FELINE CORONAVIRUS INFECTIONS

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IX Curso Internacional de Medicina en Pequeños Animales
Viña del Mar, 25 al 27 de Agosto, 2006

I. LEARNING OBJECTIVES
A. Describe the relationship between non-pathogenic and pathogenic coronaviruses in the feline population.
B. Describe the reasons that some cats infected with non-pathogenic coronaviruses develop feline infectious peritonitis (FIP).
C. Discuss the reasons that some cats develop effusive FIP and some develop the non-effusive form of the disease.
D. Discuss the diagnostic methods used to confirm a diagnosis of FIP, including the strengths and weaknesses of the various tests.
E. Describe the basic therapeutic strategies used to support cats with FIP.
F. List the basic principles used to prevent the development of FIP in cat populations.

II. KEY FACTS
A. Feline coronaviruses (FCOVs) are distributed widely in the feline population.
B. Most FCOVs are non-pathogenic, have an affinity for intestinal epithelial cells, and cause no significant clinical disease.
C. Rapid replication of non-pathogenic FCOVs in the intestinal tract may give rise to mutant pathogenic FCOVs with a different tissue tropism, and the ability to spread systemically leading to the development of FIP.
D. A robust cell-mediated immune response, rather than a strong humoral response, appears to prevent the systemic spread of pathogenic FCOVs.
E. The lesions of FIP are associated with an immune-mediated coronaviral vasculitis.
F. Effusive FIP appears to be the result of an inappropriate humoral immune response leading to antibody-mediated inflammation, and an inadequate cell-mediated response.
G. Histopathologic examination of tissues, and to a lesser extent the careful analysis of effusion fluid, are the gold standards of diagnosis for FIP.
H. FIP is a progressive and fatal disease. Some treatments may improve quality of life and longevity.
I. Prevention of FIP depends more on good husbandry than on vaccination.

III. VIROLOGY
A. Feline coronaviruses (FCOVs) are large enveloped positive-stranded RNA viruses.
B. FCOVs are relatedly antigenically to coronaviruses from other species (canine coronavirus, transmissible gastroenteritis virus of swine).
C. Non-pathogenic FCOVs are ubiquitous in feline populations, especially those in which animal density is high.

IV. PATHOGENESIS OF INFECTION
A. Non-pathogenic FCOVs are highly infectious between cats.
B. Non-pathogenic FCOVs also are called feline enteric coronaviruses (FECVs), because of
their affinity for replication in the epithelial cells of the tips of the villi in the small intestine.

C. FECVs are incapable of causing multi-organ systemic disease (feline infectious peritonitis), but may occasionally cause self-resolving diarrhea in kittens.

D. FECVs may mutate in the intestinal tract of infected cats, giving rise to FCOVs with increased pathogenicity and the ability to cause systemic disease (FIP).

E. Chronic stress appears to increase the rate of FECV replication in the intestinal tract, enhancing the chance of mutation.

F. Pathogenic mutated FCOVs replicate in macrophages, enhancing their ability to spread throughout the body and end up in perivascular locations.

G. Systemic disease (FIP) is more likely to occur if the infected cat develops a strong humoral response to pathogenic FCOV, and an ineffective cell-mediated immune response.

H. Systemic spread of pathogenic virus may be prevented at this stage of infection if the cat develops a strong cell-mediated immune response.

I. Tissue damage occurs due to an inflammatory response in perivascular locations initiated by antigen-antibody-complement complexes.

J. The resulting clinical disease is described more accurately as an immune-mediated coronaviral vasculitis, rather than infectious peritonitis. Lesions may be found in many organs beyond the peritoneal cavity.

K. FIP is considered a fatal disease; few cats recover from documented infection.

V. TRANSMISSION AND RISK FACTORS

A. FCOVs are transmitted through the fecal-oral route. This may occur directly through grooming (for example, from queen to susceptible kittens), or via contaminated litter boxes or fomites. Some FCOV strains are capable of remaining viable on dry surfaces for several weeks.

B. Infection occurs as a result of exposure to non-pathogenic FCOVs. Cats with clinical FIP do not appear to shed pathogenic mutant FCOVs that are transmitted to other in-contact cats.

