As long as we've known about, tried to diagnose, and attempted to treat feline infectious peritonitis (FIP), it still eludes us! This complex (....and getting complexer all the time) infection of kittens and adult cats is caused by a feline coronavirus. But that’s the easy part...everything about this disease, from pathogenesis to transmissibility, 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. 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. Nonetheless, deaths appear to be sporadic and unpredictable. 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).
Clinical FIP is seen primarily in cats between six months and five years of 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.

THE CLINICAL DISEASE

Generally speaking, FIP occurs in two distinct forms: an effusive form characterized by peritonitis or pleuritis, or both, and a noneffusive, 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. Cell-mediated immunity is probably the only beneficial protective response in this disease, since antibody actually appears to enhance virus uptake by phagocytic cells, a preferred site for virus replication.

The noneffusive 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. Cell-mediated immunity, if the response is strong enough, will prevent the development of signs of illness in the infected cat.

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 OF FIP VIRUS

The actual route by which FIP virus is spread is still not known. It appears most likely that infection results following direct contact, either by ingestion (most likely) or by inhalation of virus, between an infected cat and a susceptible cat. 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. The potential for transmission by insects is not known. Transmission in utero is strongly supported by several reports, however, this route has not been definitely proven.
FIP virus is relatively unstable outside the host. However, recent studies suggest that infectious concentrations of virus can persist for as long as two weeks, considerably longer than previously thought, under laboratory conditions. For what it's worth, most common household detergents rapidly inactivate the virus and disinfectants, including Clorox bleach diluted 1:32 in water. However, the fact is that by the time clinical signs develop and a kitten or cat becomes moribund, there is very little virus around to disinfect.

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.

To get down into the diagnostic "weeds", 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 (see Figure 1). 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 ANTIBODY TEST.** Commercial laboratories offering an "FIP-antibody titer" 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.

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 to any other diagnostic procedure available.

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 it 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.

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)

   Pfizer Animal Health 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.

   In a challenge of immunity test conducted at Pfizer, 17 of 20 cats (85%) vaccinated intranasally were protected against a rigorous FIP virus challenge.
that killed 10 of 12 (83%) of nonvaccinated controls. On a second challenge of the surviving cats, 16 of the remaining 17 (94%) survived, while only 2 of the remaining 6 (33%) nonvaccinated controls survived. Still to be determined are issues such as protection conferred in the real world, the duration of immunity (remember...serum antibody titers are not necessarily predictive of immunity nor duration of immunity), and impact of vaccination on latent FIP infections.
ADDITIONAL READING (FIP)


FIP Factoids

- The common Feline Enteric Coronavirus (FeCV) appears to be the parent of FIPV.
- There is good evidence that certain cat breeds, and lines within breeds, are predisposed to FIP. Persian 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.
- 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 shedding in infected cats is bimodal....more on the significance of this fact during the presentation...