What’s New in the Treatment of Parvoviral Enteritis

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Introduction

- What is parvovirus?
  - Non-enveloped single stranded DNA virus
  - Family: Paroviridae
  - Genetically similar to Paroviridae in cats and mink
  - Replicates in actively dividing cells
  - Ubiquitous
  - Can persist in environment for months

Epidemiology

- 2 Types
  - CPV-1
  - CPV-2

- CPV-1
  - First discovered in the early 1960's
  - Caused mild signs of diarrhea
  - Relatively non-pathogenic
  - Called “minute virus of canines”

- CPV-2
  - Discovered in the late 1970’s
  - Caused widespread pandemic in adult domestic and wild dogs
  - CPV-2 replaced by 2 more virulent variants of parovirus
  - Now 3 subtypes are recognized worldwide
Epidemiology cont’d

- **CPV-2 subtypes**
  - **CPV-2a**
    - Discovred in 1979
    - This progressively worsened in virulence and pathogenicity
  - **CPV-2b**
    - Discovred in 1984
    - Classic parvoviral enteritis
    - Vomiting, diarrhea, myocarditis and CHF in naïve dogs
    - Most prevalent form of canine parvovirus worldwide
    - Accounts for >80% of cases in US today
  - **CPV-2c**
    - Newest genetic variant
    - Found in Europe, Asia, North and South America

Pathophysiology

- **CPV-2**
  - Transmitted through oral-fecal contamination
  - Once ingested
    - Virus replicates in oropharyngeal lymphoid tissue, mesenteric LNs and thymus
    - Then transferred in plasma to rapidly dividing cells of bone marrow and GI crypt epithelium within 4-5 days of exposure
    - Virus further replicates and destroys rapidly dividing cells of bone marrow progenitor cells and intestinal crypt epithelium
  - Virus replicates in crypt cells and causes collapse and necrosis of intestinal villi
    - Leads to a breakdown of normal blood epithelial barrier
  - This leads to:
    - Systemic sepsis
    - Septic shock
    - Systemic inflammatory response syndrome (SIRS)
    - Multiple organ dysfunction syndrome (MODS)
    - Death
  - Animals treated early and aggressively can survive
    - Mortality rates in most studies indicate >85% with aggressive care
  - Will shed the virus in their feces for over 1 month following exposure
  - 1 gram feces contains up to 10 million infective doses
Signalment
- Unvaccinated dogs of any age and breed can potentially become infected following natural exposure of CPV
- Majority of cases of clinical disease are seen in younger puppies
  - 6-20 weeks of age
  - No gender predilection until > 6 months of age
    - Males appear overrepresented

Clinical signs
- Clinical signs vary and worsen over time
  - Lethargy
  - Inappetence
  - Vomiting
  - Diarrhea (often hemorrhagic)
  - Weakness
    - Polyuria
    - Polydipsia
    - Hypoglycemia
    - Depletion of glycogen stores
    - Sepsis
  - Severely affected animals can develop
    - Seizures
    - Thromboembolic disease
    - Disseminated Intravascular Coagulation (DIC)

Diagnosis
- Fecal ELISA
  - Inexpensive
  - Rapid results cage side test
  - False negative results can occur
    - Early in the course of the disease
  - False positives can occur if patient was vaccinated with AEV within 5-15 days of testing
    - Positive test with associated clinical signs supports a diagnosis of parvovirus
  - One study demonstrated that clinically ill dogs that developed parvovirus following vaccination were infected with field strains of virus, not reversion of the virus from the AEV
Laboratory Findings

- **CBC**
  - Anemia
    - GI loss, decreased bone marrow production
      - Results from suppression of leukocyte precursors in the bone marrow as well as impaired release via the intestinal crypts
    - Occurs in ~50% of patients
  - Leukopenia (low WBC count)
    - Positive correlation with survival within 24 hours of admission into hospital
    - Total WBC count >4500
    - Lymphocyte count >1000
    - Monocyte count >150

- **Other non-specific biochemical findings**
  - Hypoproteinemia/hypoalbuminemia
    - Lack of production as well as loss through GI tract
  - Hypoglycemia
    - Toy breeds, depleted glycogen stores, sepsis (i.e. consumption)
  - Hypokalemia
    - Loss through gastrointestinal tract and decreased intake
    - Extrahepatic cholestasis of sepsis
    - Increased T bilirubin and ALP
    - Total cholesterol and HDL
      - Studies show that significantly decreased levels are negatively correlated with survival.