C. Young cats are most likely to become infected with FCOVs, especially if they live in multiple-cat households in which chronic FCOV carriers are present, and if they must share litter boxes and food and water bowls.

D. Infection is perpetuated in multiple-cat households by the presence of chronic FCOV carriers which shed virus in their feces, and by continual re-infection of cats as they lose their acquired immunity. New cats added to the group also may introduce non-pathogenic FCOVs.

VI. CLINICAL SIGNS

A. Enteric coronavirus infection
   1. Usually asymptomatic; however, transient diarrhea and occasional vomiting may be noted in some cats. It is uncommon to make a clinical diagnosis of FECV-induced gastroenteritis in feline patients.

B. Feline infectious peritonitis
   1. Many cases of FIP occur in cats from 6 months to 3 years of age; however, the disease may be noted at any age. There may be a second smaller peak of incidence in older cats which becoming immunoincompetent. Both forms of FIP share some common features including chronic antibiotic-resistant fever, weight loss, lymphadenopathy, inflammatory lesions in a variety of tissues due to vasculitis, and a variably progressive course leading to death or euthanasia.
2. **Effusive FIP**
   a. First signs are often noted 1-2 months after a stressful episode (kitten moving to a new home) or exposure to infection with FCOVs.
   b. The effusive form of FIP is considered to be the more severe manifestation of systemic illness. It probably is associated with a strong (but detrimental) humoral response to a large amount of pathogenic virus, in the absence of any cell-mediated response.
   c. Clinical signs are associated with widespread immune-mediated vasculitis, leading to the leakage of protein-rich fluid into a variety of body cavities.
   d. Signs at clinical presentation may include weight loss, antibiotic-resistant fever, dyspnea, icterus, and abdominal masses (mesenteric lymph nodes, omentum with adhesions). Ascites (fluid wave), muffled heart sounds (pleural and/or pericardial effusions), and scrotal enlargement may be noted.
   e. In spite of supportive treatment, most patients with effusive FIP live only for a few weeks.

3. **Non-effusive FIP**
   a. Clinical signs are less obvious and may include progressive weight loss, anorexia, chronic unresponsive fever, lymphadenopathy, and some localizing lesions.
   b. The disease is characterized by the development of multiple perivascular pyogranulomas on serosal surfaces and within tissues without effusion.
   c. Non-effusive FIP is considered to be a more chronic, smoldering form of the disease. The humoral response to virus may be less robust, decreasing antibody-mediated disease. A partial cell-mediated immune response may decrease the severity of the lesions.
   d. Ocular lesions are common in patients with non-effusive FIP and include iritis, keratic precipitates, hypopyon, retinal perivascular cuffing, retinal hemorrhages, and retinal detachments.
   e. Neurologic signs occur in about 25-33% of cats with non-effusive FIP. Clinical signs include depression, ataxia, tremors, seizures, and paresis. On necropsy, CNS lesions are found in most cats with non-effusive FIP, even in the absence of overt neurologic signs. Hydrocephalus is a common finding on necropsy and from CT scans.
   f. Occasionally, affected cats may be presented with a solitary large pyogranulomatous mass in the ileoceccolic or colonic areas with regional lymphadenopathy, following a history of chronic vomiting and diarrhea.
   g. Cats with non-effusive FIP have a progressive illness which is fatal weeks to months after diagnosis.

VII. **DIAGNOSIS**
   A. Presently, the only definitive method to confirm a diagnosis of FIP is by histopathologic examination of tissues, supported ideally by immunohistochemical identification of FCOV antigen in typical pyogranulomatous lesions.
   B. Current serologic tests for coronaviral antibody are incapable of distinguishing between infections caused by nonpathogenic and pathogenic coronaviruses, and should never be used as the basis for making a diagnosis of FIP. Many patients with look-alike diseases
(such as lymphocytic cholangitis) may be seropositive from previous exposure to, or current infection with, non-pathogenic coronaviruses that have nothing to do with the presenting illness.

C. A diagnosis of FIP is made by excluding other diseases, and by careful assessment of the patient’s signalment, background, history, physical findings (including careful ocular and neurologic examinations), laboratory analysis (hematology, serum chemistries, and urinalysis), effusion fluid analysis, coronaviral antibody titer, and histopathologic analysis of tissues taken by biopsy or at necropsy.

