued

Chloride 106 mmol/L (108-118 mmol/L)
Bicarbonate 23 mmol/L (16-26 mmol/L)
Phosphorus 4.8 mg/dL (3.0-6.2 mg/dL)
Calcium 10.3 mg/dL (9.7-11.5 mg/dl)
BUN 6 mg/dL (5-21 mg/dL)
Creatinine <0.2 mg/dL (0.3-1.2 mg/dL), glucose 133 mg/dL (64-123 mg/dL)
Total protein 4.3 g/dL (5.4-7.6 g/dL)
Albumin 2.4 g/dL (3.0-4.4 g/dL)
Globulin 1.9 g/dL (1.8-3.9 g/dL)
ALT 22 U/L (19-67 U/L), AST 15 U/L (19-42 U/L)
ALP 179 U/L (21-170 U/L)
Creatine kinase 274 U/L (51-399 U/L)
Gamma GT <3 U/L (0-6 U/L)
Cholesterol 278 mg/dL (135-361 mg/dL)
Total bilirubin 0.1 mg/dL (0-0.2 mg/dL)
Magnesium 2.0 mg/dL (1.5-2.6 mg/dL).

Imaging Findings:

Abdominal radiographs: The stomach wall appeared thickened. Numerous round gas opacities were present in a loop of intestine in the right cranial abdomen, which were believed to represent gas in the ascending colon or duodenum. Multiple additional gas opacities were present in a loop of intestine in the mid right abdomen at the level of the fourth lumbar vertebra. There was reduced serosal detail compatible with the age of the animal. Changes were considered consistent with the presence of gastroenterocolitis.

Microbiologic Testing:

Fecal Parvovirus Antigen ELISA: Negative

Fecal Enteric Real-time PCR Panel: PCR positive for CPV in fecal specimen. PCR negative for *Clostridium difficile* toxin A and toxin B genes, *Cryptosporidium* spp., *Salmonella* spp., and *Giardia* spp. DNA.

Fecal Zinc Sulfate Centrifugal Flotation: Negative for parasite ova.

Diagnosis: Enteritis and leukopenia secondary to canine parvoviral infection.

Treatment: Sam was admitted to isolation and treated aggressively with intravenous lactated Ringer's solution that was supplemented with 20 mEq KCl/L, famotidine (0.5 mg/kg IV q12h), ondansetron (0.5 mg/kg IV q12h), ampicillin (22 mg/kg IV q6h), and enrofloxacin (5 mg/kg IV q24h). Because of persistent vomiting, maropitant citrate (1 mg/kg IV q24h) was added as a second antiemetic. Blood glucose concentration was monitored three times daily, but supplementation with dextrose was not required. Bloody diarrhea that contained sloughed intestinal mucosa occurred every few hours for the first 24 hours. The neutrophil count was 9 cells/µL the following day, but by day 4 of hospitalization was 261 cells/µL, with 241 moderately toxic bands/µL and a lymphocyte count of 1226 cells/µL. There was gradual clinical improvement during this time, and Sam began to ingest small quantities of cottage cheese and rice on day 4. He was discharged from the hospital on day 5.

Comments: Despite the negative fecal antigen ELISA assay, CPV enteritis was suspected in this dog based on the history, clinical signs, and severe leukopenia. The finding of leukopenia and diarrhea is not diagnostic for parvoviral enteritis, because it can also be caused by other severe enteritides such as salmonellosis. The positive fecal real-time PCR assay for CPV supported the diagnosis, but because positive fecal PCR results can occur in healthy dogs with some assays, and also after vaccination, the fecal PCR result alone did not confirm the diagnosis of CPV enteritis. The diagnosis was therefore made on the basis of the combination of findings. The neutropenia in this dog was profound. Infection likely occurred before the owner acquired the puppy because the diarrhea began only 2 days after the puppy was purchased.

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