

FELINE INFECTIOUS PERITONITIS

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Feline infectious peritonitis (FIP) is a common, usually fatal disease caused by infection with feline coronavirus (FCoV). It is the leading cause of death in catteries, large multiple-cat households, and shelters and accounts for one in 200 feline cases presenting at teaching hospitals around the country. The disease was first described in 1963 but was not classified as a coronavirus until 1979. FCoV is a member of the *Coronaviridae* family and is in a similar classification as transmissible gastroenteritis virus, porcine respiratory coronavirus, canine coronavirus, and some human coronaviruses. FCoV is a positive, single-stranded, enveloped RNA virus, typically 100 nm in diameter. The envelope contains petal-shaped projections called *peplomers*, which are involved in the virus attachment to the cell surface proteins. FCoV attaches primarily to enterocytes, which is where replication of avirulent FCoV is most prevalent. This may lead to mild diarrhea or asymptomatic infection.

FCoV has been detected in both domesticated and wild cats. One study states that 90% of cats in catteries and 50% of cats in single-cat households are FCoV positive. Although many cats are infected with FCoV, FIP does not develop in all infected cats. Transmission is usually via the oronasal route, but transplacental transmission has been documented. The primary source of infection for cats is through the use of litterboxes shared with infected cats; newly infected cats are usually infected with a nonpathogenic strain from a FCoV-positive cat.

Cats are initially infected with the avirulent strain of FCoV (i.e., the strain replicated in the enterocytes). FIP develops when a mutation occurs at a certain area of the FCoV genome. Researchers are presently focusing much of their efforts on the *3C* and *7B* genes. The mutation changes the cell surface, thereby making the virus susceptible to engulfment by macrophages. Once inside the macrophage, the mutated virus binds to ribosomes and is able to replicate. Transmission of the mutated version of the virus is unlikely.

The virus itself does not cause the clinical problems associated with FIP; rather, the body's immune response to the virus is responsible. Therefore, FIP is an

immune-complex disease. Mutated virus has been detected in various organs 14 days after the mutation has occurred.

Cats may present with signs of an effusive (wet) or noneffusive (dry) form of the disease. The effusive form is characterized by fluid buildup in the peritoneal and pleural spaces. In contrast, cats presenting with the noneffusive form typically have vaguer clinical signs. Lesions can be found in the peritoneum, kidney, and uvea. These lesions are the result of Type III and Type IV hypersensitivity responses to the FCoV antigen.

DIAGNOSTIC CRITERIA

Historical Information

Gender Predisposition: Male, sexually intact cats appear to be overrepresented.

Age Predisposition

- More than 50% of cats with FIP are younger than 12 months.
- Predominant age range:
 - Effusive form: 6 months to 2 years (young cats).
 - Noneffusive form: Older than 10 years (old cats), although younger cats have also presented with the dry form.

Breed Predisposition: Purebred cats are most susceptible, with Abyssinians, Bengals, Birmanians, Himalayans, ragdolls, and rexes having a significantly higher risk.

Owner Observations: Cats with FIP usually present with nonspecific clinical signs that are due to the vasculitis and organ failure produced by the FIP virus.

- Effusive FIP:
 - Abdominal distension; owners often suspect pregnancy.
 - Labored breathing.
 - Weight loss.

ON THE NEWS FRONT

A connection has recently been seen between the coronavirus that causes severe acute respiratory syndrome (SARS) in some humans and the coronavirus that causes FIP. Although they are not in the same class or family, SARS and FIP both occur as a result of mutations in a pathogenic strain of coronavirus.

An in-practice test for feline coronavirus antibodies (FCoV Immunocomb, Biogal, Galed Labs, Israel) is being evaluated. One study suggests that the test is comparable to the immunofluorescent antibody test most often used. It may have potential utility as a good screening test for cats before they are introduced into an FCoV-free facility.

Thromboxane synthetase inhibitor, thalidomide, and pentoxifylline are being tried in the treatment of FIP; however, their use is controversial, and little is known about the efficacy and side effects of these agents.