D. Algorithms have been developed, in which points are assigned for positive findings in each of these areas. A confident diagnosis of FIP can be made if the cumulative point total exceeds a certain threshold.

1. **Hematology**
   a. Lymphopenia, neutrophilia with a left shift, and non-regenerative anemia may be noted.

2. **Serum chemistries**
   a. Hyperglobulinemia is a common finding. Serum electrophoresis usually reveals a polyclonal gammopathy.
   b. Other laboratory changes reflect the varying involvement of visceral organs; for example, hyperbilirubinemia (liver) and azotemia (kidneys).

3. **Coagulation assays**
   a. Changes indicative of disseminated intravascular coagulation may be noted, resulting from the widespread vascular damage. This is a poor prognostic sign.

4. **Urinalysis**
   a. No significant changes noted

5. **Effusion fluid analysis**
   a. General characteristics
      (1) Usually straw-colored and cloudy. A stable froth develops on shaking due to high protein content. May clot when left standing at room temperature or when refrigerated.
      (2) Classified as non-septic exudate or modified transudate, based on protein level and cell counts. Often erroneously described as a pyogranulomatous fluid.
      (3) Albumin:globulin ratio is important. A ratio of >0.8 excludes a diagnosis of FIP. A ratio of <0.45, with a protein level of >3.5 g/dl, and typical cytologic content (non-degenerative neutrophils, macrophages, a few plasma cells and lymphocytes, and a granular background of stained protein precipitates), is diagnostic for FIP.

6. **Serologic testing**
   a. A positive FCOV antibody titer (performed by indirect immunofluorescent antibody techniques) does not indicate that a sick cat has FIP, is actively infected at that time with pathogenic or non-pathogenic virus, or is a shedder of the virus. It simply indicates that the cat has been exposed at some time to FCOV antigen.
   b. The level of FCOV antibody titer does not correlate with the severity of clinical disease, although very high titers (>1:16,000) may support a diagnosis of FIP if other typical changes are present. Rising antibody titers have little diagnostic significance, because of the normal fluctuation
in titer levels.

c. Low titers do not exclude a diagnosis of FIP, although a result of “no detectable antibody” would make the diagnosis unlikely. Many laboratories give the low cut-off point (reported as negative) at titers of 1:100-1:400; some patients with FIP will have titers of these levels.

VIII. TREATMENT
A. At the present time, both forms of FIP are considered incurable. Some supportive treatments may extend longevity and improve quality of life temporarily.
B. Oral prednisolone (1-2 mg/kg PO q12h) may be used to decrease the adverse inflammatory response and the detrimental humoral immune response; however, the drug may dampen any beneficial cell-mediated response as well. Corticosteroid treatment seems to improve quality of life, but not improve longevity.
C. Pentoxifylline (100 mg PO q12h) has been used anecdotally (in combination with prednisolone) because of its beneficial effects in improving circulation and reducing inflammation in vascular diseases. It is not licensed for use in cats.
D. Recombinant feline interferon omega (not available presently in the USA) may ameliorate some of the signs of FIP.
E. Supportive care is important; for example, antimicrobial therapy to prevent secondary infections, and nutritional and fluid support.

IX. PREVENTION
A. Most efforts at prevention are directed toward:
1. Minimizing early FCOV infections of kittens in catteries.
2. Preventing the introduction of FCOVs in cat populations in which the virus is not present.
3. Decreasing the incidence of FIP in populations in which cases have occurred.
B. Strategies include early weaning and isolation of kittens, reducing stress and overcrowding, enhancing preventive health care and nutrition, and reducing litter-box and fomite contamination with FCOVs.
C. The commercial intranasal vaccine (Primucell FIP) has not gained widespread acceptance as an effective means for preventing FIP. The vaccine induces local surface immunity in the oronasal cavity to prevent primary infection, and stimulates a cell-mediated immune response to prevent systemic infection. Contrary to previous concerns, the vaccine does not appear to cause antibody-enhancement of disease.

Generico: Pentoxifilina
Laboratorio: CHILE, MINTLAB
Composición: Cada comprimido de liberación sostenida contiene: Pentoxifilina 400 mg.

References