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Chapter 10

Feline Infectious Peritonitis (Feline Coronavirus)

Robert G. Sherding

Feline infectious peritonitis (FIP) is a progressive and highly fatal systemic disease of cats caused by feline coronavirus. Feline coronavirus most frequently causes inapparent enteric infection with fecal shedding of virus. Mild enteritis and diarrhea are seen rarely (see Chapter 14). A mutation of feline coronavirus during intestinal replication enables it to infect macrophages and cause FIP. Despite its name, the lesions of FIP are widespread and not restricted to the peritoneum. Effusive and non-effusive forms of FIP occur. Since its recognition in the 1950s, FIP has been one of the most studied diseases of cats, yet a definitive diagnostic test, an effective treatment, and a reliable vaccine are lacking. With the decline in prevalence of feline leukemia virus from vaccination, FIP has become the deadliest infectious disease of cats.

ETIOLOGY

Feline Coronavirus

- Feline coronavirus (FCoV) is a single-stranded enveloped RNA virus with distinctive petal-shaped peplomers projecting from the surface. There are two serotypes of FCoV that differ in cell culture characteristics. Serotype I predominates in North America and Europe, whereas Serotype II is more closely related to canine coronavirus (CCV) and predominates in Japan.
- Coronaviruses are found in many animals and are generally adapted for infecting epithelial cells of the respiratory or gastrointestinal tract. FCoV is closely related to CCV, swine transmissible gastroenteritis virus (TGEV), porcine respiratory virus, and some human coronaviruses. The CCV that causes enteritis and diarrhea in dogs (see Chapter 14) can infect cats and cause antibodies that crossreact with FCoV. Experimentally, CCV can cause enteritis, diarrhea, and even FIP in cats.

Pathogenesis of Feline Infectious Peritonitis

▼ ***Key Point*** FIP-causing coronaviruses are genetic mutants of harmless enteric FCoV.

- It was previously thought that cats were infected by two similar but distinct coronaviruses, the innocuous feline enteric coronavirus and the deadly FIP virus, but these are now considered phenotypic variants (biotypes) of the same virus. The non-mutated enterotropic FCoV typically causes a clinically inapparent infection of intestinal epithelial cells with fecal shedding of virus. During replication in the cat's intestinal tract, FCoV mutates frequently, especially in kittens, and this sporadically results in critical genetic mutations that enable FCoV to infect and replicate in macrophages.

▼ ***Key Point*** Any cat with inapparent FCoV infection has the potential to develop FIP if the virus mutates during replication to allow the mutated FCoV variant to infect macrophages. Viral replication in macrophages is the defining event in FIP.

- Macrophages then replicate the mutated coronavirus and carry it to target tissues such as the peritoneum, pleura, kidney, uvea, and nervous system, resulting in widespread immune-mediated vasculitis, disseminated perivascular pyogranulomatous inflammation, and exudative fibrinous polyserositis. These are the characteristic lesions of FIP.
- The pathogenesis involves circulating immune complexes, complement fixation, cytokine release, apoptosis of activated T lymphocytes, and vascular damage with necrosis and increased permeability.

▼ ***Key Point*** It is not the virus that causes widespread damage in FIP. The disease is a consequence of the cat's immune reaction to the virus.

- Natural immunity to FCoV is poorly understood but is presumed to be cell mediated rather than antibody mediated. Circulating FCoV antibodies can actually enhance progression of the disease.

EPIDEMIOLOGY

Prevalence

- FCoV is ubiquitous in cats worldwide. In many regions, 50% of cats are positive for coronaviral antibodies (i.e., seroprevalence). The majority of these seropositive cats represent current or past inapparent infection with non-mutated FCoV. Only some of these develop into mutated FIP-causing infections; thus, the prevalence of FIP is much lower.
- The prevalence of FCoV infection is highest in cats confined in crowded groups, such as catteries, shelters, and multiple cat households, where the seroprevalence ranges from 50% to 90%.
- In endemic catteries where the seroprevalence approaches 90%, most FCoV-infected cats remain healthy and only 5% develop FIP.
- The seroprevalence of FCoV in free-roaming feral and stray cats is 12% to 15%. The lower prevalence is presumed to relate to less social interaction and less exposure to fecally excreted virus than cattery cats.
- The seroprevalence in single-cat households is 15% or less.
- In a large survey of North American veterinary teaching hospitals, FIP was diagnosed in 1 of every 200 new feline accessions. This population mostly represents sick cats seen by veterinarians.
- FCoV can infect most wild felids, including the lion, cougar, cheetah, jaguar, leopard, bobcat, sand cat, caracal, serval, and lynx. Cheetahs are especially susceptible to developing FIP.

Risk Factors

▼ ***Key Point*** Whenever FCoV exists in a cat, so does the potential for developing FIP.

- FCoV infection occurs most often in young kittens after maternal antibodies dissipate, between 6 and 16 weeks of age; thus, the infection rate is highest in catteries where kittens are raised in association with virus-excreting adult cats.
- Young cats have increased risk for developing FIP. The peak incidence for FIP is between 6 months and 3 years of age, although cats of any age can be affected.
- Crowded group confinement (multicat households, purebred catteries, shelters) increases risk.
- Factors intrinsic to the shelter experience increase fecal shedding of FCoV up to 1 million-fold after 1 week.

▼ ***Key Point*** Most cats with FIP come from catteries and shelters.

- Any factor that increases FCoV replication in the intestines of an infected cat will increase the probability of the virus mutating to a form that can cause FIP. Thus, viral load, stress, immune impairment, corticosteroids, surgery, and concurrent disease (e.g., feline leukemia virus or feline immunodeficiency virus) can be risk factors for FIP.
- Inherited genetic susceptibility to FIP is a factor in some purebred cats and in cheetahs.