- Stunted growth.
- Ocular lesions (uveitis).

- Noneffusive FIP:
 - Neurologic signs: Seizures, dementia.
 - Weight loss, vomiting, diarrhea.
 - Icterus.
 - Lethargy.
 - Unkempt haircoat.

Other Historical Considerations/Predispositions

- Animals usually have been on multiple antibiotic regimens with no success.
- Risk factors for developing FIP include:
 - Recent episode of stress, such as vaccinations, elective surgery, or placement in a new home.
 - Cats from multiple-cat households, catteries, shelters, or pet stores.
 - Purebred cats.
 - Animals with a poor immune status because of FeLV or FIV infections.
 - Animals previously treated with glucocorticoids.
- Ownerless, free-roaming cats are less susceptible.

Physical Examination Findings

Some patients may present with signs of both the dry and the wet forms of FIP (“mixed form”).

Effusive Form (Exudative, Wet)

- In one study of FIP-positive cats, 62% had ascites, 17% had pleural effusion, and 21% had both.
- Abdominal distension with possible fluid wave.
- Dyspnea; open-mouth breathing.
- Tachypnea.
- Muffled heart and lung sounds.
- Pyrexia; fever of unknown origin.

Noneffusive Form (Nonexudative, Dry, Granulomatous, Parenchymatous)

- **General findings:** Jaundice, enlarged mesenteric lymph nodes, scrotal enlargement, irregular shaped kidneys, palpation of abdominal mass.
- **Ocular signs:** Retinal changes, including cuffing of the retinal vasculature, uveitis, hyphema, and aqueous flare, are seen most commonly.
- **Central nervous system signs:** Ataxia, personality changes, nystagmus, seizures, incoordination, cranial nerve defects.
- **Gastrointestinal signs:** Typical of intestinal obstruction; chronic diarrhea, possible vomiting, thickened intestinal area on palpation (usually at the ileocecolic junction).

Laboratory Findings

- Complete blood count: \$
 - Lymphopenia and neutrophilic leukocytosis (stress leukogram).
 - Regenerative or nonregenerative anemia.
 - Thrombocytopenia is common in cats with disseminated intravascular coagulation.
- Chemistry: \$
 - Hyperproteinemia due to hyperglobulinemia.
 - Elevated liver enzymes and total bilirubin.
 - Azotemia if kidneys are affected.
- Low albumin:globulin (A:G) ratio in effusion samples. There is a high probability a cat has FIP if the A:G ratio is below 0.8 and a low probability of FIP if the A:G ratio is above 0.8. \$

Other Diagnostic Findings

Note: Because the clinical findings associated with the two forms of FIP can overlap, the diagnostic findings listed below that are associated with the effusive form are marked with an “E” and those that are associated with the noneffusive form are marked with an “N.”

- **Thoracic and abdominal radiography:** Pleural and abdominal effusion. (E) \$
- **Ocular examination:** Possible iritis (color change of the iris to brown), keratic precipitates on the cornea, cuffing of the retinal vasculature (grayish lines on

the sides of blood vessels), retinal hemorrhages, or pyogranulomas. (E/N) \$

- **Neurologic examination:** Usually signs of multifocal and/or diffuse disease, including ataxia, nystagmus, and seizures. (N) \$
- **Protein electrophoresis:** Polyclonal gammopathy, elevated globulins (usually α_2 - and γ -globulins). (N/E) \$
- **Coronavirus serology** (feline coronavirus antibody test), especially in a household with few cats: Positive titer represents only exposure to FCoV and should be interpreted with caution. Titers greater than 16,000 combined with typical clinical signs are suggestive of FIP. A negative titer does not rule out FIP. Antibody detection has also been performed on effusions and cerebrospinal fluid (CSF), although results may be of little diagnostic value. (N/E) \$
- **Thoracocentesis/abdominocentesis and fluid analysis:** (E) \$
 - Straw-colored effusion.
 - May froth when shaken.
 - Protein greater than 3.5 g/L.
 - Total cell count higher than 20×10^6 ml.
 - Presence of nondegenerative neutrophils, macrophages, and/or lymphocytes (pyogranulomatous).
 - Usually characterized as a modified transudate or exudate because of the high protein concentration.
- **CSF analysis:** High protein (50–350 mg/dl) and cell count (100–10,000 nucleated cells/ml). Caution: Animals may be at risk for herniation after spinal tap. (N/E) \$
- **Acute-phase protein measurement:** α_1 -Acid glycoprotein (AGP) greater than 1,500 $\mu\text{g/ml}$ in plasma or effusion. (N/E) \$
- **Rivalta's test:** (E) \$
 - Used to differentiate transudates from exudates, particularly effusions of FIP-positive cats from effusions of other causes. The positive reaction is due to high levels of protein in addition to high levels of inflammatory cells and fibrin.
 - To perform the test, put 5 ml distilled water in a reagent tube; add 1 drop of acetic acid (98%), and mix thoroughly. To the surface of this mixture, carefully layer 1 drop of effusion fluid. A positive test is indicated when the drop retains its shape, remains attached to the surface, or slowly floats to the bottom of the tube. The result is negative when the drop disappears entirely and the solution remains clear.
 - The test has a positive predictive value of 86% and negative predictive value of 97%.

- **Measurement of enzyme activity:** Serum samples can be submitted for analysis of lactate dehydrogenase (released by inflammatory cells), α -amylase (if the pancreas is affected), and adenosine deaminase. All are elevated in cats with FIP. (N/E) \$
- **Polymerase chain reaction (PCR) assay of feces:** Identifies cats shedding FCoV. \$
- **Reverse transcription-PCR on CSF, effusion, or feces:** Sensitive means of differentiating previous exposure to coronavirus from an active, ongoing infection, but does not differentiate between virulent and avirulent FCoV. (Note: All PCR samples should be handled carefully, kept frozen, and analyzed as soon as possible after collection.) (N/E) \$\$
- Definitive diagnosis is made only by **biopsy and histopathologic examination** of suspected affected tissues; pyogranulomatous inflammation with vasculitis and perivascular cuffing is diagnostic. Fluorescent antibody testing and immunohistochemical testing of tissues can confirm FIP. \$\$\$-\$\$\$

Summary of Diagnostic Criteria

- Making a definitive diagnosis of FIP is extremely challenging because of the lack of pathognomonic hematologic or biochemical abnormalities and low sensitivity and specificity of currently available diagnostic tests. Some researchers suggest combining history, clinical signs, laboratory changes, and magnitude of titers to determine the likelihood of FIP.
- Rivalta's test is a very simple, in-practice diagnostic test that can provide useful information.
- Exploratory laparotomy or percutaneous biopsy with histology is the most accurate antemortem diagnostic test but is invasive and expensive.
- Most other tests discussed here have been used primarily in the research setting.

Diagnostic Differentials

- **Neoplasia** (lymphoma, multiple myeloma): Cytology of bone marrow aspirates reveals plasma cells and lymphocytes.
- **Lymphocytic cholangitis:** Ultrasound reveals "sludge" in the gall bladder, but a liver biopsy might be necessary to differentiate as this finding may be noted in any anorectic cat.
- **Pyothorax:** Degenerate polymorphonuclear cells and bacteria on cytology; positive culture.
- **Chylothorax:** Milky white fluid, small lymphocytes on cytology.
- **Cardiomyopathy:** Heart murmur, gallop rhythm, transudate to modified transudate with low cell count.
- **FeLV:** Positive antigen titer.
- **FIV:** Positive antigen titer.

