Feline Infectious Peritonitis

Susan Little, DVM, DABVP (Feline), Melissa Kennedy, DVM, PhD, DACVM, Glenn A Olah, DVM, PhD, DABVP(Feline)
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One of the most poorly understood and enigmatic feline viruses is the feline coronavirus (FCoV), a large enveloped positive-stranded RNA virus. Two primary forms of FCoV are recognized, a relatively harmless enteric form (FECV) and the feline infectious peritonitis (FIP) disease causing form (FIPV). FIP is invariably a lethal, systemic immune-mediated disease. The most popular etiological hypothesis is that it arises in some cats infected with the FECV form when this relatively benign form mutates into a pathogenic FIPV form. This theory has been referred to as the ‘internal mutation theory’ (Vennema et al., 1998; Pedersen et al., 1984; Pedersen et al., 2009). Although FECV is very common among cats, especially in multi-cat households, catteries, and shelters, mortality from FIPV is fortunately generally low. Multi-cat situations of several years’ duration will likely have a brush with FIP. It is no cause for either fear or ostracization. It is, however, a reason to make efforts to understand this disease and its means of control.

Dr. Jean Holzworth reported the first description of feline infectious peritonitis in 1963; however, there are reports of clinical cases that were likely FIP going back to 1914 (Holzworth, 1963; Pedersen, 2009 (review)). The disease was thought to be viral when first described, but no specific etiologic agent was identified until 1968 when Zook and co-workers observed viral particles in tissues of cats with FIP (Zook et al., 1968). Eventually, in 1970 Ward identified FIPV to be a coronavirus due to its close similarity to other members of the family Coronaviridae (Ward, 1970). Since its recognition in the 1960s, FIP has seen a steady increase in disease incidence, and it is currently one of the leading infectious causes of death among young cats from shelters and catteries (Pedersen, 2009 (review), 2014 (review)). Even though we have known about this virus for a long time, only in the past 10-20 years has research started to shed more light on this ever-present feline disease. This article is designed to present some of the newer information and rectify some of the older ideas still found in print and other media.

Feline coronavirus is unique when compared to other feline viruses in several ways:

a) Systemic antibodies have no protective function for the cat and may actually play a role in FIP itself through what is referred to as antibody-dependent enhancement (ADE) (Pedersen, 2014a (review) and references therein). ADE occurs when non-neutralizing antibodies against the virus facilitate the virus entry into host cells, thus increasing viral infectivity in the target cells (Scott et al., 1995a).

b) Antibody titers do not distinguish between the harmless FECV form and the FIPV form; therefore, titer levels must be interpreted with caution (Hartmann et al., 2003; Bell et al., 2006; Pedersen, 2014 (review)). Although very high titers (> 1:1600-3200) in a cat with clinical signs and other diagnostic data consistent with FIP would be strongly suggestive of FIP (Hartmann et al., 2003), zero titer or low titers do not confirm or exclude the disease.

c) One FIP vaccine is commercially available (Felocell FIP, Primucell FIP) and it is marketed by Zoetis, Inc. (previously a subsidiary of Pfizer). There is no consensus on its efficacy or safety. To make matters
worse, some studies suggested in some cats that this vaccine might actually contributed to disease progression through ADE process (McArdle et al., 1995; Scott et al., 1995a).

d) FCoV is a large RNA viruses and like other RNA viruses, its replication is error-prone and has a high estimated mutation rates of $\approx 4 \times 10^-4$ nucleotide substitutions/site/year (Drake, 1993; Licitra et al., 2013 and references therein, Aguas and Ferguson, 2013).