Transmission

- FCoV is primarily excreted in feces from cats with inapparent enteric infection. Healthy carriers often shed FCoV in their feces for at least 10 months, and some cats shed persistently for many years, possibly for life. One-third of healthy FCoV-seropositive cats are actively shedding virus. In high-density endemic catteries, up to 60% of healthy cats may be shedding virus at any given time.
- FCoV is usually inactivated in 24 to 48 hours at room temperature, but the virus can survive up to 7 weeks in dried fecal debris; thus, environmental contamination with small particles of used litter is an important source of infection. Contaminated surfaces, food and water dishes, and human clothing, shoes, and hands can act as fomites. Most disinfectants and detergents easily destroy FCoV.
- Transmission to uninfected cats most frequently occurs through oronasal contact with virus-containing feces or contaminated material from the environment. Contaminated litter and dust particles deposited on the fur are ingested during normal grooming activity.

▼ ***Key Point*** Indoor confinement in crowded groups increases exposure to large doses of infectious virus in feces in shared litter boxes.

- In catteries, kittens are most frequently infected as they lose maternal-derived immunity after 6 weeks of age through contact with feces from virus-shedding adult cats. Removing kittens from contact with adult cats at 5 to 6 weeks of age prevents infection (see "Prevention").
- FCoV can also be excreted in saliva, respiratory secretions, and urine, but these are unlikely to be important sources of infection.
- Transplacental transmission is possible but uncommon.
- Cats with FIP shed mostly the avirulent non-mutated FCoV, not the virulent mutated virus that causes FIP; thus, FIP itself is not directly contagious. Cats with FIP also excrete less FCoV than healthy carriers.

CLINICAL SIGNS

Cats with non-mutated FCoV infection of the intestinal tract infrequently develop clinical signs (see Chapter 14). This section describes the clinical manifestations of mutated, FIP-producing FCoV infection. Cats with FIP often present initially with nonspecific and non-localizing signs, such as fever, anorexia, inactivity, weight loss, vomiting, diarrhea, dehydration, and pallor (anemia). As the disease progresses, these signs worsen and additional clinical signs develop that indicate either body cavity effusions in the "wet" form of the disease or organ-specific abnormalities in the non-effusive or "dry" form (Table 10-1). Approximately 75% are effusive and 25% are non-effusive. Some cats manifest features of both effusive and non-effusive disease or change over time from one form to the other.

Incubation and Clinical Course

Incubation and Onset of Feline Infectious Peritonitis

- The natural incubation period is extremely variable, ranging from a few weeks to several years. Cats are at greatest risk for developing FIP within the first 6 to 18 months after initial infection with FCoV.
- This encompasses the unpredictable but often prolonged period of time it takes a carrier of the harmless, non-mutated FCoV to develop the critical viral mutation and then the time it takes the mutated virus to produce clinical disease.
- The onset of clinical signs is often insidious, but occasionally it is sudden, especially in young kittens.

Table 10-1. CLINICAL SIGNS AND LABORATORY ABNORMALITIES IN FELINE INFECTIOUS PERITONITIS

Nonspecific Signs
Chronic unresponsive fever of unknown origin
Unexplained anorexia, lethargy, and weight loss
Effusion Signs
Fluid distension of the abdomen
Dyspnea due to pleural effusion
Muffled heart sounds due to pericardial effusion
Scrotal swelling
Organ-Specific Signs
Abdominal disease
Enlarged, firm, irregular kidneys
Icterus and hepatomegaly
Intestinal pyogranulomatous mass
Splenomegaly
Pancreatitis
Mesenteric lymphadenopathy
Omental adhesions and mass
Neurologic signs (multifocal and progressive)
Uveitis (iridocyclitis; chorioretinitis)
Pyogranulomatous interstitial pneumonia
Testicular enlargement (orchitis)
Laboratory Abnormalities
Anemia (nonregenerative)
Neutrophilic leukocytosis or leukopenia; lymphopenia
Elevated serum protein (hyperglobulinemia)
Elevated serum liver enzymes and bilirubin (also bilirubinuria)
Azotemia of primary renal origin
Proteinuria of renal origin
Pyogranulomatous or fibrinous body cavity effusion
Elevated CSF protein and leukocytes (neutrophils)

CSF, cerebrospinal fluid; FIP, feline infectious peritonitis.

▼ ***Key Point*** Chronic fluctuating fever that is unresponsive to antibiotics is a frequent early sign of FIP.

Clinical Course

- Once viral dissemination occurs and clinical illness develops, FIP is virtually always progressive and fatal. However, there is considerable variation in the duration of clinical illness before death; 3 to 6 weeks is typical, but prolonged illness exceeding 6 months can occur, as can intermittent illness punctuated by periods of remission.
- For effusive FIP, the clinical course is usually acute (days to weeks).
- For non-effusive FIP, the course is often chronic and insidious (weeks to months).
- Cats with only ocular involvement sometimes survive for a year or more.

Effusive (Wet) Form of Feline Infectious Peritonitis

▼ ***Key Point*** In cats with the effusive (wet) form of FIP, the predominant location of the inflammatory fluid is the abdominal cavity in 62%, the thoracic cavity in 17%, or both cavities in 21%.