CHECKPOINTS

- Vaccine production has been a challenge because of the preexisting antibodies seen in a large portion of the cat population. It has been shown experimentally that these cats may get an enhanced form of the disease as a result of antibody-dependent enhancement, which has occurred after FIP vaccination during many vaccine experiments.
 - A temperature-sensitive mutant vaccine (Primucell, Pfizer Animal Health) has been licensed in the United States since 1991. This intranasal vaccine produces local immunity at the site where FCoV first enters the body. The safety and efficacy of this vaccine are continually questioned.
- **Toxoplasmosis:** Positive serologic titer with appropriate clinical signs.
 - **Bacterial peritonitis/pleuritis:** Bacteria on cytology, positive culture.
 - **Chronic upper respiratory disease:** Ocular/nasal discharge or sneezing in unvaccinated cats and kittens.
 - **Dirofilariasis:** Heartworm-positive test.

TREATMENT RECOMMENDATIONS

Initial Treatment

- **Thoracentesis** is indicated in cats with pleural effusion. A 19- to 21-gauge butterfly catheter is attached to a stop-cock and a 30-ml syringe and inserted at the seventh or eighth intercostal space. After draining the fluid, if there is a high suspicion of FIP, dexamethasone (1 mg/kg q24h) can be administered into the thorax or abdomen until fluid subsides. Note that there may be concerns with recommending dexamethasone when the underlying cause of illness may not be known.
 - **Abdominocentesis** is generally not performed unless respiration is compromised by pressure on the abdomen.
 - **Oxygen therapy:** Cage oxygen or nasal oxygen at 100 ml/kg/min.
 - **Fluid therapy** is indicated for dehydrated or azotemic patients.
 - **Broad-spectrum antibiotics** (e.g., ampicillin, 10–20 mg PO q8h) are indicated for secondary bacterial infections associated with immunosuppressive therapy.
 - **Immune suppressive therapy:**
 - Prednisone: 2–4 mg/kg PO q24h.
 - Cyclophosphamide: 2.5 mg/kg PO on 4 consecutive days/wk.
- Chlorambucil: 20 mg/m² PO q2–3wk.
 - **Note:** Cyclophosphamide and chlorambucil should be used only in cats that are otherwise systemically well.

Alternative/Optional Treatments/Therapy

Surgery \$\$-\$\$\$

Cats with granulomatous obstruction of the small intestine may benefit from mass removal and intestinal anastomosis.

Antiviral Drugs

Ribavirin has been shown to prevent viral proteins from forming. Severe toxicity, including liver toxicity, hemolysis, thrombocytopenia, and hemorrhage, may occur in cats.

Immunomodulating Drugs

- **Human interferon α** has both immunomodulatory and antiviral activity. Development of neutralizing antibodies usually occurs 3 to 7 weeks after administration, making the cat refractory to treatment. \$\$
 - High dose: 10⁴–10⁶ IU/kg SQ q24h.
 - Low dose: 1–50 IU/kg PO q24h. To make a 3,000 IU/ml dilution, a 3 million-U vial of interferon is added to a 1-L bag of saline. Then, 1.5 ml of the resulting 3,000 IU/ml dilution is added to 150 ml of saline to make 30 IU/ml. Both the 1-L bag and the 150-ml bag can be frozen and used later. The disadvantage of this method is that each bag of saline is about 10% overfilled. Measuring out the saline alleviates this problem.
 - Adverse effects: If given orally, side effects are unlikely in cats. If given parenterally at higher dosages, fever, myelotoxicity, myalgia, allergic reactions, and malaise have been seen in cats.
- **Recombinant feline interferon (rFeIFN)** (available in Europe and Japan). Administered at 10⁶ IU/kg SQ q4h until clinical improvement is seen; then given q7d. The animal does not form neutralizing antibodies. Can be combined with dexamethasone or prednisolone.
- **Thromboxane synthetase inhibitor** (ozagrel hydrochloride): 5 mg/kg SC bid in combination with prednisolone (2 mg/kg/day) has been used with success in two cats with abdominal effusion.
- **Thalidomide:** 50–100 mg/day, given at night, has been reported in only four cats to date; all the cats died. Reduces the humoral immune response as well as inflammation. Cell-mediated immunity remains intact. Side effects have not been described, but owners would need to give consent because this drug is not approved for use in cats. \$\$\$\$

- **Pentoxifylline** (10–15 mg/kg PO q8h) has been suggested by some infectious disease clinicians. It can be obtained through a compounding pharmacy. 💰

Supportive Treatment

- Stress should be minimized, and a well-balanced, nutritionally complete diet should be provided. Placement of a feeding tube may be necessary for patients that are reluctant to eat.
- Vitamin therapy:
 - Vitamin A (200 IU/day PO) given as fish oil for a maximum of 4 to 6 weeks.
 - Vitamin B complex is a good appetite stimulant. Dosage for children can be used for cats.
 - Vitamin E is an antioxidant and is given PO at a dosage of 25–75 IU/cat bid.

Patient Monitoring

- Once stabilized, the animal should be monitored at home for recurrence of clinical signs. If clinical signs do reappear, stabilization methods should be repeated.
- Regular rechecks of the hematocrit, globulins, A:G ratio, AGP, and weight should be performed every 7 to 14 days.
- Complete blood cell counts should be checked regularly in patients receiving myelosuppressive medications.

Home Management

- The amount of stress experienced by infected cats should be limited.
- Proper nutrition should be provided.
- Litterboxes should be kept clean.
- Infected cats should be monitored for progression of clinical signs.

Milestones/Recovery Time Frames

- The absence of fever, return of appetite, and weight gain are positive signs.
- Improved respiration following thoracocentesis may last for a few days to weeks.
- FIP is a chronic, usually fatal disease, and response to treatment is usually short-lived. Death often occurs within days to months of the diagnosis despite supportive care and treatment.

PROGNOSIS

Favorable Criteria

- Weight gain; improved appetite.
- Normal body temperature.

- Decreasing globulin levels.
- Increasing A:G ratio.
- Increased hematocrit and presence of reticulocytes on blood smears.

Unfavorable Criteria

- Increasing globulin levels and AGP.
- Decreasing A:G ratio.
- Weight loss.
- Cats with the effusive form may die within 2 months of onset of clinical signs.
- Cats with the noneffusive form may have a more chronic disease course.

PREVENTION

- The best way to prevent FIP is by preventing FCoV infection.
- Kittens are usually exposed in a cattery after maternal antibodies decrease to a level that is no longer protective.
- Early weaning (4–6 weeks) and hand-raising the kittens away from all adult exposure can effectively prevent FCoV infection and subsequent mutation to FIP.
- After 10 weeks of age, kittens can be serologically tested.
- Random antibody titer sampling of three or four cats housed in groups can be done to determine if FIP is endemic to the colony. Individually housed cats may need to be tested on a case-by-case basis. Retesting can be done every 3 to 16 months to determine clearance of infection.

RECOMMENDED READING

- Addie DD, Paltrinieri S, Pedersen NC, et al: Recommendations from workshops of the second international feline coronavirus/feline infectious peritonitis symposium. *J Feline Med Surg* 6:125–130, 2004.
- Addie DD, Jarrett O: Feline coronavirus infections, in Greene C (ed): *Infectious Diseases of the Dog and Cat*, ed 3. St. Louis, Elsevier, 2006, pp 88–102.
- Hartmann K, Binder C, Hirschberger J, et al: Comparison of different tests to diagnose feline infectious peritonitis. *J Vet Intern Med* 17:781–790, 2003.
- Hartmann K: Feline infectious peritonitis. *Vet Clin North Am Small Anim Pract* 35:39–79, 2005.
- Ishida T, Shibanaï A, Tanaka S, et al: Use of recombinant feline interferon and glucocorticoid in the treatment of feline infectious peritonitis. *J Feline Med Surg* 6:107–109, 2004.
- Sparks AH: Feline coronavirus infection, in Chandler EA, Gaskell CJ, Gaskell RM (eds): *Feline Medicine and Therapeutics*. Ames, IA, Blackwell Publishing, 2004, pp 623–636.