FECV is a very common, highly infectious feline virus. It belongs to the Alphacoronavirus genus, which has members that infect other species (man, swine, cattle, birds, dogs). The majority of cats with FECV (about 90% or more) remains healthy or shows only mild limiting (i.e., diarrhea) disease. But in a small number of cases, FECV infection is the first step in a chain of events leading to FIP. This happens because coronaviruses are made of large numbers of nucleotides, the basic unit of genetic material, and they are very prone to mutations (Drake, 1993, Aguas and Ferguson, 2013). As a virus reproduces itself, errors are made in copying these nucleotides. It is an inherent lack of proofreading activity of RNA virus polymerases that lead to constant creation of new viral genetic variants (Santiago and Sanjuan, 2005). In addition, the more nucleotides, the more errors are possible. While most of these errors are harmless, some will have the effect of giving FECV the ability to cause disease. These mutant FECV strains are called FIPV. Currently, three different genes have been associated with the FECV-to-FIPV mutation or biotype conversion. Each mutation is a result of positive selection pressures, initially switching from only infecting intestinal epithelium cells to infecting monocyte/macrophage cells, and ultimately spreading to the rest of the body even in the face of host immunity (Vennema et al., 1998; Chang et al., 2012, Pedersen et al., 2012; Pedersen, 2014 (review); Porter et al., 2014).

Research further supports that mutant FECVs likely arise within an individual cat (Pedersen et al., 2012; Harley et al., 2013). Thus, we know that the vast majority of cats do not "catch" FIP, but they likely develop mutant FECVs via ‘internal mutation’. Non-pathogenic FECV infects and replicates within the cells of the intestinal tract and may be shed into the feces. But FIPV has developed the ability to survive and replicate within a type of white blood cell of the immune system that is called a monocyte (when in blood) and a macrophage (when in tissues). This ability of the virus to replicate to high levels in monocytes and macrophages is critical step to the development of FIP. FIPV are able to spread throughout the cat’s body, and are no longer localized in the intestinal tract and so are rarely shed into feces. Transmission of FIP from cat to cat is considered to be rare. This fact has caused leading FIP researchers to state that cats that are ill with FIP are unlikely to be a risk to other cats and thus do not need to be isolated.

Recent investigations have identified mutations in FCoV found in tissues other than the intestines (Chang et al., 2012, Pedersen et al., 2009; Pedersen et al., 2012; Licitra et al., 2013; Pedersen, 2014a (review) and references therein; Porter et al., 2014). Mutations occurring in one gene (ORF 3c accessory gene) will lead to loss of replicate in the intestinal epithelium (Pedersen et al., 2012). The investigators speculate that this gene may be required for efficient intestinal replication, and its mutation results in loss of this ability. Thus, this mutation may lead to increased virulence of the virus but prevent its replication in the gut, thereby preventing shedding in feces of the affected cat.

Mutations in the spike (S) protein gene appear to be responsible for the change of the site of virus infection and replication switching from intestinal epithelium toward macrophages and monocytes (Licitra et al.,
2013, Porter et al., 2014). FCoV spike (S) protein is critical in target cell receptor binding (S1) and fusion (S2). Therefore, it is not surprising that recent studies have identified additional mutations in the spike (S) protein gene some of which encode the fusion protein and S1/S2 cleavage site (Chang et al., 2012; Licitra et al., 2013; Bank-Wolf et al., 2014; Porter et al., 2014). Porter and coworkers have shown that specific spike (S) protein gene mutations do indeed shift toward viral macrophage tropism and systemic spread of the virus, but do not necessarily contribute to conversion of FECV to FIPV (Porter et al., 2014).

Nevertheless, mutation in the spike (S) protein gene would still seem to be essential for FECV to FIPV conversion; however, it is not likely to be the only mutation required for this conversion. Terada and coworkers showed that a type I FIPV strain remained fully virulent despite a large gene deletion with predicted loss of 245 amino acid sequence in the N terminus of the spike (S) protein (Terada et al., 2012; Pedersen, 2014a (review)). This deletion would not affect the fusion peptide or S1/S2 cleavage regions of the spike (S) protein and, thus, this begs the question as to what is the role of the N terminus of the spike (S) protein. Lastly, loss of virulence has been associated with ORF 7b accessory gene mutations in FIPV, but ORF 7b accessory gene mutations are not thought to be involved in FECV-to-FIPV transformation (Pedersen et al., 2009; Pedersen 2014a (review) and references therein).