Abdominal Effusion (Peritonitis)

- Effusive FIP involving the peritoneal cavity causes progressive, non-painful, fluid distension of the abdomen.
- Effusion is detected by palpation and percussion of a fluid wave. In the early stages, a small amount of abdominal fluid may be detected by palpation of intestinal loops that feel excessively slippery, as though the serosal surfaces are highly lubricated. Pain on palpation is infrequent.
- Extension of the peritoneal inflammation may involve the gastrointestinal tract (vomiting, diarrhea), hepatobiliary system (jaundice), or pancreas (vomiting due to pancreatitis).
- Scrotal swelling may occur in intact males as a direct extension of the peritoneal inflammation and effusion into the testicular tunics.
- Adhesions may organize the mesentery, omentum, and viscera into an irregular, firm mass that is palpable in the cranioventral abdomen.

- Abdominal effusion is confirmed by radiography, ultrasonography, or abdominocentesis, and the results of fluid analysis are highly indicative of FIP (see "Diagnosis").

Thoracic Effusion (Pleuritis)

- Dyspnea, tachypnea, and exercise intolerance are the major presenting signs because lung expansion is restricted by compression from fluid in the pleural space.
- Cats with pleural effusion may prefer a sitting or sternal recumbent posture to facilitate breathing. Increased respiratory distress may occur with exercise, with physical restraint in the hospital, or with repositioning in lateral recumbency (i.e., orthopnea).
- Thoracic effusion may cause muffled heart and lung sounds on auscultation and hyporesonance and a horizontal fluid line on thoracic percussion.
- Thoracic effusion is confirmed by radiography or thoracocentesis (see Chapter 164). The results of fluid analysis are highly indicative of FIP (see "Diagnosis").

Pericardial Effusion

- Pericardial effusion due to fibrinous pericarditis may occur in FIP, with or without other effusions. In one survey, FIP was the second most frequent cause of feline pericardial effusion, accounting for 14% of cases.
- Pericardial effusion in FIP does not usually cause overt clinical signs. It may be suspected from auscultation (muffled heart sounds), thoracic radiography, or electrocardiography, and it is confirmed by echocardiography (see Chapter 151).

Non-effusive (Dry) Form of Feline Infectious Peritonitis

▼ ***Key Point*** The non-effusive (dry) form of FIP is characterized by multifocal pyogranulomatous inflammation and necrotizing vasculitis in various organs, such as the abdominal viscera (e.g., liver, spleen, kidneys, pancreas, and intestines), eyes, central nervous system (CNS), and lungs.

Pyogranulomas appear as multiple discreet or coalescing gray-white nodular masses of variable size on the surface and within the parenchyma of affected organs. These are often mistaken for tumors. Effusion is often minimal or absent. The specific organs affected and the degree of resulting organ failure determine the presenting clinical signs.

Kidney Disease

- Pyogranulomatous nephritis causes the kidneys to become palpably enlarged, firm, and irregular ("lumpy"), associated with pyogranulomas scattered over the surface and infiltrating throughout the renal cortex.
- Extensive renal involvement occasionally causes renal failure with polyuria-polydipsia and azotemia (increased blood urea nitrogen [BUN] and serum creatinine).
- Proteinuria is a frequent laboratory finding in renal FIP. In addition, large quantities of circulating immune complexes may lead to subclinical glomerulonephritis with any of the other forms of effusive and non-effusive FIP.

Liver Disease

- Pyogranulomatous hepatitis (hepatomegaly, jaundice, and signs of hepatic failure) may occur in FIP.
- The most consistent laboratory abnormalities are bilirubinuria and hyperbilirubinemia. Mild to moderate elevations of serum liver enzymes (alanine aminotransferase, alkaline phosphatase) and serum bile acids also may occur.

Disease in Other Abdominal Organs

- Pyogranulomatous lesions may cause palpable enlargement of the visceral lymph nodes, spleen, or omentum.
- Pyogranulomatous enterocolitis may cause diarrhea and diffuse or masslike intestinal thickening, especially in the ileocecocolonic region.
- Pancreatic involvement can occasionally cause pancreatitis and, rarely, diabetes mellitus.

Ocular Disease

- Ocular lesions of FIP are usually bilateral and affect the vascular tunic or uvea (uveitis). Lesions may sometimes cause blindness.
- Manifestations of exudative anterior uveitis (iridocyclitis) may include miosis, aqueous flare, keratic fibrinocellular precipitates, hypopyon ("mutton-fat" deposits of cells and fibrin), hyphema, anterior chamber adhesions (synechia), corneal edema, and deep neovascularization of the cornea (see Chapter 136).
- Chorioretinitis from posterior uveal involvement is detected by ophthalmoscopic examination and may include perivascular cuffing, exudative retinal detachment, and retinal hemorrhages (see Chapter 138).

Neurologic Disease

- Multifocal pyogranulomatous meningoencephalitis and myelitis are frequent in FIP. Inflammatory lesions are perivascular and often involve the meningeal and ependymal layers. In one report, 29% of cats with FIP developed neurologic signs. In a retrospective survey of 286 cats with neurologic disease, lesions indicating FIP of the CNS were found in 16%. In another large

survey, FIP was the most common spinal disease in cats.
- The neuroanatomic distribution of the lesions determines clinical signs; some of the most common are ataxia, tremors, vestibular dysfunction, seizures, posterior paresis, hyperesthesia, and behavioral changes. The relentless progression and multifocal nature of the signs are characteristic features of neural FIP.
- Neuropathies occasionally involve the cranial nerves (e.g., trigeminal or facial) or peripheral nerves (e.g., brachial or sciatic).
- Cats with neural FIP often develop secondary hydrocephalus when the inflammatory process obstructs the flow of cerebrospinal fluid (CSF). In one study of 24 cats with neural FIP, 75% had hydrocephalus. Dilatation of the ventricular and central canal system is identified on computed tomography (CT) and magnetic resonance imaging (MRI) scans. Meningeal enhancement also is seen on MRI.
- The diagnosis of neural FIP depends on CSF analysis (see the section on diagnosis).

