Feline Infectious Peritonitis

Feline infectious peritonitis (FIP) frequently results in death in cats. It is caused by a mutated, highly contagious coronavirus, and it is more common in indoor cats in multicat households. A complex interaction between the coronavirus and the feline immune system causes disseminated vasculitis, which is the hallmark of FIP. New tests are being developed, but the antemortem diagnosis of FIP continues to be difficult and frustrating. Current treatments are crude and involve supportive care and immunosuppression. Minimizing exposure is the best method of preventing infection.

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Abstract: Feline infectious peritonitis (FIP) frequently results in death in cats. It is caused by a mutated, highly contagious coronavirus, and it is more common in indoor cats in multicat households. A complex interaction between the coronavirus and the feline immune system causes disseminated vasculitis, which is the hallmark of FIP. New tests are being developed, but the antemortem diagnosis of FIP continues to be difficult and frustrating. Current treatments are crude and involve supportive care and immunosuppression. Minimizing exposure is the best method of preventing infection.

Causative Agents

Feline coronavirus is a large, enveloped RNA virus that exists in two forms: feline enteric coronavirus (FECV) and feline infectious peritonitis virus (FIPV). FECV is virtually nonpathogenic, whereas FIPV is almost invariably fatal.1 All FECV carriers have the potential to develop either enteritis or peritonitis, although only about 5% of infections develop into FIP.1 Currently available diagnostic tests cannot differentiate FECV from FIPV with 100% accuracy.

Multicat households have a much higher prevalence of FECV (75% to 100%) than single-cat households (25%).2-4 Animal shelters and catteries facilitate the transmission of FECV because of high environmental stress and sharing of contaminated litterboxes.4,5 Increases of up to a millionfold in fecal shedding of FECV were seen in FECV-positive cats after entering an animal shelter.6 Half of the cats that were originally FECV negative were shedding FECV within 1 week of entering the shelter.6

Pathogenesis

FECV, which is highly contagious, is transmitted primarily via the fecal–oral route, although it may also be transmitted by inhalation.1 It replicates in the epithelial cells of the intestinal tract. Fecal shedding begins within 2 days of infection, and seroconversion occurs within 18 to 21 days after exposure to the virus.1 FECV replicates only in enterocytes. It can exist in the systemic circulation but cannot sustain viral production there, so progression to FIP does not occur.7 However, if a crucial deletion mutation (typically of the 3C or 7B gene) occurs, the virus can be taken up by macrophages and gain access to the systemic circulation, where it transforms into the highly pathogenic FIPV.8 FIPV infection is sustained in monocytes and macrophages, where the virus undergoes replication and spreads systemically.7

Traditionally, FIP has been divided into two distinct clinical forms: effusive (wet) and noneffusive (dry). Approximately three times as many cats present with the wet form as with the dry form.9 However, these divisions are not absolute, as a combination of both forms is often present in cats with FIP.10 The macrophage is the key inflammatory cell in both forms of FIP.11

Cats that are infected with FECV but do
FIP occurs primarily in indoor cats housed in large groups.

**QuickNotes**

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Feline Infectious Peritonitis (FIP) occurs primarily in indoor cats housed in large groups. Cats that do not develop FIP are believed to mount a strong cell-mediated response, although other, undetermined factors are likely involved. A lack of cell-mediated immunity, combined with a strong humoral response by the host, leads to the effusive form of FIP. Host antibodies and viral antigens form immune complexes that are deposited on the vascular endothelium, causing vasculitis with resultant leakage of proteinaceous fluid. Adhesion of infected monocytes to the endothelium activates complement, causing the release of vasoactive amines that retract the vascular endothelium, allowing further protein and fluid exudation. When virus-infected monocytes enter tissue, they attract antibodies that fix complement, drawing in more macrophages and neutrophils and creating a perivascular pyogranulomatous inflammation.

Experimentally infected monocytes and macrophages do not express surface viral proteins; rather, viral proteins are rapidly internalized following exposure to FIPV-specific antibodies. This allows the virus to evade antibody-dependent lysis, so the humoral response fails to clear FIPV infection. If a partial cell-mediated response is mounted, the noneffusive form of FIP results, and large pyogranulomas form in many organs. The vasculitis present in dry FIP is not severe enough to cause the effusion that occurs in wet FIP.

