Feline Infectious Peritonitis (FIP): More Complex than We Thought

Richard B. Ford, DVM, MS
Diplomate ACVIM, Diplomate (Hon)ACVPM
North Carolina State University

As long as we've known about, tried to diagnose, and attempted to treat feline infectious peritonitis (FIP), it still eludes us! Afterall, the clinical manifestations of this disease are certainly NOT limited to the peritoneum. This complex (....and seemingly getting more complex all the time) disease of kittens and adult cats is attributed to infection by a Feline Coronavirus (FCoV). But that's the easy part...everything about this disease, from pathogenesis to diagnosis to transmissibility to immunization, is tough to understand...and the more we learn about it, the tougher it's getting!

The first references to the fact that cats infected by this virus developed disease were described as early as 1960. However, it was not until 1966 that FIP was described as a distinct clinical entity and the infectious nature of the disease was described. And 25 years later, the first (and still only) FIP vaccine was introduced in the US (and is now available in some European countries). Although the initial name, "feline infectious peritonitis", has remained the popular name for this disease, the virus by no means is restricted to the peritoneum.

In fact, coronaviruses are a widely distributed group of viruses capable of infecting several species of birds and mammals. They can cause upper respiratory and gastrointestinal disease, hepatitis, vasculitis, peritonitis, pleuritis, and encephalitis. Perhaps the best known of these viruses are the FIP virus in cats, canine coronavirus in dogs, and transmissible gastroenteritis virus of swine.

The feline enteric coronavirus (FECV), another very common virus known to infect the GI tract of kittens-especially those living in multiple-cat households, has "traditionally" been described as causing mild, transient diarrhea in kittens. In other kittens, infection causes no clinical signs at all...but...THAT'S WHAT WE USED TO THINK! Some compelling evidence about the role of the FECV in the pathogenesis of FIP has recently been published and sheds quite a different picture of this so-called benign virus.

EPIZOOTIOLOGY

The overall prevalence of FIP is not precisely known. In the general population, it has been reported by some sources to be less than 1% of all cats presented to university teaching hospitals. In multiple cat households and catteries, the prevalence is probably considerably higher. Under the worst conditions, the morbidity (clinical illness) due to FIP is typically around 3-4% in cluster households. (**NOTE:** that compares to 28%-30% for FeLV endemic households).Nonetheless, the disease we call FIP is highly lethal and carries a poor prognosis for survival.

Clinical FIP is seen primarily in cats through 2 years age, with the highest incidence occurring between six months and two years. In our experience, however, we have diagnosed fatalities caused by FIP in cats as young as two months of age. FIP infection in adult cats must be regarded as a chronic infection that has persisted for months or years. This may account for the fact that clinical signs attributed to FIP virus are occasionally recognized in adult cats 10 years of age and older *despite an excellent history that the cat has lived indoors as the lone cat in the household for all of its life!* Don't disregard the fact that the infection was likely acquired from the queen and coronavirus transmission occurred during the first several weeks of life. This may explain why a second "spike" in diagnosed cases of FIP occurs in cats that are 10 years and older.

THE CLINICAL DISEASE

Generally speaking, FIP occurs in two distinct forms: an effusive form characterized by peritonitis or pleuritis, or both, and a non-effusive, or dry, form that causes granulomatous lesions in major organs, such as lymph nodes, kidneys, the eyes, and the central nervous system (CNS).

Effusive FIP is characterized by a widespread vasculitis that is responsible for the outpouring of protein- and fibrin-rich fluid. Although antibody titers do not correlate with immunity, titers will rise simultaneously with the development of lesions of effusive FIP. The presence of effusion in cats with FIP has been attributed to a *strong* humoral immune response to the virus, but a *weak* cell-mediated immune (CMI) response. NOTE: CMI is key in protecting cats from FIP.

The non-effusive form of FIP, clearly the most difficult to diagnose, is characterized by a dramatic granulomatous reaction in localized tissues, such as the nervous system or the eye. Again, antibody is not protective. An "intermediate" CMI and humoral response is responsible for the lack of effusion.