Pulmonary Disease

- Pyogranulomatous pneumonia can be found in cats with FIP on thoracic radiographs or at necropsy, but in most cases this is clinically silent or only causes a mild cough.
- This appears radiographically as a diffuse, poorly defined, patchy or nodular interstitial pulmonary infiltrate.

Reproductive Disease

- Testicular enlargement caused by pyogranulomatous orchitis has been reported in FIP.
- Contrary to what has been speculated in the past, FCoV is not directly associated with cattery reproductive problems, neonatal deaths, or birth of weak or "fading" kittens.

DIAGNOSIS OF ENTERIC FELINE CORONAVIRUS

Fecal Virus Detection

- Non-mutated FCoV infection is characterized by persistent viral replication in enterocytes and fecal shedding of virus. Active fecal shedding of FCoV can be confirmed by reverse transcription polymerase chain reaction (RT-PCR) assay of feces (see the later section on RT-PCR assay) or by electron microscopy of feces. False negatives occur with both of these diagnostic techniques.
- The quantity of fecal virus can fluctuate, so ideally feces should be checked daily for 4 to 5 consecutive days before determining a cat is a non-shedder.

Intestinal Biopsy

- Intestinal biopsy shows nonspecific lesions of villous tip injury, with stunting and fusion of villi.
- Immunofluorescence or immunohistochemical staining for viral antigen in intestinal biopsies is confirmatory.

DIAGNOSIS OF FELINE INFECTIOUS PERITONITIS

The diagnosis of FIP is usually suspected from clinical signs and the results of routine laboratory evaluations (see Table 10-1). There is no single reliable confirmatory test for FIP; thus, base the clinical diagnosis of FIP on the combined results of well-chosen laboratory evaluations (e.g., hematology, serum chemistry, cytology, serology, and virology), diagnostic imaging, and histopathology (Table 10-2).

▼ ***Key Point*** Clinical signs and laboratory abnormalities in cats with FIP are not specific for the disease; however, collectively these may provide strong circumstantial evidence for a presumptive diagnosis of FIP.

Routine Laboratory Evaluations

- Hematology often reveals nonspecific abnormalities reflecting the chronic inflammatory response, such as nonregenerative anemia, neutrophilic leukocytosis or leukopenia, and stress lymphopenia.
- Total serum protein and serum globulins (especially gamma and alpha$_2$) are increased by the chronic immune stimulation in 70% of non-effusive cases and 50% of effusive cases, whereas serum albumin is often decreased. One study showed that a decreased serum albumin-to-globulin ratio (A/G < 0.8) indicates a high probability of FIP (92% positive predictive value); while an A/G > 0.8 suggests that FIP is unlikely (61% negative predictive value). Serum protein electrophoresis is usually not necessary.
- Serum chemistries may detect involvement of abdominal organs such as the liver (increased serum liver enzymes, bilirubin, and bile acids), kidneys (increased creatinine and BUN), or pancreas (increased pancreatic lipase immunoreactivity).
- Urinalysis findings may include proteinuria or bilirubinuria.
- Disseminated intravascular coagulation sometimes develops in FIP, resulting in prolonged coagulation times, decreased platelets, and increased fibrin degradation products (see Chapter 23).

Diagnostic Imaging

Diagnostic imaging is useful for identifying organ sites of involvement in FIP. Imaging also facilitates procurement of diagnostic fluid or biopsy specimens.

Table 10-2. DIAGNOSTIC FEATURES OF FELINE INFECTIOUS PERITONITIS

Parameter or Procedure	Findings Suggestive of FIP
Age	6 mo to 3 yr (but all ages affected)
Habitat	Cattery or multicat household
Signs (see Table 10-1)	Fever (unresponsive)
	Effusion (abdominal, thoracic)
	Liver disease (jaundice, etc.)
	Renal disease (renomegaly)
	Intestinal disease (GI signs)
	Ocular disease (uveitis)
	CNS disease (multifocal)
	Pulmonary disease (cough)
Clinical course	Progressive
Complete blood count	Anemia (nonregenerative)
	Neutrophilia or neutropenia; left shift
	Lymphopenia
	Neutrophil inclusions (immune complexes?)
Plasma proteins	Increased total serum protein
	Hyperglobulinemia (gamma, alpha$_2$)
	A/G ratio < 0.8
	Hyperfibrinogenemia (400–700 mg/dl)
Serum chemistries	Abnormal liver tests (increased ALT, ALP, bile acids, bilirubin)
	Azotemia (increased BUN, creatinine)
	Increased PLI assay (pancreatitis)
Urinalysis	Proteinuria, bilirubinuria
Radiography and ultrasonography	Effusions (abdominal, thoracic)
	Organomegaly (liver, kidney, intestine, etc.)
	Organ infiltration (lung)
CT and MRI brain imaging	Hydrocephalus, meningeal enhancement
Fluid analysis of effusion:	Yellow, clear, sticky, foamy, fibrinous
Protein	4–10 g/dl (A/G ratio < 0.8, globulin > 50%, gamma globulin > 32%)
Leukocytes	1,000–20,000 cells/µl
Cytology	Pyogranulomatous exudate
Cerebrospinal fluid analysis:	
Protein	50–350 mg/dl
Leukocytes	100–10,000 cells/µl
Cytology	Neutrophils > mononuclear
Serology	High FCoV antibody titer (see text)
RT-PCR assay	FCoV nucleic acid (in blood, fluid, or tissue)
Histopathology	Vasculitis and pyogranulomatous inflammation
	Positive immunofluorescence and immunohistochemistry

A/G, albumin-to-globulin ratio; ALP, alkaline phosphatase; ALT, alanine transaminase; BUN, blood urea nitrogen; CNS, central nervous system; CT, computed tomography; FCoV, feline coronavirus; FIP, feline infectious peritonitis; GI, gastrointestinal; MRI, magnetic resonance imaging; PLI, pancreatic lipase immunoreactivity; RT-PCR, reverse transcription polymerase chain reaction.