The patterns of expression of various cytokines in the peripheral blood monocytes, macrophages, lymphoid tissue, and ascitic fluid of cats with FIP are being studied extensively. Tumor necrosis factor (TNF)-α, interferon (INF)-γ, interleukin (IL)-6, IL-10, and IL-12 appear to play roles in the development of FIP. Increases in INF-γ and IL-10 may be protective, whereas increases in TNF-α, IL-6, and IL-12 appear to be associated with disease progression. The role of all of these cytokines in the development of humoral (Th2) and cell-mediated (Th1) immune responses may be instrumental in understanding the pathogenesis of FIP.

**Signalment**

All felids are susceptible to FIP. Among nondomestic cats, cheetahs are particularly vulnerable. Among domestic cats, young cats aged 3 months to 3 years and geriatric cats older than 13 years are most frequently affected. Sexually intact cats, males, and purebred cats have a higher incidence of FIP. Susceptibility to FIP is a polygenic inherited trait in Persians and Birmans. However, a recent study revealed differences between breeds in the prevalence of FIP (Box 1).

**Clinical Signs**

FECV infection may manifest as a benign illness limited to mild diarrhea that rarely requires veterinary attention. Some cats show no clinical signs of infection. Cats with wet FIP are typically ill and debilitated. Fever or uveitis may be present. These cats exhibit abdominal distention, pallor, tachypnea, dyspnea, or muffled heart sounds as a result of fluid accumulation in the peritoneal or pleural cavities. Clinical signs of the dry form can be vague and nonspecific, including lethargy, poor appetite, weight loss, icterus, and an intermittent fever that does not respond to antibiotics. Kittens may have stunted growth and diarrhea. Ocular lesions include iritis, uveitis, and cuffing of the retinal vasculature. Pericardial effusion is less common. Effusion into body cavities is a nonspecific finding without cytologic evaluation of the fluid; similar effusions occur in a variety of diseases (e.g., lymphoma, hepatic neoplasia, cholangiohepatitis, congestive heart failure, bacterial peritonitis/pleuritis).

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Diagnostic Tests

No single sensitive, specific, noninvasive diagnostic test for FIP is currently available. Therefore, test results must be combined with the history and clinical signs to establish the diagnosis.

The complete blood cell count (CBC) often reveals lymphopenia, neutrophilia, nonregenerative anemia, and thrombocytopenia. Lymphopenia is due to virus-induced apoptosis of lymphoid tissue. Neutrophilia characterizes a stress leukogram secondary to infection. Nonregenerative anemia is due to chronic inflammation. Thrombocytopenia may be due to immune-mediated destruction or decreased bone marrow production of platelets.

Hyperglobulinemia is observed in more than 70% of patients with FIP. Elevated serum globulin levels may be due to the antibodies produced during the host’s humoral immune response to the virus, as well as the presence of complement and immune complexes. Mild hypoalbuminemia may be due to decreased albumin production by the liver or increased loss from endothelial leakage. The serum albumin:globulin ratio (A:G) should be calculated: a value of <0.8 indicates that the cat likely has FIP (92% positive predictive value [PPV]), whereas a serum A:G >0.8 makes FIP unlikely (61% negative predictive value [NPV]). An elevated bilirubin level is likely due to liver necrosis. Liver enzyme levels are frequently normal. Additional serum biochemical abnormalities reflect the organs affected by vasculitis and subsequent lack of blood supply. Disseminated intravascular coagulopathy and coagulopathies caused by liver necrosis and increased platelet reactivity can also be seen.

Serum protein electrophoresis may reveal a polyclonal or a monoclonal gammopathy, so this test does not help distinguish FIP from other diseases that cause hyperglobulinemia.

Alpha-1-acid glycoprotein (AGP) is an acute-phase protein, the serum level of which is elevated in many infectious and inflammatory diseases. AGP controls lymphocyte production of cytokines by modulating neutrophil and lymphocyte responses. Levels of AGP in serum and effusions increase twofold to fivefold in cats with FIP, more than in diseases such as neoplasia and cardiomyopathy. The role of AGP in the development of FIP is unclear, but the protein may prove to be a useful biomarker. Serum amyloid A (SAA), another acute-phase protein, increases 10-fold in the serum of cats with FIP compared with healthy cats exposed to FECV. SAA may also be useful as a biomarker in the future. At this time, no validated commercial test is available for routine evaluation of AGP and SAA levels.