Cell-mediated immunity does not always lead to complete elimination of the virus. Apparently, virus can persist in the body of some cats for an indefinite period of time. With advancing age or drug-induced immunosuppression (FeLV infection or steroids), the FIP infection may again become active.

TRANSMISSION

The actual route by which feline coronavirus (FCoV) is spread is generally believed to be via the fecal-oral route (esp, queen to kitten). Transmission in utero has been suggested; however, this route has not been definitely proven. The virus is probably excreted into the environment by a number of routes, including oral and respiratory secretions, feces, and possibly, urine. It appears that close, sustained contact between cats (esp. a carrier queen and her kittens) is required for effective transmission of the virus. NOTE: the virus appears to remain infectious for up to 7 weeks in a dry environment….it's more resilient than originally thought. Therefore, cluster households where breeding is prevalent (lots of kittens) pose the greatest risk of transmission of FCoV.

IMPORTANT: FCoV is commonly found in individual as well as households of cats; up to 90% of healthy cats living in a household can be found to have FCoV (fecal shedding).

Most common household detergents rapidly inactivate the virus and disinfectants; Clorox bleach diluted in water (1 part bleach to 32 parts water) is preferred.

The clinical disease we call 'FIP' is apparently results subsequent to 3 factors:

1) exposure to and infection with FCoV (which is very common)...*and,*

2) mutation of the "very common" FCoV into a virulent coronavirus called the FIP virus (FIPV), (NOTE: this mutation appears to occur within the individual cat...mutated virus does not appear to spread among cats)...*and,*

3) a genetic predisposition of the individual cat to develop disease once the mutation occurs. (Persian and Burmese are at the top of the genetic predisposition list...but other breeds and mixed-breed cats can certainly be susceptible).

(NOTE: some studies have challenged the mutagenesis concept of FIP pathogenesis…more to come on that in the years ahead…)

DIAGNOSIS OF CLINICAL FIP

Clearly, the effusive form of FIP is far easier to diagnose than the noneffusive form. Once a pleural or peritoneal effusion develops, gross and microscopic examination of the fluid is usually sufficient to make a clinical diagnosis. In the noneffusive form, the disease is far more difficult to diagnose because of the virus's ability to localize in discrete organs and the absence of obvious clinical signs.

Hematology and Biochemistry: In both the effusive and noneffusive forms of FIP, the total white blood cell (WBC) count is typically elevated with an absolute neutrophilia and a normal to low lymphocyte count. Cats with concurrent feline leukemia virus (FeLV) infection may have profound panleukopenia. In most cases of FIP, a mild to moderately severe anemia exists.

Fluid Analysis: Peritoneal and pleural effusions (**when present!**) are characteristic and essentially diagnostic. The fluid is light to dark yellow in color and has a sticky, viscous consistency. The fluid is technically an exudate since it is high in protein (characteristically from 5 to 12 g/dL) and has a high Specific Gravity ranging from 1.017 to 1.047. Cytological assessment of the fluid is not particularly impressive. Despite the high viscosity, expect the fluid to be relatively hypocellular consisting principally of WBCs, predominantly neutrophils and macrophages, with occasional mesothelial cells.

An **Albumin:Globulin** ratio (determined on abdominal fluid) that is greater than 0.81 is highly predictive for ruling out a diagnosis of FIP. Likewise, an albumin concentration (in the abdominal effusion) greater than 48% of the total protein or a gammaglobulin less than 32% of total protein are very good predictors that the effusion is **not** due to FIP. On the other hand, an effusion in which the globulin fraction is greater than 32% of the total protein (in the fluid) is highly predictive of FIP.

Plasma Proteins: Of particular importance in the diagnosis of the noneffusive form of FIP is the fact that approximately 75% of the cats affected have plasma proteins that are greater than 7.8 g/dl. Characteristically, the albumin is lower than normal and the globulin fraction is abnormally high.