- **Coagulation defects**
  - Thrombocytopenia
    - Prolonged coagulation times
    - Hypercoagulability
      - Determined by thromboelastography and decreased antithrombin activity
    - Increased plasma citrulline concentrations
      - Indicator of GI cell mass
        - Found to be significantly decreased in dogs with CPV
      - Studies indicate not a reliable prognostic indicator for mortality vs survival
Laboratory Findings Cont’d

- **Acute Phase proteins**
  - Studies determined out of all acute phase proteins (CRP, Ceruloplasmin, Haptoglobin, Albumin).
  - CRP was found to be superior for predicting outcome (survival vs non-survival).
  - C-reactive protein
  - Studies correlate these values in predicting mortality
  - Values > 92.4 mg/L carried 91% sensitivity to predict mortality
  - Negative association with survivability was noted in CRP values at time of admission, 12 hours, and 24 hours after admission, but not negatively associated with the degree of change in these values.
  - Can be used as a prognostic tool in combination with CBC changes to predict mortality early on in disease.

Treatment & Monitoring

- **Fluid balance**
  - Of the utmost importance in treatment.
  - Majority of animals have significant fluid losses through vomiting/diarrhea.
  - Calculating initial fluid losses and degree of dehydration, as well as considering maintenance fluids and ongoing losses, is very important.
  - Initial fluid choice should be a balanced electrolyte solutions
    - Plasmalyte, LRS, Normosol.
  - Initial fluid resuscitation is important in animals presenting in hypovolemic shock.
  - Weighing patients frequently can help guide fluid therapy.
    - Acute loss of body weight can be equated to fluid loss.
    - 1 gm of weight loss is roughly equal to 1 ml water.
  - As fluid losses subside, the fluid rate can be altered.

- **Blood Pressure**
  - Severe dehydration secondary to decreased intake and gastrointestinal losses leads to hypovolemia and hypoperfusion.
  - Adequate fluid therapy is extremely important.
  - Serum lactate values can be used to guide degree of perfusion or lack thereof.
    - serum lactate numbers are higher in puppies so evaluating trends can be considered more useful than single absolute number.
    - Lactate values for adult dogs should not be used for puppies ≤70 days.
    - Adult dogs range from 0.5 to 1.2 mmol/L, whereas puppies can be considered normal with values of 0.8 to 1.6 mmol/L.
Treatment & Monitoring

Heart rate, rhythm, contractility
- Inflammatory cytokines can lead to depressed myocardial contractility and ventricular arrhythmias
  - Fortunately not very common
- Monitoring HR and rhythm can be useful in determining level of cardiovascular stability

Blood glucose
- Hypoglycemia is common and should be monitored (ideally every 8-12 hours)
  - This occurs secondary to sepsis and depleted glycogen stores
- Dextrose supplementation if necessary
  - Initially starting at 2.5-5% dextrose/L
  - 50-100 ml 50% dextrose/L
- Frequent monitoring needed to ensure hypoglycemia or hyperglycemia is not persistent as both have been shown to increase morbidity/mortality

Albumin & Colloid Osmotic Pressure
- Hypoalbuminemia and decreased COP are common secondary to protein loss in diarrheic feces
- Study done to determine if a single dose of CPV immune plasma would be beneficial in treatment of CPV
  - Study indicated no significant differences in neutrophil/monocyte counts, weight change, number of days requiring hospitalization and cost of care between treated and control group
  - FFP @ 15-20 ml/kg for each 0.5 g/dl albumin increase concentration desired
  - Typically cost prohibitive esp for larger puppies
- Hydroxyethyl starches can be used (Hetastarch, Vetastarch, etc)
  - Most recent literature in humans correlates use to increased morbidity and mortality in patients with sepsis
- Canine/Human Serum Albumin
  - Must weigh benefits vs potential consequences
Treatment & Monitoring

- Oxygenation/ventilation
  - Patients that develop aspiration pneumonia, ARDS, pulmonary edema are at risk of pulmonary dysfunction.
  - Provide supplemental O2 if SpO2 < 94%.

Acid/Base and Electrolytes

- These patients frequently develop metabolic acids as well as hypomagnesemia, hypochloremia, hypokalemia.
- Monitoring acid/base and electrolytes daily can help determine if supplementation is needed.

Coagulation

- Many of these patients are hypercoaguable.
- Monitoring of PT, PTT, platelet count changes can be useful.
- FFP or Cryoprecipitate can be used as needed.
Treatment & Monitoring

- RBC and Hemoglobin Concentration
  - Adequate oxygen delivery requires hemoglobin
  - Loss of blood through hemorrhagic feces if severe enough can impair O2 delivery
  - Monitoring PCV every 12-24 hours can help determine if pRBC transfusion is necessary

- Renal Function/Urine Output
  - These are end organ indicators of perfusion and fluid balance
  - Until adequate volume resuscitation and replenishment of dehydration deficits have improved, renal values if elevated will not decline and the patient will not begin to urinate
  - Frequent urination in a patient with normal renal function combined with appropriate weight gain is an indicator of adequate hydration and perfusion in the face of GI fluid losses

- Mentation
  - Changes can occur from pain, hypoglycemia, hypotension, thromboembolic disease
  - Seizures - make sure to check BG
  - If low, bolus dose of 0.5 ml/kg of 25% dextrose followed by CRI of 2.5%-5% solution
Treatment & Monitoring

- WBC, Immune Status, Antibiotic Selection
  - Immune status often severely impaired in these patients
  - Broad spectrum bactericidal antibiotics should be used
    - Consider those that will affect Gram-, Gram +, aerobic and anaerobic bacteria
    - Ampicillin, Unasyn, or Cefazolin in combination with Enrofloxacin commonly used
  - Can use Aminoglycosides (Gentamicin, Amikacin) but due to nephrotoxic properties, patient must be adequately hydrated and monitoring of renal values and urine for glucosuria and renal tubular casts should be performed

- Drug Doses and Metabolism
  - Often these patients are on multiple medications
  - Determine if any drugs are interfering with other drugs MOA

- Analgesia/Pain control
  - Cramping and ileus can inhibit feeding tolerance
  - Most opioids can promote ileus
    - Lidocaine CRIs (30 mcg/kg/min) +/- Buprenorphine (0.005-0.02 mg/kg q8-12h) can be useful to provide comfort without worsening ileus

- GI motility and integrity
  - Severely compromised in these patients due to villous damage/necrosis leading to bacterial translocation
  - Blunting of villi and enterocyte atrophy combined with ileus and hypoalbuminemia leads to malabsorption of nutrients
  - Anti-emetics/promotility agents commonly used
    - Dolasetron, Ondansetron, Maropitant, Metoclopramide, Cisapride, Lidocaine
  - Presence of GI parasites can worsen patient morbidity
    - Fecal analysis +/- empiric deworming should be considered
Treatment & Monitoring

Nutrition

- NG tube placement can be used to initiate early enteral feedings as well as to provide gastric decompression if needed
- Research supports that early enteral feeding decreases enterocyte atrophy and improves patient morbidity and mortality in these patients even in the face of vomiting
- Enteral is preferred over parenteral nutrition or PPN

RER = 30* BW(kg) + 70= Kcal/day needed

Nursing care/Patient mobilization

- Very important to maintain patient cleanliness

Bandage/wound care

- IV catheters should be checked daily and re bandaged and examined for evidence of thrombosis or contamination

TLC

- Given to every critically ill patient

Additional Alternative therapy

- Several alternative therapies have been investigated for use in patients with parvoviral enteritis
  - Anti-inflammatories
  - Hyperimmune serum
  - Antiviral drugs- Oseltamivir (Tamiflu)
  - Recombinant human granulocyte colony stimulating factor (rhG-CSF)

- In addition to increasing costs, none of the aforementioned therapies have been associated with a proven benefit in survival or decreasing patient mortality.
**Additional Alternative therapy**

- More recently canine specific granulocyte colony stimulating factor (rcG-CSF) was studied.
  - Mean WBC and neutrophil counts were significantly higher in the 28 dogs treated with rcG-CSF compared to disease-matched dogs not treated with rcG-CSF.
  - Mean duration of hospitalization was reduced in rcG-CSF treated dogs compared to untreated dogs.
  - Survival times were decreased in dogs treated with rcG-CSF compared to untreated dogs.
  - This suggests that treatment with rcG-CSF was effective in stimulating neutrophil recovery and shortening the duration of hospitalization in dogs with parovirus infection.
  - Indicates the need for additional studies to evaluate overall safety of the treatment.
  - The only treatment that has been shown to date to improve treatment outcomes is early use of enteral nutrition, which has changed the paradigm of withholding food from these patients.

**Prevention**

- Cornerstones of preventing CPV
  - Decreasing environmental contamination
  - Inducing immunity

- Decreasing environmental contamination
  - Can remain in the environment for up to 1 year
  - Any infected area should be cleaned thoroughly with soapy water to remove debris
  - Areas should then be disinfected with 1 part bleach to 32 parts water
  - No new unvaccinated dogs should be allowed into the exposed area for 1 year following contamination.
Prevention

- Inducing immunity
  - Done through use of high titer MLV
  - Vaccination earlier than 6 weeks of age can be counterproductive
  - Circulating maternal antibodies can interfere with development of an immune response
  - Booster vaccines every 3 weeks up to 12 weeks of age
  - Vaccines can be given through 16 weeks of age for predisposed breeds
  - Rottweilers, Dobermans, Pitbulls
  - For pregnant unvaccinated bitches a killed vaccine is recommended
  - Repeat vaccination at 1 year of age then every 3 years in combination with other vaccines
  - Although vaccines appear to be cross protective against new CPV-2c strain
  - Should remain on list of differentials in adult dogs that have been previously vaccinated if clinical signs are consistent with CPV

Questions?