Analysis of Effusion Fluid

FIP effusion fluid is typically a straw-colored, modified transudate that contains a high level of protein (>3.5 g/dL) and few cells (<5000 nucleated cells/mL). The fluid may also be classified as an exudate or, rarely, as chyle. The high protein content comes from leakage of globulins across the damaged
vascular endothelium. Neutrophils and macrophages in the fluid are consistent with pyogranulomatous inflammation.

The A:G ratio of the effusion should be measured: a ratio of <0.5 is strongly correlated with FIP, with a PPV between 66% and 95%, depending on the prevalence of FIP in the cat’s environment.\(^3\) An A:G ratio >0.81 has a 100% NPV, essentially ruling out FIP.\(^1,3,12,40\) In some cases, the results of the CBC, serum chemistry, fluid analysis, and cytology—combined with a thorough history and physical findings—may be sufficient for a presumptive diagnosis of FIP.

Rivalta’s test can be performed to exclude FIP as a cause of effusion.\(^3,10\) This test has an 86% PPV and a 97% NPV for FIP.\(^10\) One drop of 98% acetic acid (not vinegar) is mixed into a test tube containing 5 mL of distilled water.\(^3,10\) One drop of effusion fluid is gently added to the mixture. If the drop dissolves and disappears, the result is negative, so FIP can be ruled out as the cause of effusion. If the drop holds its shape due to high levels of protein, fibrin, and inflammatory mediators, the result is positive.\(^41\) Diseases other than FIP that produce positive results on Rivalta’s test are lymphoma and bacterial peritonitis, which can usually be distinguished by cytologic evaluation of the fluid.\(^10\) Rivalta’s test is not frequently used because 98% acetic acid is not readily available in most veterinary practices.

**Polymerase Chain Reaction**

Reverse transcription polymerase chain reaction (RT-PCR) can identify feline coronavirus in effusion fluid, feces, tissue, or blood.\(^10,42,43,46\) Messenger RNA (mRNA) is only present when the virus is replicating, which is important in differentiating between FIPV and FECV.\(^46\) Although FECV can be present in the circulation, it does not replicate within monocytes, so no mRNA should be identified.\(^46\) When FIPV is circulating and replicating within monocytes and tissue macrophages, it produces mRNA, which can be identified using RT-PCR.\(^46\) Because it can be difficult to work with mRNA,
a DNA copy (cDNA) is created in RT-PCR by reverse-transcribing the mRNA. The cDNA is then amplified using primers specific for the highly conserved M gene so that large quantities of cDNA are available for identification of the virus. Of cats with confirmed FIP, 93% tested positive with RT-PCR, and no false positives occurred in the study group.

However, RT-PCR results may be incorrect. False negatives can occur because of degradation by RNases, ubiquitous enzymes that can easily contaminate a sample. Laboratory contamination and cross-reaction with other coronaviruses (e.g., canine coronavirus, transmissible gastroenteritis virus) can produce false-positive results.

Auburn University’s College of Veterinary Medicine Molecular Diagnostics Laboratory is the only laboratory to offer the FIP mRNA Multi Test. Samples of whole blood, effusion fluid, and tissue/aspirate of an affected organ are submitted for RT-PCR testing. The PPV and NPV of this combined test are both reportedly close to 100%.

Cerebrospinal Fluid Analysis and Central Nervous System Imaging
Neurologic abnormalities are present in approximately 35% of cats with FIP. CSF analysis may reveal an elevated protein content or pleocytosis (lymphocytes and neutrophils). FIP should be strongly suspected in a cat with inflammatory CNS disease and hydrocephalus identified on magnetic resonance imaging or computed tomography.

Histopathology
Histopathology is the gold standard for the diagnosis of FIP. Without histopathology, any diagnosis of FIP is considered presumptive. However, cats with FIP are extremely debilitated, making exploratory surgery for biopsies risky and impractical. Fine-needle aspiration and Tru-Cut biopsy of the liver and kidneys have been evaluated as diagnostic tests for FIP. Lesions consistent with FIP can be identified using these techniques, and combining fine-needle aspiration and Tru-Cut biopsy of the liver has the highest sensitivity (86%). However, false negatives and inadequate samples are common, yielding a very low diagnostic sensitivity (11% to 38%).

In many cases, lesions are observed only at necropsy. The classic lesions are pyogranulomatous inflammation that has caused vasculitis, necrosis, and fibrosis. The wet form of FIP affects a large number of blood vessels, causing the typical effusion, and small plaques form on the surfaces of abdominal and thoracic organs. In the dry form, larger pyogranulomas affect the kidneys, liver, eyes, and CNS. Solitary mural FIP lesions of the colon or ileocecal junction may be grossly mistaken for neoplasia. Meningitis, ependymitis, and hydrocephalus are seen in the neurologic form of FIP. Lymphoid depletion is commonly observed in the spleen and lymph nodes of cats that succumb to FIP. Lymphoid tissue is hyperplastic in cats that survive infection.

Immunofluorescent staining identifies the coronavirus within macrophages in effusion fluid or tissue. This test is 100% specific but only 50% sensitive for FIP when performed on effusion samples. In other words, FECV should not be found in macrophages in effusion samples, so a positive result indicates that the cat has FIP. Low numbers of macrophages with insufficient virus to create fluorescence can lead to a false-negative result. RT-PCR can also be performed on tissue that has not been preserved in formalin.

Treatment
No curative treatment exists for FIP. Therapy is directed at suppressing the formation of immune complexes and thus trying to control the vasculitis that characterizes the disease. Supplemental therapies to increase the overall well-being of the cat, including fluids and nutritional support, should be provided.

If an owner or breeder chooses to test healthy cats, cats identified as FECV seropositive should not be subjected to stress because the onset of clinical signs is frequently seen after events such as elective surgery or introduction to a new home. Avoiding stress in group-housing situations is especially important. Cats with diarrhea suspected to be due to FECV should be managed with supportive care to maintain hydration, weight, and intestinal bacterial balance.

Because the immune system of cats with FIP

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is impaired, immunosuppressive therapy may be contraindicated. However, prednisone, intracavitary dexamethasone, and cyclophosphamide may be used to control the immune response to the virus and temporarily improve the cat’s quality of life. Ribavirin is an antiviral agent with activity against FECV, but its use is limited by its severe toxicity in cats, which causes hemolysis, bone marrow suppression, and liver damage.

Various supplements have been used anecdotally with variable reports of success. High-dose injectable human INF-α (10⁴ to 10⁶ IU/kg SC q24h) inhibits viral nucleic acid and protein synthesis. Cats develop neutralizing antibodies to human INF-α within 3 to 7 weeks, limiting its usefulness. Low-dose oral human INF-α (1 to 50 IU/kg PO q24h) has immunomodulatory effects that may cause progression of FIP and is not recommended. Feline INF-ω inhibits FECV in vitro and is available in some countries. A recent report described a small number of cats with suspected (not definitively diagnosed) FIP that were treated with glucocorticoids as well as feline INF-ω. No well-controlled studies have been performed to assess the effectiveness of feline INF-ω against naturally occurring FIP. Propionibacterium acnes is a nonspecific immunostimulant that may enhance cell-mediated immunity, but no efficacy against FIP has been documented.

Prognosis

Because there is no definitive treatment, the prognosis for FIP is grave. Cats with the effusive form of FIP usually survive less than 2 months after presentation and sometimes for only days or weeks. The clinical signs are devastating and rapidly progressive, so euthanasia is justified when the cat has a diminishing quality of life. The average survival time for cats with noneffusive FIP is unpredictable, with clinical signs waxing and waning for weeks to months.

Prevention

Catteries and Shelters

Minimizing exposure is the mainstay of preventing the spread of this highly contagious disease. Cats should be housed in groups of five or fewer, with no contact between groups. Sanitation is extremely important, and attention should be given to any potential vector (e.g., litterboxes) when housing groups of cats. One litterbox should be provided for each cat, and the litterboxes should be cleaned daily to reduce fecal contamination.