[*IMPORTANT*] Electrophoresis of the serum proteins, routinely available through most commercial clinical pathology labs, will demonstrate an increase in the gammaglobulin fraction of serum in about 75% of cats affected with the **NONEFFUSIVE** form of FIP. The elevated serum globulin level, combined with evidence of ocular/CNS disease is highly suggestive of the noneffusive form of FIP. This is a particularly important diagnostic tool in cats suspected of having FIP but in which a significant accumulation of fluid is lacking.

FeLV Status: While many reports suggest that 40-50% of cats with FIP will also have a positive FeLV test, this assertion has not been established as a consistent finding. Only one report has shown such a high correlation between FIP-positive and FeLV-positive cats. Clinical experience indicates that the percentage of FIP cats that are FeLV positive is considerably lower. In no way should FIP be considered one of the FeLV-related diseases.

Histopathology: Biopsy is the only "test" that CAN confirm an antemortem diagnosis of FIP. Any FIP diagnosis made **without** histologic confirmation must be considered presumptive.

ANTIBODY vs. ANTIGEN TESTING

Several assays are currently available to detect coronavirus antibody in serum. REMEMBER: THERE IS NO “FIP TEST”. Commercial laboratories offering "FIP-antibody titers" are actually reporting "coronavirus antibody titers." While it has been proposed that the disease can be diagnosed by virtue of a high antibody titer, none of the so-called antibody tests for FIP are diagnostic. A negative titer, on the other hand, can indicate lack of exposure to a coronavirus and therefore be interpreted as NOT FIP…(but…the high incidence of FCoV exposure among normal cats makes a NEGATIVE FCoV titer pretty rare!)

It is critical to note that a laboratory report of "positive" titer refers only to the presence of a significant level of antibody. IN NO WAY DOES A "**POSITIVE**" TEST INDICATE A DIAGNOSIS OF FIP. Furthermore, **the diagnosis of FIP can not be made on the basis of a single coronavirus antibody titer determination**. A positive titer certainly does not indicate that a cat is doomed to develop FIP at some future date.

Titer Applications: Despite all the frustration associated with interpreting coronavirus antibody tests, there are some situations in which determination of antibody titers can be of use to the practitioner:

1. Based on the current knowledge of feline coronavirus serology, there is little or no value in performing routine antibody titer screening. While the presence of antibody does not diagnose the disease, knowledge that coronavirus antibody is absent may be helpful in ruling out FIP virus as the culprit in a disease outbreak. However, a NEGATIVE titer, as reported by a laboratory, may, in fact, NOT BE A "ZERO" TITER. If compelled to perform titers, check with the laboratory to determine the meaning of "NEGATIVE". Cats dying of fulminate FIP typically have a low or "NEGATIVE" titer.

2. Determination of coronavirus antibody titers is a poor clinical aid in the diagnosis of a sick cat with signs suggestive of FIP. A positive coronavirus titer may be the least significant test to perform compared any other diagnostic procedureavailable.

3. Recently available through commercial laboratories is the **reverse transcriptase-polymerase chain reaction (RT-PCR) assay** for coronavirus **antigen.** The assay offers the ability to detect viral antigen in effusions, serum, plasma, and in feces. This is NOT an FIP Test! The value of RT-PCR is that can detect viral antigen (compared to antibody). It does not distinguish between FIPV and FECV or any other feline coronaviruses…of which there appear to be a bunch!

The RT-PCR assay does not distinguish between FIPV and the FECV however, it has allowed investigators to study feline coronavirus shedding patterns of cats living in cluster households. **This, combined with evidence that FECV is, in fact, the parent of FIPV, has provided new, clinically germane information about this complex disease:**