It has been estimated that in multi-cat households where FECV has been introduced, 80%-90% of all the cats will be infected. In the general cat population, infection rates may reach 30%-40%. Multi-cat situations and catteries are especially likely to be FECV-positive since traffic of cats and kittens in and out of the establishment is common. However, the incidence of cases of FIP is quite low in comparison. Generally, most of these establishments experience far less than 10% losses to FIP over the years. Rare instances have been documented in which an apparent epidemic of FIP is associated with mortality rates of over 10% in a short period of time. One possible factor in these epidemics is the shedding of virulent virus, an uncommon situation. Usually, losses are sporadic and unpredictable. The peak ages for losses to FIP are from 6 months to 2 years old (with the highest incidence at 10 months of age). Age associated immunity to FIP appears to be possible, although cases of FIP have been reported in cats over 2 years old including elderly cats. Transmission of FIP from a queen to her unborn kittens has not been shown to occur, but transmission of
FECV from queen to kittens is common.

What are the factors that predispose a small percentage of cats with FECV to the development of FIP? Research is currently trying to find more answers to this question, but some facts are becoming clear. Dr. Janet Foley and Dr. Niels Pedersen of the University of California at Davis have identified three key risk factors: genetic susceptibility, the presence of chronic FECV shedders, and cat dense environments that favor the spread of FECV (Foley and Pedersen, 1996; Foley et al., 1997a, 1997b).

Drs. Foley and Pedersen identified a genetic predisposition to the development of FIP in 1996 (Foley and Pedersen, 1996). They examined pedigree and health data from 10 generations of cats in several purebred catteries and found that the heritability of susceptibility to FIP could be very high (about 50%). It is likely a polygenetic trait rather than a simple dominant or recessive mode of inheritance. Inbreeding, by itself is not a risk factor. Several breeds, including the Bengal, Birman, and Himalayan, are more likely to develop FIP. In addition, susceptibility along familial lines has also been documented. Selecting for overall disease resistance is a helpful tool for breeders.

The disease itself is primarily mediated by the immune response to the virus, rather than the virus itself. The mutant virus replicates efficiently in monocytes and macrophages throughout the body. In cats that develop FIP, the virus is not effectively cleared for reasons that remain unknown. These animals mount a strong antibody response, but this is ineffective at clearing the virus – antibodies target mainly pathogens and viruses outside the infected cells. Effective viral clearance requires cell-mediated immunity, in which cells of the immune system target infected cells, thus eliminating these “virus factories.” Why some cats mount this ineffective response is the subject of much investigation, and as suggested above, likely has a genetic component. The probable defect in immunity to FIP is in cell-mediated immunity. This type of immunity is important in defense against pathogens that replicate within a cell (as opposed to those that colonize extracellular spaces). Therefore cats that are susceptible to FIP are also likely susceptible to some other infections as well, especially intracellular fungal and viral infections. This finding gives breeders the ability to achieve success in reducing the risk of FIP by using pedigree analysis to select breeding cats from family backgrounds that have strong resistance to FIP and other infectious diseases.

Thus, to produce FIP, it takes not only the mutant virus, but a cat predisposed to mount an ineffective and inappropriate immune response to the virus – the “right” virus and the “right” cat. This is why FIP is uncommon, though infection with FCoV is widespread among cats.

The lesions of FIP arise from the immune response to the virus. Infected cells accumulate along the walls of blood vessels, and even migrate into the surrounding tissue. The inappropriate antibody-mediated response by the immune system leads to tissue damage at these sites through a variety of mechanisms. So-called “innocent bystanders” – uninfected cells – are often killed in the process. This leads to an intense inflammatory response that may be widespread along the blood vessels (effusive FIP) or it may be localized to specific tissues, such as the eye, or kidney (non-effusive FIP). Because this antibody response is ineffective at clearing the infection, the virus continues to replicate and accumulate, as does the inflammatory response. This progresses to multi-organ failure and inevitably death.

There are two forms of FIP. The effusive (or wet) form is characterized by accumulation of fluid in the chest or abdomen. This fluid is high in protein content, fibrin content, often a yellow color, and sticky.
The yellow fluid found in the abdomen of a kitten that died from wet FIP.

The non-effusive (or dry) form of FIP is characterized by inflammatory lesions called pyogranulomas and can be found in almost any organ of the body, including the nervous system. Signs of illness common to both effusive and non-effusive forms of FIP include loss of appetite, weight loss, lethargy, and fluctuating fever that is not responsive to antibiotics. Cats with the effusive form may develop a swollen abdomen or difficulty breathing because of fluid accumulation in the chest.

A kitten with the distended abdomen typical of the wet form of FIP.