Radiography and Ultrasonography

Radiography is useful for confirming abdominal or thoracic effusion, abdominal organ enlargement (e.g., kidney and liver), or pulmonary infiltration. Affected abdominal organs (liver, kidney, spleen, pancreas, intestines, omentum, and lymph nodes) also can be imaged, aspirated, and biopsied using ultrasonography.

CT and MRI of the CNS

In cats with neurologic FIP, secondary obstructive hydrocephalus is a common finding on CT and MRI scans. Contrast enhancement of the meninges and ependyma also may be seen on MRI.

Fluid Analysis of Effusions

▼ ***Key Point*** Fluid analysis is usually sufficient for the clinical diagnosis of effusive FIP. The typical fluid in effusive FIP is a highly proteinaceous pyogranulomatous exudate.

- FIP fluid appears clear, viscous, and straw yellow or golden. It may be tenacious or sticky and contain

flecks or strands of fibrin. The fluid gets frothy when shaken because of its high protein concentration, and it may clot when refrigerated.

- FIP fluid has a high protein concentration, approaching that of plasma, ranging from 4 to 10 g/dl. Effusive FIP is highly likely if the total fluid protein is more than 3.5 g/dl and the globulin portion is greater than 50%. The A/G is usually less than 0.8. A gamma globulin percentage of greater than 32% by fluid protein electrophoresis is also highly indicative of FIP. An A/G ratio of greater than 0.8, or an albumin percentage greater than 50%, indicates that a disease other than FIP is highly likely.
- FIP fluid usually has a nucleated cell count ranging from 1,000 to 20,000 cells/µl, which is low compared with other exudates.
- The cytologic pattern of FIP fluid is pyogranulomatous exudate. The predominant cells are well-preserved (non-degenerate) neutrophils and macrophages with variable numbers of plasma cells and lymphocytes.
- Additional evaluations on effusions can include assay for anti-FCoV antibodies (see "Coronaviral Antibody Tests") and RT-PCR assay to detect coronaviral nucleic acid (see the later section on PCR assay). Antibody and RT-PCR assays on effusions may have higher diagnostic value than serum testing.
- Staining macrophages in effusions for intracellular FCoV antigen using either immunofluorescence or immunohistochemistry is the most definitive confirmatory test for effusive FIP, with 100% positive predictive value (see "Immunofluorescence and Immunohistochemistry").

Cerebrospinal Fluid and Aqueous of the Eye

- Analyses of CSF for neural FIP and aqueous fluid from the anterior chamber of the eye for ocular FIP have high diagnostic value. Both the protein concentration and the nucleated cell count (neutrophils, macrophages, lymphocytes) are increased in the CSF of most cats with neural FIP (see Table 10-2) and in the aqueous humor of cats with intraocular FIP.
- CSF and anterior chamber fluid can also be evaluated for the presence of anti-FCoV antibodies (see the following section). In FIP, the ratio of CSF or ocular antibodies to serum antibodies is generally much higher than the ratio of CSF or ocular total protein to serum total protein.
- A PCR assay of CSF and anterior chamber fluid for coronaviral nucleic acid is not as useful (see the section on PCR assay).

▼ ***Key Point*** Neurologic FIP is highly likely in cats that have the combination of progressive neurologic signs (especially if multifocal), increased CSF protein and leukocytes (especially neutrophils), and hydrocephalus on imaging.

Coronaviral Antibody Tests

Testing for coronaviral serum antibodies is informative as an epidemiological screening tool and as a diagnostic aid for FCoV and FIP if a reliable laboratory is used and the results are interpreted properly.

Principles of Feline Coronavirus-Antibody Testing

▼ ***Key Point*** A positive coronaviral antibody test means only that a cat has been exposed to some coronavirus at some time.

- Serology does not provide a definitive diagnosis of FIP because the antibodies in cats infected with harmless non-mutated FCoV are not distinguishable from the antibodies in cats with FIP. A large percentage of the healthy cat population is seropositive for FCoV antibodies, and most of these cats never develop FIP. In addition, seropositivity does not distinguish active from past infection.
- Antibodies to the related non-FCoVs (e.g., CCV and TGEV) crossreact with FCoV antibodies, lowering specificity further.
- Seroconversion after initial exposure to FCoV takes 1 to 3 weeks.

▼ ***Key Point*** A positive coronaviral antibody test does not confirm a diagnosis of FIP, and the absence of FCoV antibodies does not rule out a diagnosis of FIP.

- Many commercial diagnostic labs measure FCoV-antibody titers; however, methodologies are variable; thus, results cannot be compared between labs. For example, whether a feline or non-feline viral antigen is used in the test procedure will influence the titer values that indicate the lowest and highest titer levels.
- Use a reliable commercial diagnostic laboratory that measures quantitative FCoV-antibody titer levels. Avoid using rapid in-office enzyme-linked immunosorbent assay (ELISA) tests that merely report positive or negative results without titer quantification—this is less useful than titer information, and these tests give less consistent results than conventional serologic tests.
- Commercially available ELISA tests for detection of antibody to the 7b gene have been marketed as "FIP-specific tests." However, mutation of this gene is not specific for FIP, and this test has no advantage over conventional serologic assays.
- Serum or plasma samples for FCoV antibody testing can be refrigerated or stored at −20°C without affecting the test.
- FCoV antibodies also can be measured in effusions, CSF, or anterior chamber fluid (aqueous). Some studies suggest that these are more diagnostically

useful than serum testing but have similar interpretation pitfalls.

Indications

▼ ***Key Point*** Use the FCoV-antibody titer as a diagnostic aid for FIP rather than as a definitive diagnostic test. Interpret a positive titer to indicate that FIP is *possible* (low titer) or *probable* (high titer), when accompanied by supportive clinical findings. Interpret a negative titer to indicate that FIP is *unlikely.*

- Diagnostic aid in sick cats suspected of FIP
- Diagnostic aid in cats suspected of FCoV enteritis
- Healthy cats that have been exposed to cats with FIP or FCoV
- Screening catteries for the presence of FCoV
- Aid the process of creating an FCoV-free cattery
- Screening new cats before entering FCoV-free catteries

Positive Antibody Test Results

A positive FCoV-antibody titer in a cat can indicate any of the following:

- Clinical FIP caused by a mutant variant of FCoV
- Healthy carrier of non-mutant FCoV
- Recovered from previous FCoV infection
- Seroconversion to other non-FCoVs
- False-positive as a result of recent vaccination

Guidelines for Interpretation

▼ ***Key Point*** Coronaviral-antibody titers are not sufficiently specific to be used as a definitive diagnostic test. A positive titer, no matter how high, does not confirm a diagnosis of FIP.

- In healthy cats, the height of the antibody titer correlates with the virus replication rate in the intestine, the likelihood of fecal shedding, and the amount of virus shed in the feces.
- In general, low titers have the least diagnostic value.
- The highest measurable titer level for the assay used by the lab is highly suggestive of FIP but is still not confirmatory by itself. One study found 94% probability of FIP at the highest titer level.
- Rising antibody titers are not helpful because they are seen in healthy cats with non-mutated FCoV, and titers fluctuate unpredictably in both FIP and avirulent infections.
- Healthy carriers of non-mutated FCoV living in endemic cattery and multicat environments tend to have higher titers than individual pet cats; thus, high titers might be less meaningful in cattery cats. Less than 10% of cattery cats with titers ever develop FIP.

▼ ***Key Point*** A healthy cat that is negative for antibodies is likely to be free of FCoV and thus is not shedding virus, is not infectious to other cats, and is not at risk for FIP.

- False-negative test results are infrequent but occur in up to 10% of confirmed FIP cases; thus, a negative titer does not entirely rule out FIP. False-negative titers can result from low antibody levels seen with peracute infection (less than 10 days after exposure), the terminal stages of infection, or with consumption of antibody in immune complexes. A laboratory error or an insensitive assay system also explains some false negatives.
- The evaluation of FCoV antibodies in effusions was found to have good predictive value for FIP (90% positive, 79% negative), suggesting that fluid testing may be more diagnostically useful than serum testing.

Polymerase Chain Reaction

▼ ***Key Point*** Interpret the RT-PCR test with other clinical findings, and do not use this as the sole basis for diagnosis of FIP.

- The RT-PCR viral assay is used to detect coronaviral nucleic acid in blood, fluids, tissue, or feces.
- A positive result indicates the presence of FCoV, but it does not distinguish between the mutated, FIP-producing variants and non-mutated FCoV. Viremia occurs not only in FIP but also in healthy FCoV carriers. One study found that up to 80% of cats in endemic catteries can be viremic and RT-PCR–positive, and this was not predictive of FIP. Thus, RT-PCR by itself is not a reliable confirmatory diagnostic test.

▼ ***Key Point*** PCR assays do not distinguish between mutated and non-mutated FCoV.

- In general, effusions and tissue specimens are more likely than blood to be positive in cats with FIP. Plasma is more sensitive than serum. The lowest yield is in CSF and urine, so these are not recommended for routine PCR testing.
- Fecal RT-PCR can be used to document fecal shedding of FCoV, especially in healthy cats as a component of a cattery control program. Evaluate feces daily for 4 to 5 consecutive days. Retesting over several months is required to identify chronic persistent shedders.
- A false-negative RT-PCR results from degradation of sample RNA and poor laboratory technique. The primers used also may not detect all strains of FCoV.
- Samples for PCR require careful handling to avoid invalid results. Keep samples frozen and assay them as soon as possible for optimal results.

Histopathology

- Histopathology is considered the "gold standard" for confirming FIP. Thus, biopsy of affected tissues is a valuable diagnostic procedure for identifying the distinctive FIP lesions of vasculitis and pyogranulomatous inflammation.
- Coronavirus can be identified in tissue specimens by PCR, immunofluorescent antibody, and immunohistochemistry techniques (see the next section).

Immunofluorescence and Immunohistochemistry

- Staining of macrophages in tissue specimens and effusions for intracellular FCoV antigen using either immunofluorescence or immunohistochemistry is the most definitive confirmatory test for effusive FIP, with 100% positive predictive value (i.e., virtually no false positives).
- Do not rule FIP out when these tests are negative. False negatives occur frequently when there are insufficient infected macrophages in the specimen or when the viral antigen is masked by competitive binding with FCoV antibodies.

TREATMENT

▼ ***Key Point*** No treatment has been proved to reduce the risk of developing FIP in healthy antibody-positive FCoV carriers.

Treatment has not been proved to lower the high mortality rate of FIP (>95%) or to slow progression of the disease. Various antiviral, immunomodulating, and immunosuppressive drugs have been used to treat FIP, but efficacy is highly questionable. Some cats show temporary improvement of clinical signs with supportive care and anti-inflammatory therapy using corticosteroids. The best candidates for palliative medical therapy are cats that are eating, active, and in good body condition. Spontaneous remissions occur but are extremely rare. Euthanasia is appropriate in severely affected cats with poor quality of life.

▼ ***Key Point*** Nearly all cats with confirmed clinical FIP eventually die, regardless of treatment.

Antiviral Therapy

- Some antiviral drugs (e.g., acyclovir and zidovudine [AZT]) have no activity against FCoV. Other antiviral drugs (e.g., ribavirin) show in vitro activity against FCoV but are either too toxic for cats or ineffective when used clinically to treat FIP.
- Ribavirin-treated kittens, for example, had more severe clinical signs and a shortened survival time compared with untreated kittens. Ribavirin also causes serious side effects of hemolysis, bone marrow toxicity, and liver toxicity in cats.
- Interferons in high doses have both immunomodulating and antiviral activity (see below).
- New anticoronaviral drugs under development for treatment of human severe acute respiratory syndrome coronavirus might have future application in cats.

Immunomodulator Therapy

- Immunomodulators are intended to stimulate compromised immune function. Anecdotal reports of clinical improvement with these agents have not been substantiated by controlled studies; thus, conclusive evidence of efficacy in FIP is lacking.
- Nonspecific immune stimulation can theoretically potentiate the immune-mediated consequences of FIP.
- Immunomodulator agents that have been used unsuccessfully to treat FIP include *Propionibacterium acnes* (ImmunoRegulin), thioproline (Promodulin), acemannan (Carrisyn), levamisole, and cyclosporine.
- Human and feline interferons have been used to treat FIP (see below).

Interferon Therapy

Recombinant forms of interferon given parenterally in high doses can have both antiviral and immunomodulatory effects. Feline interferon-omega and human interferon-alpha have both been used to treat FIP.

Feline Interferon-Omega

- Recombinant feline interferon-omega (rFeIFN-ω) is available in Europe and Japan. To treat FIP, rFeIFN-ω (Virbagen Omega, Virbac) has been given at 1,000,000 U/kg SC every other day until clinical remission then once or twice weekly. Expense will be prohibitive for many owners.
- In a preliminary uncontrolled study of 12 FIP cats using rFeIFN-ω with prednisone (2 mg/kg PO q24h, tapered to 0.5 mg/kg q48h), 33.3% of the cats achieved complete remission for more than 2 years, 33.3% achieved partial remission but died after 2 to 5 months, and 33.3% failed to respond and died.

Human Interferon-Alpha

- Parenteral high-dose human interferon-alpha (rHuIFN-α) (100,000–1,000,000 U/kg IM) does not appear to be effective in FIP, and it is unsuitable for long-term treatment because cats develop antibodies against the human protein after 3 to 7 weeks that inhibit the drug's activity.
- Oral low-dose human interferon-alpha (Roferon, Hoffman-LaRoche; Intron-A, Schering-Plough) diluted to 30 U/ml and given at 30 units PO, daily for 7 days on alternate weeks, has reportedly improved appetite and well-being with minimal side effects. The rHuIFN-α given orally is destroyed by gastric acid

and does not achieve systemic levels, but it may exert immunomodulating activity on oropharyngeal lymphoid tissue leading to cytokine release.

Palliative Medical Therapy

Some cats transiently improve with supportive care combined with palliative medical therapy using a high dose of corticosteroid, with or without a cytotoxic alkylating agent such as chlorambucil or cyclophosphamide (Table 10-3).

- Corticosteroids and alkylating drugs have no effect on the virus, but by virtue of their anti-inflammatory and immunosuppressive effects, they are aimed at controlling the widespread immune-mediated inflammatory reaction that occurs in FIP.
- These drugs may adversely affect cellular immunity mediated by T lymphocytes and macrophages and thus have the potential to promote the viral infection.

▼ ***Key Point*** Only use immunosuppressive drugs to treat overt FIP. In healthy FCoV carriers and seropositive cats, these drugs could have the unwanted effect of promoting the onset of FIP.

- The principal side effects of alkylating drugs are anorexia and bone marrow suppression; thus, monitor a complete blood count periodically (see Chapter 26 for more details on the use of these drugs).
- Persistent drug-induced anorexia is a frequent problem when these drugs are given daily. An alternative is pulse administration, using a large dose of the drug once every 2 to 3 weeks. In this way, a few days after each dose the appetite usually rebounds and is maintained between treatment cycles.
- Regardless of the regimen chosen, if no response is noted within the first 2 to 4 weeks, consider the therapy ineffective and either modify or discontinue it. If a positive response occurs, continue the treatment indefinitely.

Supportive Treatment

These measures may improve quality of life and possibly survival time.

- Minimize stress as an exacerbating factor.
- Perform intermittent body cavity drainage of effusion as needed to relieve dyspnea.
- Give parenteral fluid therapy.
- Give nutritional support (via tube-feeding techniques; see Chapter 3).
- Give aspirin (10 mg/kg q72h) to inhibit platelet aggregation caused by vasculitis.
- Give antibiotics as needed to control complicating bacterial infections.
- Treat anterior uveitis with topical corticosteroids and atropine (see Chapter 136).
- Give blood transfusions (for severe nonregenerative anemia).

Table 10-3. TREATMENT FOR FELINE INFECTIOUS PERITONITIS

Mechanism of Action	Drug or Treatment*	Dosage
Immunomodulator and antiviral	Feline interferon-omega (Virbagen Omega)	1 million U/kg SC q48h until remission, then weekly
Immunomodulator	Human interferon-alpha (Roferon, Intron-A)	30 units PO q24h for 7 days on alternating weeks
Anti-inflammatory and immunosuppressive	Prednisone	2–4 mg/kg, q24h, PO
Immunosuppressive†	Chlorambucil (Leukeran) *or*‡	20 mg/m^2, every 2–3 wks, PO
	Cyclophosphamide (Cytoxan)	2–4 mg/kg, 4 days each week, PO, *or* 200–300 mg/m^2, every 2–3 wks, PO
Platelet aggregation inhibitor	Aspirin	10 mg/kg, q72h, PO
	Ozagrel HCl	5 mg/kg, q12h, SC
Topical ophthalmic for uveitis	Prednisone acetate (1%)	2–3 drops/eye q6h
	Atropine (1%)	1–3 drops/eye up to q6h for mydriasis
Supportive treatment	Minimize "stress"	—
	Parenteral fluid therapy	As needed to maintain hydration
	Nutritional therapy via tube feeding	See Chapter 3
	Body cavity drainage (thoracentesis)	As needed to relieve dyspnea
	Blood transfusion	As needed for severe anemia
	Antibiotics for complicating infections	Dosage based on the drug

*Cats most likely to respond are in good physical condition, are eating, and are free of neurologic signs, severe anemia, and feline leukemia virus or feline immunodeficiency virus infections.

†For conversion of body weight to body surface area (m^2), refer to conversion tables in Chapter 26.

‡Choose only *one* of these two alkylating agents, and combine with a corticosteroid.

PREVENTION

Vaccination

▼ ***Key Point*** The currently available FIP vaccine does not appear to be effective and is not recommended.

- A modified-live, temperature-sensitive strain of FIP coronavirus became available in 1991 as an intranasal vaccine for use in cats 16 weeks of age and older (Primucell FIP, Pfizer).
- The vaccine virus replicates locally in the nasopharynx and intestines but not systemically because of temperature sensitivity. It is supposed to stimulate local nasal and gut mucosal immunity, salivary immunoglobulin A antibody, and cell-mediated immunity. It does not protect against enteric FCoV infection.
- The lack of proven efficacy in kittens younger than 16 weeks of age is a fundamental pitfall, because under most circumstances kittens first become infected with FCoV between 6 and 16 weeks of age.
- The 2000 Report of the American Association of Feline Practioners Panel on Feline Vaccines states: "At this time there is no evidence that the vaccine induces clinically relevant protection and its use is not recommended."
- Various genetically engineered recombinant vaccines are under development and may become available in the future.

Control of Feline Infectious Peritonitis in Catteries

Control of FCoV infection in catteries, shelters, and multicat households is aimed at limiting virus spread, minimizing exposure, and reducing stress. Infection with FCoV is ubiquitous, so complete eradication is rarely feasible, and even if eradication is successful, reinfection frequently occurs. Test and removal based on FCoV antibody testing is not practical since it is typical for 80% to 90% of cats in endemic catteries to be seropositive. Depopulation and starting over would be required.

General Principles

▼ ***Key Point*** Do not consider healthy FCoV antibody-positive cats to be harmless. Seropositive cats frequently shed FCoV in their feces that contaminates the environment and infects other cats, and FCoV always has the potential to mutate and cause FIP.

- Be familiar with risk factors and transmission of FCoV (see "Epidemiology").
- Use good husbandry practices (e.g., good sanitation, ventilation, and feeding practices) and limit feco-oral contamination.
- Minimize overcrowding and stress. High-density housing allows a high level of fecal contamination of the environment, facilitating feco-oral spread of infection.
- Control feline leukemia virus in the cattery with vaccination, testing, and removal (see Chapter 8).
- Do not breed male and female cats that have a history of producing kittens that later developed FIP, because they potentially may pass on a genetic susceptibility to FIP.
- The risk of infection from cat shows and breeding exchanges is considered low; however, in these situations do not allow sharing of food, water, or litter.
- Only allow healthy seronegative cats to enter a coronavirus-free cattery. Ideally, before a cat can be safely mixed with other cats, confirm the absence of fecal shedding based on at least 4 consecutive negative fecal RT-PCR tests (although this may not be practical in many situations).

Control of Viral Exposure

The greatest source of viral contamination of the environment is from small particles of fecal debris and litter that are carried throughout the facility by movement of air, animals, and people. Any contaminated material can end up on the fur and thus be ingested by the cats. Consider the following control measures to reduce the environmental virus load and to minimize exposure:

- Use at least one litter box for every two cats. Locate litter boxes away from food and water bowls to avoid cross-contamination. Ensure that the area is easy to clean and disinfect.
- Scoop feces from litter boxes daily, and replace litter and disinfect litter boxes as often as possible (at least weekly).
- Dispose of used litter in sealed plastic bags.
- Use dedicated food and water bowls for each animal, and clean and disinfect bowls regularly.
- Brush the fur of cats regularly to remove contaminated fecal particles and litter that could be ingested during grooming.
- Reduce cross-contamination between cats by housing cats individually or in stable small groups of four or less.
- Avoid having too many kittens because they shed the greatest amount of virus.
- Ideally, identify and eliminate persistent carriers that continuously shed large amounts of virus by using fecal RT-PCR tests repeated over several months.

Control of Viral Spread in Kittens

Isolation and early weaning can be effective for controlling the spread of FCoV in kittens, as well as herpesvirus and calicivirus.

- Isolate queens 1 to 2 weeks pre-partum so that queens can give birth and nurse kittens in isolation from other cats in the cattery.
- Wean the kittens early and remove them from the mother at 5 to 6 weeks of age, coinciding with the time when maternal-derived immunity dissipates, then keep the litter of kittens isolated from all other cats until at least 16 weeks of age.
- Maintain strict quarantine procedures to prevent environmental or fomite transfer of FCoV.
- Confirm seronegativity at 12 to 16 weeks of age or prior to moving kittens to a new home to document effectiveness.
- The disadvantages of this approach are that it requires facilities for isolation and quarantine and that early weaning may adversely affect social development of the kittens.

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