Queens should be isolated from all other cats 2 to 3 weeks before delivery. Strict isolation and sanitation should be continued until the kittens are weaned at 5 weeks of age. The kittens should be maintained in isolation until they are removed from the cattery. Infected queens can produce kittens negative for FECV if the kittens are strictly isolated and weaned early. No cat that produces two or more kittens with FIP should be bred, since a genetic predisposition has been shown.

Any cat entering a cattery should be screened with FECV serology or fecal RT-PCR and isolated before introduction to the general cat population. Kittens can be screened as young as 10 weeks of age. Cats with high titers, low titers, and negative titers should be housed separately. As its titer decreases, a cat can be housed with other nonshedders. Chronic shedders should be removed to eliminate a source of FECV in the cattery. A cat, and ultimately a cattery, may be considered FECV negative after 5 consecutive months of negative fecal RT-PCR tests and serology tests.

Individual Households

An exposed, seropositive, ill cat should be suspected of having FIP and should be appropriately evaluated, isolated, and treated. A healthy cat that has been exposed to a cat that succumbed to FIP should be carefully monitored for any clinical signs of illness. FECV can remain infectious in the environment for more than 7 weeks. Therefore, an owner should wait at least 3 months before introducing another cat into the house.

Vaccination

An intranasal, temperature-sensitive vaccine that stimulates mucosal immunity against FECV was released in 1991. In field trials, the vaccine appeared to be safe and effective for cats that had not been exposed to FECV before vaccination. The efficacy of the vaccine is questionable in cats already exposed to FECV because mucosal immunity cannot protect against viral mutation. Unfortunately, most at-risk kittens are already exposed to FECV before the vaccine can be administered.

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Reverse transcription polymerase chain reaction is a promising test for the accurate diagnosis of FIP.
starting at 16 weeks of age. The American Association of Feline Practitioners lists the FIP vaccine as “not generally recommended.”

**Conclusion**

FIP is a devastating disseminated vasculitis in cats that results from a complex interaction between a mutated FECV and the feline immune system. The virus is highly contagious, so the disease is more common in multicat households and in purebred cats in catteries. Researchers are continuing to elucidate the complex pathophysiology of the disease, which should eventually lead to more effective methods of prevention and cure. The recent development of RT-PCR testing is providing encouraging results for possible antemortem diagnosis of FIP, although the laboratory providing this test has not published any information regarding its validation methods. Current treatments are crude at best and involve supportive care and, sometimes, blanket suppression of the host’s humoral and cell-mediated immune responses. Minimizing exposure is the best method for prevention of infection.

**References**

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1. Which is the key inflammatory cell in the development of FIP?
   a. T cell  
   b. neutrophil  
   c. macrophage  
   d. eosinophil

2. Which breed of cat has a genetic susceptibility for the development of FIP?
   a. Persian  
   b. Manx  
   c. Siamese  
   d. Ragdoll

3. What percentage of cats exposed to FECV develop clinical FIP?
   a. <10%  
   b. 20% to 30%  
   c. 50% to 60%  
   d. 90% to 100%

4. What finding on brain magnetic resonance imaging is suggestive of FIP?
   a. hydrocephalus

5. What A:G ratio in effusion fluid is suggestive of FIP?
   a. <0.5  
   b. 0.6 to 0.8  
   c. 0.8 to 1.0  
   d. >1.0

6. What histologic lesion is not suggestive of FIP?
   a. perivascular inflammation
   b. hepatic nodular regeneration
   c. tissue necrosis
   d. lymphoid depletion

7. Why should anticoronavirus titers not be used to definitively diagnose FIP?
   a. They cannot distinguish between FIPV and FECV.  
   b. Laboratory reporting of titers is inconsistent.

8. Why are indoor cats more at risk for developing FIP than outdoor cats?
   a. population density  
   b. environmental stress  
   c. shared litterboxes  
   d. all of the above

9. What nondomestic feline is most susceptible to FIP?
   a. lion  
   b. tiger  
   c. cheetah  
   d. cougar

10. What type of immune response produces dry FIP?
    a. strong humoral response  
    b. strong cell-mediated response  
    c. partial cell-mediated response  
    d. INF-γ