As with so many aspects of FIP, testing remains problematic. To date, there is no way to screen healthy cats for the risk of developing FIP. Antibody titers are poorly correlated with risk of FIP and should not be used to screen healthy cats. In addition, cats that have been vaccinated with some types of vaccines may test falsely positive on coronavirus antibody tests due to cross-reaction between components of the cell culture used to produce the vaccine and test system components. It remains true that a negative antibody titer does not rule out FIP and very high titers (> 1:1600-3200) are highly suggestive of FIP. Interpretation of FeCoV titers should be done cautiously and never solely relied upon without other diagnostic information.
Finding the virus itself in a cat is also not diagnostic for FIP, even in body sites outside of the intestinal tract. As stated above, the virus is common, and can be found in the blood of infected yet healthy cats. There are now DNA based blood tests offered by a few labs that are purported to be FIP specific. However, there are no published studies that have identified the genetic difference between FECV and FIPV, and most experts doubt the validity of these tests. A test from Auburn University, called the mRNA test for coronavirus, detects virus actively replicating outside the intestinal tract. This approach shows promise as an aid in the diagnosis of FIP, as efficient replication outside the gut primarily occurs in FIP. As previously mentioned, it has been postulated that mutations in the FECV spike (S) protein is necessary for macrophage tropism and spreading of the virus from the intestinal tract to the rest of the body (Chang et al., 2012; Licitra et al., 2013; Porter et al., 2014). Specific mutations in the spike protein have indeed been identified in ~64-90% of FIP phenotypes. On the other hand, it has been shown that specific spike (S) protein mutations correlate with macrophage tropism, but not necessary pathogenic FIP phenotype (Porter et al., 2014). Recently, a test that supposedly can identify spike (S) protein mutations associated with FIP has been developed and marketed by IDEXX Laboratories, Inc. However, if specific spike protein mutations only represent macrophage tropism and viral spread and not mutation to FIP, then this test may only hold promise in ruling out FIP as a possible cause of disease. In addition, it is suspected that not every cat harboring a FIP variant will develop FIP disease. The fact remains that we have no easy screening test for FIP in well cats. Neither do we have a foolproof way to diagnose FIP in a sick cat.

Dr. Andrew Sparkes and his colleagues at the University of Bristol, England, have suggested that by combining several test results (e.g., albumin/globulin ratio, globulin levels, lymphocyte counts) with clinical findings can help rule in or rule out FIP with some degree of certainty (Sparkes et al., 1991, Sparker et al., 1994). Although antemortem diagnosis should not rely on serology alone, very high FIP titers (< 1:1600-3200) in combination with test results that correlate with FIP (building the diagnostic “brick wall” for FIP, with each brick a separate test result) is strongly suggestive of FIP (Bell et al., 2006; Hartmann et al., 2003; Pedersen 2009, 2014b and references therein). On the other hand, high serum albumin/globulin ratios (> 0.8) suggest that FIP is not the cause of disease (Jeffery et al., 2012). A test referred to as the Rivalta’s test can help with diagnosis if effusion fluid can be obtained (Fischer et al., 2013). The diagnostic gold standard still remains examination of affected tissue using a biopsy or findings at necropsy.

Unfortunately, there is no known effective treatment for cats with FIP. Treatments are aimed at palliative care and patient comfort. Drugs that suppress the immune system response to FIPV (such as prednisolone) may temporarily stabilize patients. Newer therapies, such as recombinant feline interferon and pentoxifylline, have shown some limited success in a small number of patients but require more investigation before they can be recommended (Ritz et al., 2007; Fischer et al., 2011). Feline interferon is not available in all countries.

Drs. Legendre and Bartges at College of Veterinary Medicine, University of Tennessee, in a preliminary experiment, tested an immunomodulatory drug in three cats with the dry form of FIP and possibly demonstrated efficacy in prolonging life and alleviating signs (Legendre and Bartges, 2009). The drug, a polypropenyl immunostimulant (PPI), is an investigatory veterinary biologic and an agonist of Toll-like receptors 2 and 4 that promote a Th-1 immune response to enhance cell-mediated immunity which is required for elimination of the viral infection. As reported in the original paper, two of the three cats treated with PPI were still alive two years after diagnosis, while the third cat survived 14 months. A limited
number of cats with the effusion form of the disease were also treated, but no benefit was noted.

