Update on the treatment of parvoviruses

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CANINE PARVOVIRUS

Agent. Canine parvoviruses are non-enveloped DNA viruses which require rapidly divided cells to reproduce. Currently, most worldwide cases with clinical diseases are infected with CPV-2b or CPV-2c. The small animal parvoviruses are quite resistant to environmental destruction but are susceptible to bleach. Infections in dogs came from feline panleukopenia virus and emerged in the late 1970s. The primary means of transmission is horizontal transmission via oronasal – fecal transmission. Vertical transmission via in utero infection can occur and can leads to myocarditits. CPV-2b and CPV2c can also infect cats.

CPV-2 first enters the oronasal cavity and infects lymphoid tissue followed by viremia for at least 1-5 days. Rapidly dividing cells of the gastrointestinal tract, myocardium, CNS, skin, kidney and other organs are targeted. Most notably, CPV-2 infects the crypt epithelial cells causing villus blunting. Decreased absorption (manifested as diarrhea), necrosis (sloughing of blood) and inflammation result. Lack of gastrointestinal integrity allows normal GI flora to penetrate into the blood stream and can lead to bacteremia with or without sepsis. Canine parvoviruses are shed primarily in feces for 3 to 14 days post infection, often starting before clinical signs appear. Clinical signs usually develop starting 5 to 12 days after exposure. Dogs with maternal or vaccinal antibodies can usually limit viremia and fully immunized dogs have sterilizing immunity.

Clinical findings. Any dog can be infected, but disease is thought to be more severe in some breeds like the American Pit Bull Terrier and Rottweilers. Severity of disease depends on virulence of the strain, size of inoculum, age, breed, and host's defenses. Clinical signs of CPV infection are most severe in pups less than 12 weeks that do not have prior immunity. Most dogs have enteritis characterized by foul smelling bloody diarrhea and vomiting. Leukopenia and fever are also common. Dogs may also have signs of sepsis like red mucous membranes and some dogs will develop disseminated intravascular coagulation. CPV-2 can infect the primary CNS with resultant hemorrhage into brain or spinal cord. *In utero* infection or infection in pups less than 8 weeks can lead to myocarditis and result in sudden death or congestive heart failure. Depending on the presence of prior immunity, some dogs may have subclinical infections.
Diagnostic evaluation. Dogs under two years of age with acute bloody diarrhea should be considered at high risk for CPV-2, particularly if the vaccine history is incomplete. Another differential diagnosis in dogs with appropriate clinical signs is salmonellosis; this should be considered in dogs that look clinically like parvovirus, but are well vaccinated. The clinical diagnosis is usually supported by documenting parvovirus antigen in feces by ELISA or PCR assays which are commonly part of diagnostic PCR panels in the United States. However, the PCR assays are so sensitive, CPV-2 DNA can be amplified from feces of dogs vaccinated with modified live strains of the virus. At least one of the ELISA antigen tests (SNAP®Parvo;

IDEXX Laboratories) has a cut point for a positive test result that excludes most vaccinated dogs. Thus, the ELISA may be superior to PCR for screening dogs and can also be performed in the veterinary clinic. Some dogs will have completed the shedding period by the time the test is run, leading to false negative results. Electron microscopy, virus isolation and seroconversion can also be used to document active or recent infection.

Treatments. Greater than 90% of dogs with CPV-2 enteritis will survive if administered supportive care shortly after clinical signs develop. Fluid replacement, electrolyte balance (particularly potassium), control of hypoglycemia, control of oncotic pressure (hypoalbuminemia can develop), treatment of bacteremia and sepsis (antibiotics), control of nausea and vomiting, and "feeding the gut" as early as possible are paramount to success.

Fluid therapy should be designed to correct losses, hyponatremia and hypokalemia. Oncotic pressure should be maintained with plasma transfusions, hetastarch, or related compounds. Broad spectrum antibiotics with like a first generation cephalosporins are often used in routine cases with therapy escalated to include drugs with a better gram negative spectrum in dogs showing signs of sepsis. Injectable enrofloxacin or amikacin can be added to the protocol to enhance the gram negative spectrum. Many clinics use second generation cephalosporins like cefoxitin as their primary antibiotic as this drug has an enhanced gram negative spectrum compared to first generation cephalosporin. Recently it has been shown that maropitant can be used successfully as an antiemetic agent, but also lessens abdominal pain. It is important to "feed the gut" early in cases with enteritis and so at Colorado State University, nasoesophageal or nasogastric tubes are often used to start to deliver elemental diets as soon as possible. Highly digestible diets with or without probiotics are often used in the recovery phase.

Many different adjunctive therapies like passive immune therapy (hyperimmune serum infections), granulocyte colony stimulating factors, oseltamivir (Tamiflu) are used to attempt to improve survival but has not been shown to be effective in controlled studies. Interferon omega has been beneficial in some puppies. Prognosis is variable. Intussusception may occur as a sequel to severe enteritis and so all parvovirus puppies should be palpated daily.

Not all clients can afford hospitalization and intensive care. Thus, researchers at Colorado State University evaluated an out-patient protocol. That protocol is attached as an Appendix to these proceedings. The authors concluded that this protocol was adequate for owners that could not afford more extensive therapy.

Prevention and public health considerations. Extreme care should be taken to prevent spread to other animals by disinfection with bleach, separation from other hospitalized animals, and vaccination of other dogs in the household. No zoonotic potential is recognized; the parvoviruses of humans are species specific.

Because canine parvovirus (CPV-2), canine adenovirus 1 (CAV-1; infectious canine hepatitis), and canine distemper virus (CDV) can be life-threatening diseases, all dogs should be vaccinated. For CPV-2, only modified-live products should be used because of increased risk of maternal antibody interference with killed products. Both modified-live CDV and recombinant CDV (rCDV)-containing vaccines are considered adequate by the AAHA Task Force. Because

of adverse effects associated with CAV-1 vaccines and poor immune responses associated with killed CAV-2 or modified-live topical CAV-2 vaccines, only modified-live CAV-2 vaccines for parenteral administration should be used. These vaccines cross-protect against canine infectious hepatitis induced by CAV-1 and the kennel cough syndrome induced by CAV-2. All puppies should receive at least three CPV-2, CAV-2, and CDV-containing vaccines, every 3 to 4 weeks, between 6 and 16 weeks of age, with the last booster being administered at 14 to 16 weeks of age. There is no documented breed predisposition to vaccine failure and so no indication for administering the final CPV-2, CAV-2, and CDV-containing vaccine booster after 16 weeks of age. Adult dogs with an unknown vaccination history can be given one dose of MLV CPV-2, CAV-2, and CDV-containing vaccines. Puppies housed in shelters should be vaccinated on admission and then every 2 weeks while housed at the shelter or until 16 weeks of age. Vaccinated dogs should receive a booster vaccine 1 year later and then boosters at intervals of 3 years or longer. Several CDV-containing products, including the rCDV vaccine, were recently shown to protect for at least 3 years. The currently available CPV-2b vaccines appear to cross protect against CPV-2c.

Dogs should be evaluated at least yearly for risk of infection by CPV, CDV, and CAV during the physical examination, checked for enteric parasites, and evaluated for *D. immitis* infection in appropriate regions. Positive serologic tests for CDV and CPV are predictive of resistance after challenge and can be used in lieu of arbitrary vaccine intervals if performed with validated assays. Dogs should complete the puppy series and be boosted at 1 year of age before using titers to help predict vaccine need. If the vaccination status of an adult dog is unknown, the dog should be vaccinated appropriately and then serologic assessment considered in subsequent years.

FELINE PANLEUKOPENIA

Agent. Feline panleukopenia is caused by a parvovirus (FPV) that is closely related to the canine parvoviruses and mink enteritis virus. Cats can also be infected and develop clinical disease after exposure to canine parvovirus 2 strains (CPV-2) and mixed infections have been documented in some cats. The syndrome occurs worldwide and is endemic in almost all cat populations. Young cats without prior immunity are at the greatest risk of developing disease.

FPV is present in nasal secretions, feces, and urine. It is transmitted via direct contact and fomites. Following ingestion, the virus enters the body across the small intestine. Viremia occurs and the organism infects rapidly dividing cells (particularly enterocytes, lymphocytes, and bone marrow). Lesions occur at the base of small intestinal crypts and sloughing of the microvilli occurs. Some of the clinical manifestations of disease may occur secondary to gram-negative endotoxic shock because of bacterial translocation from the diseased villi. Neutropenia may occur due to neutrophil demand in the diseased intestines and bone marrow infection. Transplacental infection and early neonatal infections may cause cerebellar hypoplasia, retinitis, and optic neuritis. Maximal viremia in in cats without prior immunity occurs 2-7 days after exposure. Dilated crypts, epithelial sloughing and necrosis of crypt cells, villous loss or atrophy; cerebellar hypoplasia and myelin degeneration are common histopathological findings.

Clinical findings. The clinical manifestations of FPV are variable based on the dose of the virus, the age of the cat, potential breed predispositions, and prior immunity from maternal antibodies,

previous exposure, or vaccination. Some cats show few to no clinical signs. Others have acute fever, vomiting (most common), diarrhea (less common than in dogs with parvovirus), sternal recumbency with splayed legs and head droop, nasal discharge and conjunctivitis. Diarrhea may be bloody. Intention tremors occur in those with cerebellar hypoplasia. Overall, there is high mortality in clinically affected kittens and sudden death can occur.

Diagnostic workup. A presumptive clinical diagnosis can be made for kittens with appropriate signalment, history, clinical findings and the history of no prior vaccination. The clinical diagnosis is usually supported by documenting parvovirus antigen in feces by ELISA or PCR assays which are commonly part of diagnostic PCR panels in the United States. However, the PCR assays are so sensitive, FPV DNA can be amplified from feces of cats vaccinated with modified live strains of the virus. At least one of the ELISA antigen tests for dogs (SNAP®Parvo; IDEXX Laboratories) detected FPV in feline feces and has a cut point for a positive test result that excludes most vaccinated cats. Thus, the ELISA is superior to PCR for screening cats for FPV infection and can also be performed in the veterinary clinic. Some cats will have completed the shedding period by the time the test is run, leading to false negative results. Electron microscopy, virus isolation and seroconversion can also be used to document active or recent infection.

Treatments. See the section on the treatment of CPV-2 infections. As for pupplies, cats with FPV can survive with appropriate supportive care. Fluid therapy should be designed to correct losses, hyponatremia and hypokalemia. Extremely dehydrated kittens can be administered fluids by intraosseous catheter placement. Oncotic pressure should be maintained with plasma transfusions, hetastarch, or related compounds. Broad spectrum antibiotics with like a first generation cephalosporins are often used in routine cases with therapy escalated to include drugs with a better gram negative spectrum in kittens showing signs of sepsis. Injectable enrofloxacin or amikacin can be added to the protocol to enhance the gram negative spectrum. Many clinics use second generation cephalosporins like cefoxitin as their primary antibiotic as this drug has an enhanced gram negative spectrum compared to first generation cephalosporin. It is important to "feed the gut" early in cases with enteritis and so use of anti-emetics and early feeding of elemental diets or highly digestible bland diets is encouraged.

Fresh hyperimmune plasma (perhaps collected from a well vaccinated adult cat) may be administered early in the course of the disease to transfer anti-parvovirus antibodies and attempt to lessen viremia bacteremia. This has not been proven effective in a controlled study, but the dose of 2 ml per kitten delivered IV or IP is reported to help some kittens.

Prevention and public health considerations. There are no known public health risks with FPV. All healthy kittens and adult cats without a known vaccination history should be routinely vaccinated with an intranasal or parenteral vaccine that contains FPV, FCV, and FHV-1 (FVRCP). Multiple modified-live products and killed products are available, but they vary by country. In general, modified-live FVRCP vaccines are recommended for kittens housed in environments at high risk for exposure to FPV, as this type of vaccine is least likely to be inactivated by antibodies transferred to the kitten as part of maternally derived immunity. Killed FVRCP vaccines have the advantage of not replicating in the host and so are safe for administration to pregnant queens and do not colonize the host. Modified-live FVRCP vaccines

for intranasal administration can induce protection against FHV-1 as soon as 4 days after administration, so this route may be preferred for kittens housed in environments at high risk for exposure to FHV-1(Lappin and et al., 2006a). Modified-live products should not be administered to clinically ill, debilitated, or pregnant animals. Owners should be informed that the administration of intranasal FVRCP vaccines can induce transient, mild sneezing or coughing.

For kittens believed to have no more than routine risk of exposure to FPV, FCV, or FHV-1, administration of FVRCP vaccines is recommended starting no sooner than 6 weeks of age, with boosters every 3 to 4 weeks until 16 weeks of age. Older kittens and adult cats with unknown vaccination history should receive two killed or two modified-live FVRCP doses 3 to 4 weeks apart.

For kittens believed to have high risk of exposure to FPV, such as those housed in animal shelters or pet stores, modified-live FPV-containing vaccines can be administered as early as 4 weeks of age, particularly during an outbreak. However, intranasal administration of modified-live FVRCP vaccines instead of or in addition to parenteral administration of modified-live FVRCP vaccines may be superior for protection against FCV and FHV-1 in these environments. The current AAFP/ISFM Advisory Panel recommends a booster FVRCP vaccine 1 year later. According to several challenge studies, administration of FVRCP vaccines does not appear to be needed more frequently than every third year after the 1-year booster vaccine; the duration of immunity may be much longer, particularly for FPV. As previously discussed, serologic test results for antibodies against FPV, FCV, and FHV-1 can be used to help determine vaccine needs (Lappin et al., 2002). (Validated serologic tests are available from New York State Veterinary Diagnostic Laboratory, Ithaca, and Heska Corporation, Loveland, Colo.)

Suggested readings

American Animal Hospital Association. Canine vaccination guidelines. https://www.aahanet.org/PublicDocuments/CanineVaccineGuidelines.pdf

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Colorado State University

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Center for Companion Animal Studies

Updated May 27, 2013

What is the outpatient treatment protocol utilized for the treatment of parvoviral enteritis at Colorado State University?

Introduction

- Funding to evaluate the study developing this outpatient treatment protocol was provided by Zoetis Animal Health.
- This randomized clinical study will be presented as an oral abstract at the American College of Veterinary Internal Medicine Forum, Seattle, WA in June, 2013.
- The treatment guidelines provided within this protocol are only to be used under the knowledge and supervision of a licensed veterinarian.
- This protocol is not intended to be a substitute for the gold standard of care (hospitalization and administration of fluids/medications intravenously), but rather used as an alternative for clients that cannot afford the recommended treatment protocol.
- In the previous study, the survival rates for the standard of care protocol and the outpatient protocol were 90% and 80%, respectively.
- Standard of care treatment should be offered and refusal to follow that protocol documented in the medical record prior to offering this as an alternative.
- The faculty associated with this outpatient protocol will not assume any responsibility for the outcome or complications associated with the use of this protocol.

Initial Stabilization

- Upon presentation to the hospital, all dogs should have an IV catheter placed for intravascular volume resuscitation.
- An initial electrolyte panel should be obtained to determine the presence or severity of hypokalemia or hypoglycemia.
- Use the standardized chart (Table 1) to determine the intravascular volume loss to be replaced
  - Isotonic crystalloid boluses should be delivered over 15-20 minutes, with subsequent reevaluation of cardiovascular parameters.
  - Additional IV fluid resuscitation should be performed at the discretion of the veterinarian.
  - Based on the electrolyte concentrations, 25% dextrose can be supplemented IV (1-2 ml/kg) based on the presence and degree of hypoglycemia.
- After cardiovascular resuscitation and restoration of normoglycemia, the outpatient portion of the study is entered.

Basic outpatient protocol

- Start subcutaneous crystalloid fluid therapy immediately after IV fluid resuscitation.
  - Normosol-R (120 ml/kg/day) divided TID (40 ml/kg/dose)
  - In addition, replace dehydration over 24 hours
- Use the standardized chart (Table 2) for determination of hydration status.

- Divide the amount of fluids needed to rehydrate the patient by 3, and add that amount onto the maintenance SQ fluid dose for the next 3 doses.
- Do not add additives (such as dextrose or KCl) to the crystalloids.
- Provide aggressive external warming to help promote absorption of the SQ fluids.
- Monitor rectal temperature to maintain ≥ 99 °F.
- If part or all of the previous dose of SQ fluids remains at the next treatment, only give partial dose of SQ fluids (subjectively determined) or withhold additional SQ fluids that treatment period.
- Cefovicin is administered once at 8 mg/kg SQ once while at hospital.
- Maropitant is administered once at 1 mg/kg SC q24h for the duration of treatment period.
- Syringe feed small amounts of Hill's a/d q6h (1 ml/kg PO), as tolerated by patient.

Rescue protocols
- Rescue analgesia
  - In dogs with visceral pain that is deemed "uncontrolled," buprenorphine 0.02 mg/kg SQ should be administered as frequently as q6-8h.
  - In the previous study, about 20% of dogs required buprenorphine.
- Rescue antiemetic
  - In dogs with nausea that is deemed "uncontrolled," ondansetron 0.5 mg/kg SQ should be administered as frequently as q8h.
  - In the previous study, about 20% of dogs required ondansetron.

Electrolyte supplementation
- Ideally, blood glucose and electrolytes should be checked once daily by the veterinarian.
- Glucose supplementation should be provided for dogs that have a BG <80 mmol/L.
  - Dogs should be administered simple syrup (Karo) 1-5 ml bucally, every 2-6 hours.
  - In the previous study, about 75% of dogs required glucose supplementation.
- Potassium supplementation should be provided to dogs that have a serum K+ < 3.4 mEq/L.
  - Dogs should be administered oral Tumil-K (0.5-1 tsp per 10 lbs, every 4-6 hours).
  - In the previous study, about 60% of dogs required potassium supplementation.
- Glucose and/or potassium supplementation should be continued until the electrolyte abnormalities have resolved and the patient is eating enough on their own to maintain these values within the normal range.
- In addition to having their electrolytes checked once daily, dogs should also have a cursory physical examination performed by the DVM once daily.

Failure of the Outpatient protocol
- In dogs receiving the outpatient protocol, worsening clinical symptoms warrants that treatment will be switched to hospitalized treatment protocol (to allow for IV catheterization). Criteria for "worsening symptoms" may include the following:
  - Progressive dehydration, defined as loss of $\geq 10\%$ of body weight from admission or $\geq 8\%$ dehydration on two serial measurements, based on physical examination findings.
  - Hyperlactatemia, defined as ≥ 4 mmol/L.
  - Decline in mentation to stuporous/obtunded.
  - Fever, defined as > 104°F.
  - Other subjective criteria that sway the attending clinician towards transition to the Inpatient protocol are the discretion of the attending veterinarian.
  - In the previous study, 5% of dogs on the outpatient protocol were transitioned to the inpatient protocol.