FIP Facts

- The (very) common Feline Coronavirus FCoV appears to be the parent of the virulent FIP virus (FIPV). FIPV is widely regarded to be a virulent mutation of a benign FCoV. (Although this is being challenged)
- There is good evidence that certain cat breeds, and lines within breeds, are genetically predisposed to develop the disease we call 'FIP' if viral mutation does occur...ie, mutation alone may not cause the disease...genetics appear to play an important role. **Persian** and **Burmese** cats predominate, Balinese, Birman, and Himalayan are mentioned frequently as well.
- The risk of FIP is greatest among cats living in cluster (multiple-cat) households, ie, there's more virus transmission and, therefore, more virus replication, and therefore, more chance for mutation.
- Infection is most likely to occur in kittens as opposed to adult cats; clinical signs may require many years to develop if they develop at all.
- Coronavirus infection in cats is common (50-80% of all cats)...shedding among infected cats is common...but FIP is relatively uncommon.
- There is no consistently reliable diagnostic test other than histopathology (Lesion: vasculitis).
- Vaccination has significantly limited ability to prevent infection…limited to cats that have not been exposed to FCoV (and that's rare). Only one (topical)vaccine has ever been licensed (1991).

...there is, yet, another ('new-and-improved') RT-PCR test that is now commercially available. A number of investigators have discovered that RT-PCR technology can be utilized to identify m-RNA (messenger RNA) of ***replicating*** feline coronaviruses inside circulating monocytes of infected cats. The biological point of significance here is that even cats with benign (so-called) 'enteric' coronavirus can have *circulating* coronavirus in their plasma...but that's NOT necessarily an indication of FIP. However, if m-RNA can be identified in macrophages, the coronavirus is replicating...and that's diagnostic of the disease we call FIP...only the FIPV replicates inside cells.

That test is commercially available and is being utilized by veterinarians. The laboratory most often used is:

Auburn University, College of Veterinary Medicine-Molecular Diagnostics Laboratory

WEBSITE: http://www.vetmed.auburn.edu
SEARCH: Diagnostic Services; then, Molecular Diagnostics

NOTE: FALSE-positive test results have been observed. (ie, the test is not always correct!)

IMMUNITY TO FIP VIRUS

Although the nature of the immune response to FIP virus infection in cats is not well understood, experimental infection is successfully accomplished via the oral, oronasal, or intratracheal routes. Clinical signs associated with infection develop after the virus crosses the nasal and gut mucosal barrier, infects macrophages and monocytes, and causes an immune-mediated disease leading to the oftentimes fatal vasculitis.

The FIP VACCINE (topical)

Zoetis provides the only approved vaccine for use in preventing Feline Infectious Peritonitis, PRIMUCELL. It is a temperature sensitive (therefore, modified live) virus "designed" to grow only at the cooler temperatures of the upper respiratory tract. The vaccine virus will not replicate at core body temperatures. Therefore, it is effective only if exposure is VIA the oronasal mucous membranes (and this is the presumed MOST common route of infection); the vaccine is administered intranasally (applied directly onto the oral-nasal mucosa). Protection is apparently mediated by Secretory IgA produced at the level of the upper respiratory tract and oral mucous membranes combined with an enhanced cell-mediated immune response.

The vaccine has been specifically developed so that it does NOT stimulate detectable levels of serum neutralizing antibody. THIS IS GOOD...coronavirus antibody is NOT protective against FIP and cats that have circulating coronavirus antibody may actually have a more severe disease subsequent to infection, a phenomenon referred to as Antibody Dependent Enhancement (ADE) of infection. Earlier concerns that the vaccine may actually, and inappropriately, stimulate circulating antibody, should be disregarded. In the clinical setting, there is NO evidence that ADE is associated with PRIMUCELL administration. The vaccine is regarded as being quite safe. However…it is considered to be of limited value in protecting cats against FIP.

The search for an effective vaccine is still on-going.

ADDITIONAL READING (FIP)

1. Sparkes, AH, et al: An appraisal of the value of laboratory tests in the diagnosis of feline infectious peritonitis. JAAHA. 30:345-350, 1994.
2. Addie DD and Jarrett O: Feline coronavirus infections. Chapt 10 in CE Greene (ed): *Infectious Diseases of the Dog and Cat*, 4th Edition. Saunders-Elsevier, St Louis. pp. 92-108, 2012.
3. Addie DD and Ishida T. Feline infectious peritonitis: therapy and prevention. Chap 285 in JD Bonagura & DC Twedt. Kirk's Current Veterinary Therapy XIV. pp 1295-1299. 2009.

Updated January 2017