In 2010, Winn Feline Foundation awarded a grant to Dr. Legendre to further study the potential benefit of PPI in treating FIP dry form (Legendre 2013, 2014). Fifty-eight cats were identified with FIP dry form, treated with PPI, and followed for at least a year after diagnosis. Twenty-two percent of the cats lived 6 months or longer and 5% were alive at a year. Cats that responded to treatment had improvement in appetite and general well-being within 2 to 3 weeks after starting treatment. Dr. Legendre believes that PPI treatment increased survival time and quality of life; however, no placebo control group was part of this study on ethical grounds since FIP is 100% fatal. Unfortunately, clear benefit with PPI treatment cannot be made. Further studies to be considered would be a combination of an antiviral approach with an immunostimulant like PPI.

Sadly, the majority of patients eventually deteriorate to the point where humane euthanasia is chosen.

So how can FIP be controlled? In addition to efforts in breeding resistant animals, preventing or reducing the incidence of FCoV infection is important. FECV is spread primarily by the fecal-oral route, and to a much lesser degree, through saliva or respiratory droplets. The virus can persist in the environment in dried feces on cat litter for 3 to 7 weeks, so scrupulous cleaning of cages and litter pans is important to reduce the amount of virus in the environment. [This suggests that if one is introducing new cat into a household that had a previous cat die from FIP, then it would be prudent to wait at least 2 months.] Fortunately, FECV is susceptible to most common disinfectants and detergents. It is important to have adequate numbers of litter pans. Litter pans should be kept away from food bowls and spilled litter should be regularly vacuumed up from the floor.

Research has shown that there are two main patterns that occur with FECV infection. Most cats will become infected and recover, but will not be immune. They are susceptible to reinfection the next time they contact the virus. A small number of cats become infected but do not recover. They become persistent shedders of FECV in the cattery or shelter and are the source of reinfection for the other cats although they may never become ill. Therefore, the key to eliminating FECV (and thus the risk of FIP in a cattery or other multi-cat establishment would be the identification and removal of chronic shedders. Currently, however, there is no easy way to determine which cats in a multi-cat environment are persistent shedders. The traditional antibody titer for FECV cannot reliably be used to determine which cats are chronic shedders. The most effective and practical tool is PCR analysis of feces for the presence of FECV. Because shedding of the virus may be intermittent, testing of multiple samples over time is required. Drs. Marian Horzinek and Hans Lutz at the University of Utrecht, Netherlands suggested that PCR on four fecal swabs taken at one-week intervals can help determine chronic coronavirus-shedding status of a cat (Horzinek and Lutz, 2000). On the other hand, Drs. Diane Addie and Oswald Jarrett at the University of Glasgow, Scotland showed that PCR on fecal swabs taken over eight consecutive months was necessary to help identify true coronavirus-shedding status of a cat (Addie and Jarrett, 2001).

In addition to selecting disease-resistant breeding stock, breeders, shelter managers, and other multi-cat households can initiate husbandry practices that discourage the spread of FECV and development of FIP. Cat-dense environments favor the transmission of the highly contagious FECV. Dr. Addie recommends that the ideal way to house cats in catteries is individually. However, since this is not always possible, she
Dr. Addie has also described a method for early weaning and isolation of kittens born to FECV-positive queens designed to prevent infection of the kittens (Addie and Jarrett, 1992, 1995; Addie et al., 2009). It involves rigorous barrier nursing techniques to prevent the spread of the highly contagious FECV, and so is not for every breeder or cattery. The procedure involves first isolating the pregnant queen in a separate area to have the kittens. When they are 5-6 weeks old (at the time when their maternal immunity to FECV is waning), the kittens are removed from the queen and isolated by themselves. It should be kept in mind that this method has not been rigorously tested and its effectiveness has been questioned (Lutz et al., 2002). Some other difficulties with this method involve the strict infection control procedures needed and possible difficulties in socializing kittens. It been reported by breeders that some early-weaned kittens may have behavioral problems, such as inappropriate suckling on littermates. Nevertheless, when properly practiced, not only can FECV-negative kittens possibly be produced, but the kittens are often less prone to respiratory diseases and other common kitten diseases.

Probably one of the most controversial areas in any discussion of FIP is Primucell FIP®, the vaccine made by Pfizer Animal Health, available since 1991. The vaccine is a modified-live temperature-sensitive viral mutant of the type 2 FCoV strain DF2 licensed for intranasal use in cats at least 16 weeks of age. The manufacturer recommends annual revaccination although no duration of immunity studies are available. The vaccine stimulates local immunity and may also produce an antibody titer. Evaluation of the risks and benefits associated with this vaccine is a difficult venture and has engendered much controversy. Since FIP is a severe and fatal disease, the safety of any vaccine is a paramount consideration. Dr. Nancy Portorino-Reeves evaluated the safety of the vaccine by following 582 cats of various ages for 541 days that were given 2 vaccine doses. The FIP vaccine appears to be safe for use in the general cat population. It was further concluded that it does not sensitize cats to develop FIP, via an ADE process, nor do there appear to be any other systemic problems associated with use of the vaccine. In addition, Dr. Fred Scott of the Cornell Feline Health Center concluded in a published paper that the risks associated with the Primucell FIP® vaccine are minimal in most situations (Scott, 1999). He notes that the vaccine has been in use for many years with no increase in the incidence of FIP. Troubling reports of ADE-induced FIP arose from several labs in which cats vaccinated with the FIP vaccine were challenged experimentally with FIPV and actually developed accelerated disease instead of being protected. It is not known whether the phenomenon of ADE occurs in the real world and there is no easy way to find out. If it does occur, it is likely an uncommon event, but the possibility remains troubling (Scott et al., 1995a).

Discrepancies exist in studies regarding the efficacy of the Primucell FIP® vaccine as well. Some studies demonstrate protection from disease (Gerber et al., 1990; Hoskins et al., 1995a,b) while others show little or no benefit from vaccination (McArdle et al., 1995; Scott et al., 1995b). The best reported efficacy for the vaccine was demonstrated when FCoV negative cats, at least 16 weeks old, were vaccinated twice (3 weeks apart), in a study by Dr. Nancy Portorino-Reeves published in 1995 (Portorino-Reeves, 1995). In this study, after being vaccinated, these cats were placed in a large cat shelter where FIP was endemic. The vaccinated cats experienced a significantly lower mortality rate than unvaccinated cats. The efficacy of the vaccination was calculated to be 75% (preventable fraction). On the other hand, in a field study of 138 cats belonging to 15 cat breeders, in which FIP is endemic, no difference was found in the development of FIP between the
vaccinated group and the placebo group (Fehr et al., 1995). Thus, vaccination in households, shelters or catteries with known cases of FIP or in an FCoV-endemic environment, is not likely effective. Differences in experimental design of challenge trials (eg, strain and dose of challenge virus, genetic predisposition of test animals, field vs. experimental infection, etc.) may account for discrepancies in efficacy (Scherk et al., 2013 and reference therein, European ABCD: FIP, 2012 and reference therein).

One reason for a lack of vaccine efficacy may be that most kittens in catteries are infected between 6 and 10 weeks of age, long before the 16 weeks of age the vaccine is licensed (Lutz, 2002). Once a cat is infected with FCoV, the vaccine has no benefit. Some cattery owners have been using the vaccine at ages younger than 16 weeks to get around this problem. Dr. Johnny Hoskins, professor Emeritus at the Louisiana State University School of Veterinary Medicine and small animal internal medicine consultant through DocuTech Services, Inc., has outlined a vaccination protocol for catteries experiencing FIP losses in kittens less than 16 weeks of age. He recommends giving the vaccine at 9, 13 and 17 weeks with annual revaccination afterward. Use of this protocol must be made with the knowledge that no controlled studies have been done on kittens under 16 weeks of age and that this is an off-label use. It would appear that the use of the vaccine according to the manufacturer’s directions is limited to the vaccination of FCoV antibody-negative cats entering high-risk situations, such as catteries and shelters.

In conclusion, much has recently been discovered about FIP, and the jigsaw puzzle is slowly coming together, but still not complete. As more is discovered, there will be improvement in our understanding of, our ability to diagnose, prevent, treat, and control this terrible disease.

References:


