Farewell **I**ll **P**hoebe

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Introduction:

Feline infectious peritonitis (FIP) is a progressively fatal disease of both domesticated and wild felines[9,13]. FIP is an immune-mediated disease prompted by infection with the feline coronavirus (FeCoV)[5,7,10,13]. FeCoV is universally found in a majority of cats and is transmitted fecal-orally, with a higher incidence seen in high density cat populations[9,10]. Antibodies are detected in up to 90% of cats in catteries and 50% of single-cat households, with approximately 5% of these developing FIP[7]; making FIP the number one cause of infectious disease deaths in cats worldwide[,3,6,17].

History and Presentation:

History and signalment are key players in guiding the diagnosis towards FIP. This disease often occurs with a bimodal age distribution, with cats less than two years old representing a majority (70%) of the cases but also observed in cats up to 17 years of age[9,10]. In addition, purebred felines, in particular Birmans, Bengals, Abyssinians, Himalayans, Rexes, and Ragdolls are reported to have an increased risk of FIP development[9]. Likewise, intact males are at higher risk of developing this illness[9,10,13]. High density cat populations such as catteries, shelters and multi-cat households provide the perfect environment for the coronavirus to be spread[3,9,10]. Therefore, these cats are at a higher risk of becoming infected with the coronavirus which can lead to FIP.

A good history of where and when the owners obtained the pet, as well as their current environment, can aid in making a well ranked differential list. A cat that has been purchased from a breeding cattery or adopted from a shelter within the previous 18 months cannot be overlooked[3]. The incubation period of effusive FIP is days to a month, while the non-effusive form can be up to one year[3,5].

Another important factor in the diagnosis of FIP involves the concept of immunity. Cell-mediated immunity can be protective, while humoral is insufficient for this infection[9,15]. However, the formation of antibodies in response to the infection may actually be counterproductive by enhancing the uptake and replication of the virus in macrophages. This contributes to an antibody-mediated (type III hypersensitivity) vasculitis. The effusive form may be the result of failure of the cat's immune system to mount T cell immunity in the face of a strong B cell response. Alternatively, an intermediate response may occur in the non-effusive form allowing for partial containment of the virus to fewer macrophages and to more focal lesions. In the cat that resists disease, the cell-mediated response is so strong it may overcome any of the negative effects of the antibodies[15]. Therefore, cats that are immunocompromised such as young, old, stressed and sick cats are more susceptible to succumbing to their infection[3,9]. It is important to ask if the cat has been in any stressful situations, which would lead to immunocompromise, such as boarding, travel, or breeding. It should also be known if any concurrent illnesses such as upper respiratory infection, FIV or FeLV may be present. The cat's immunological response to the virus is vital in determining the progression and outcome of infection[9].

Symptoms of FIP come in a wide variety and can seem to occur suddenly due to the felines remarkable ability to mask signs along with a sometimes lengthy incubation period by the virus[5]. Early stages of FIP can have nonspecific signs such as recurrent fever that is unresponsive to antibiotics, anorexia, weight loss, dehydration and depression[3,5,9]. Some cats may develop transitory gastrointestinal signs, including mild diarrhea and vomiting, while others may display upper respiratory symptoms such as runny and watery eyes/nose and sneezing[3,5]. All of these

symptoms are very general and can be a part of multiple other disease processes, continuing to make FIP elusive to the untrained eye.

Of the two forms of FIP (effusive/ wet and granulomatous/ dry), the most common is the effusive form, present in 60-70% of cases[9]. This form is named after its most pronounced feature: effusion. Effusion can occur in the abdomen (ascites) and/or thoracic cavities (pleural or pericardial), with abdominal effusion occurring more frequently[1,3,5,6,9,17]. Fluid may develop rapidly giving the cat a pot-bellied or pregnant appearance with abdominal effusion that may spread caudally producing scrotal swelling. In addition, respiratory changes such as muffled heart/lung sounds as well as respiratory dyspnea from fluid accumulation in the chest may occur[3,5,9].

Alternatively, the dry or granulomatous form can incubate for months to years causing more gradual signs to develop. Symptoms depend on the organ involved and can include, but are not limited to: fever, ocular lesions (uveitis, keratic precipitates, retinal changes, etc[9]), CNS signs (ataxia, head tremors, nystagmus, etc[3]), large/irregular kidneys, icterus, enlarged mesenteric lymph nodes, omental masses (visceral adhesions), and thickened intestines[1,3,5,9,17]. As the disease progresses, specific organs may be targeted altering the symptoms displayed. Although FIP is difficult to diagnose, the dry form tends to be even more challenging with its nonspecific and diverse clinical signs[9].

Pathophysiology:

In order for a cat to develop FIP, it must first be infected by feline coronavirus (FeCoV). This virus is a single-stranded, enveloped, RNA virus and is one of the largest coronaviruses. The main route of transmission is fecal-oral, with the litterbox serving as the primary reservoir of infection[1,3,5,6, 7,9,13,14].

Once infected by feline coronavirus, the infection can result in four different outcomes:

1) Transient infection: This occurs in the majority (approximately 65%) of cats and is a transient feline enteric virus (FECV) infection. In this case, FECV acts as a relatively benign virus; it migrates to the enterocytes of the intestinal epithelium and replicates. These cats are minimally affected resulting in mild diarrhea for some felines and with no clinical signs in others, but intermittently to continuously shed FECV anywhere from weeks to years.
2) Persistently infected: This occurs in approximately 13% of felines. These cats continually shed, but often remain healthy with some developing chronic diarrhea.
3) FIP: Disease ensues in approximately 5-10% of cats infected with FeCoV. Although, a cat with FIP will shed the virus, it will shed the non-mutated FECV, not FIP.
4) Resistance: The least likely possibility is that the cat does not develop infection and is resistant to FeCoV. This occurs in about 3% of cats and they do not shed the virus.[1,9]

Feline Infectious Peritonitis is an immune complex disease that involves viral antigen, antibodies, and complement[13]. This occurs by two, proposed, mechanisms:

1) The FECV infects intestinal macrophages, escapes into systemic circulation, and begins to replicate in systemic tissues[9,13,14]. The virus attracts antibodies, complement is fixed, and more macrophages along with neutrophils are drawn to the site. As a consequence, pyogranulomatous changes occur[10,13].
2) Circulating immune complexes lodge into blood vessel walls, fixing complement and once again leads to the pyogranulomatous changes seen[6,10,13]. These antigen-antibody

complexes are presumed to be recognized by macrophages, but are not presented to killer cells, like they should be, consequently preventing them from being destroyed by the immune system.

In addition to the virus, chemotactic substances (complement and inflammatory mediators) are released from infected macrophages leading to the release of vasoactive amines causing endothelial cell retraction which causes increased vascular permeability allowing for exudation of plasma proteins and ultimately causing the characteristic protein-rich exudates often found with FIP. Inflammatory mediators that are released from infected macrophages activate proteolytic enzymes causing further tissue damage[13]. As long as FeCoV remains in the gut, it does not mutate into FIPV[9].

FIPV is genetically distinct form FECV and has genetic mutations consistently detected at the 3c gene. However, these differences are minimal and inconsistent, making it difficult to distinguish FECV from FIPV[4,9]. An un-mutated and intact 3c gene is required for horizontal transmission of FeCoV between cats. After 3c has mutated, it interferes with transmission. Therefore, clinical FIPV is due to the host's immune response and FIP is not commonly transmitted between cats. Hence, horizontal transmission is not of concern[9,10,14].

The true pathogenesis of FIP has yet to be determined, but two main hypotheses currently exist. The first is known as the "internal mutation hypothesis." This hypothesis suggests the Feline Enteric Corona Virus (FECV) mutates into a virulent form becoming Feline Infectious Peritonitis Virus (FIPV). Whereas the "virulent/avirulent strain hypothesis" suggests that two biotypes of Feline Coronavirus (FeCoV) circulate in cats with FIP; FIPV is the virulent biotype and FECV is the avirulent biotype[1,5-7, 9, 10].

Differential Diagnoses:

FIP can present comparably to many other diseases due to its wide variety of generalized symptoms[5]. Depending on what form of FIP is present, wet or dry, determines which clinical signs are displayed. The following are just a few differentials for each form:

1) Wet form differentials: congestive heart failure, hepatic disease, hypoproteinemia, pancreatitis, bacterial peritonitis, neoplasia, Toxoplasmosis, pregnancy, pansteatitis, and intestinal parasitism[9,10].

2) Dry form differentials: cardiac insufficiency, neoplasia, pyothorax, chylothorax, Cryptococcosis, diaphragmatic hernia, trauma (hemothorax), lung lobe torsion, and Dirofilariasis[9,10].

a. Neurological differentials: trauma/hemorrhage, infectious inflammatory diseases (bacterial, protozoal, mycotic, rickettsial, etc), granulomatous meningoencephalitis, hydrocephalus, thiamine deficiency, degenerative diseases[18].
b. Ocular differentials: mycosis (blastomycosis, crptococcosis, histoplasmosis, coccidiomycosis), neoplasia, granulomatous meingoencephalitis, hydrocephalus, immune-mediated optic neuritis, trauma[18].

Diagnostic Approach/Considerations:

Diagnosing FIP can be a very difficult process that involves multiple steps. If several of the following results occur, the index of suspension for FIP is raised. However, there is no current ante-mortem test to confirm diagnosis. The diagnosis of FIP begins with a good history, signalment, and physical exam of the patient, as discussed above. Following this, a minimum database of bloodwork and urinalysis should be performed. Several findings on a complete blood count (CBC) are common, but none are diagnostic. Results may reveal a non-regenerative mild

to moderate anemia; however, occasionally there will be a regenerative anemia. In addition, a leukocytosis with absolute neutrophilia may be present. Lymphopenia is likely to occur, while a normal lymphocyte count is unlikely in FIP cats. Lastly, thrombocytopenia may be displayed due to the development of DIC. If the blood chemistry exhibits elevated liver values in the absence of other clinical causes, the suspicion of FIP should be increased[9,10,13]. Hyperglobulinemia is another key finding especially in the dry form. Specifically, if the globulins are typed out further, an elevated gamma-globulin level should be present. Macrophages release a number of inflammatory cytokines, including interleukin-6 (IL-6). IL-6 incites B lymphocytes to differentiate into plasma cells, thus high IL-6 levels are likely the cause of the hypergammaglobulinemia in cats with FIP[1]. Hypoalbuminemia, and decreased albumin: globulin (A:G) ratio are also main features to look for on the chemistry[3,6,9,10]. Albumin may be lost due to the FIP induced vasculitis, as well as via a glomerulonephritis secondary to immune complex deposition[12]. An A:G ratio of the serum less than 0.5-0.6 is suspicious of FIP, with < 0.4 being highly suggestive of FIP and > 0.8 being extremely unlikely[3,6,9,10,13]. The most common bloodwork abnormality found in cats with FIP is an increase in total serum protein concentration. However, the A:G ratio has a significantly higher diagnostic value to distinguish FIP from other diseases[13].

Tests that are of much higher diagnostic value than those performed on blood are those performed on effusion fluid. If effusion is present, the fluid should be evaluated based on: classification, color/clarity, cell count, cytological examination, protein content, A:G ratio, immunocytology and electrophoresis[9]. If the fluid is classified as a non-septic exudate or modified transudate, the suspicion of FIP increases. An effusion A:G ratio of < 0.4 is strongly correlated with FIP as well. The color and clarity of the fluid can be of any type, but often

appears straw colored and is viscous due to the high protein content (> 3.5 g/dl)[9,14,15]. A typical FIP effusion fluid has a low cell count (< 1000 cells/μL). Upon cytological examination, it displays macrophages and non-degenerate neutrophils, but in considerably lower levels than those seen with bacterial infection[6,9,13]. Nevertheless, there are many causes for effusion including lymphoma, heart failure, pleuritis, liver disease, bacterial peritonitis and more. Due to this predicament, immunocytology can be used to detect feline corona virus antigen within macrophages in effusion fluids or tissue aspirates. This method has nearly 100% specificity, but only 50% sensitivity. Meaning that a positive is a positive, but a negative is not necessarily a negative. Electrophoresis used to be performed to look for a polyclonal gammopathy, but is now an outdated test and considered non-diagnostic for FIP. Rivalta's test on the other hand can be useful to rule out FIP. This test is performed by mixing 2-3 drops of 8% acetic acid with 10 milliliters distilled water, followed by adding a drop of the effusion to the surface. If the drop disappears and the fluid remains clear, the test is negative. If the drop floats or retains its shape as it sinks, the test is positive[3,6,9,10,15]. This test has a high negative predictive value (97%) and positive predictive value (86%) and therefore is very helpful in ruling in or out FIP[12].

Antibody titers can be used as a diagnostic means, however, there is no FIP-specific antibody test; only FeCoV antibodies can be measured. Therefore, these titers must be interpreted with caution and should never be used as a sole test in the diagnosis of FIP[13]. Many healthy, asymptomatic cats can have antibodies to FeCoV due to FECV exposure and most cats with these antibodies never develop FIP. These titers can be helpful if they are either:

1) Negative: the cat is unlikely to be exposed to/infected with FeCoV[7]

2) Very high (1:1600-3200): a high titer in a clinical cat with appropriate diagnostic findings is supportive of the tentative diagnosis of FIP[3,9,13,14].

However, the absence of antibodies does not rule out FIP[9]. Consequently, titers can aid in the diagnosis of FIP, but their use is limited. The clinical picture must be taken into account in order to use them appropriately.

More recently, viral detection of Feline Corona Virus (FeCoV) via reverse transcriptase PCR has been used as a diagnostic tool for diagnosing FIP[12]. This PCR detects viral mRNA, but it does not distinguish virulent from non-virulent biotypes leading to false positives[6,9,10,13]. In addition, viremia can exist in both healthy carriers and cats with FIP. Thus, detection of FeCoV RNA has occurred in healthy cats that do not develop FIP for up to seventy months. The results of serum/plasma PCR tests cannot be used to definitely diagnose FIP and must be interpreted carefully[13]. Although RT-PCR on plasma or serum can give false positive results, it has been shown that when performed on CSF it can be considered a reliable and specific tool for the diagnosis of FIP. In this case, it has specificity of 100% and sensitivity of 42.1% in all varieties of FIP cats, with sensitivity increasing to 85.7% when performed in cats with only neurological and/or ocular signs[8]. Therefore, PCR should be performed on CSF rather than serum/plasma to provide a more trustworthy diagnosis of FIP.

Diagnostic imaging can be used to assess the patient further. Abdominal ultrasound may be used to look for the presence of effusion, enlarged/irregular kidneys, abdominal lymphadenopathy, and diffuse intestinal changes[6,10,13]. If any of these findings are present, the index of suspicion for FIP increases; however, definitive diagnosis remains inconclusive. Likewise, a normal ultrasound does not rule out infection with FIP[10,13]. More advanced imaging such as MRI and CT may assist in localization of neurologic lesions and aid in diagnosis of CNS FIP. Occlusion of the ventricular system, causing obstructive hydrocephalus is very suggestive of neurologic FIP. A study including 24 cats with neurological FIP, demonstrated 75% of them had

hydrocephalus on gross and histological postmortem examination. Other diseases on the neurologic differential list, such as Cryptococcus, toxoplasmosis and lymphoma, have yet to be reported to cause hydrocephalus. In addition, some cases of FIP have been reported with isolated fourth ventricle and cervical syringomyelia. After intravenous injection with contrast medium, enhancement surrounding the third and fourth ventricles, mesencephalic aqueduct, and brainstem is greatly suggestive of FIP[2]. Advanced imaging can be very useful in cases of suspect neurological FIP.

In the case of a cat displaying neurologic symptoms, a cerebrospinal tap with analysis of the cerebrospinal fluid (CSF) might direct the diagnosis towards FIP. The CSF may contain increased protein levels (50-350 mg/dL) and pleocytosis (100-10,000 nucleated cells/mL) consisting of macrophages, neutrophils and lymphocytes. One study discovered that the typical CSF findings in an FIP cat was a pleocytosis of > 100 cells/μL consisting primarily of neutrophils, as well as a protein concentration > 200 mg/dL. Once again, these are relatively nonspecific findings and many cats displaying neurologic signs caused by FIP have a normal CSF[13].

The gold standard for diagnosis of FIP is histopathology and/or immunohistochemistry on tissue or fluid[1,6,9,10,13]. Routine H & E staining can be performed on histopathological tissues. Lesions with perivascular granulomatous to pyogranulomatous inflammation and vasculitis are indicative of FIP[10]. Immunohistochemistry can also be used to fluoresce the FeCoV antigen in macrophages. Both of these tests have a PPV of nearly 100%. In order to obtain these samples, invasive methods such as laparotomy are necessary. However, the patient is often not of adequate health to undergo this procedure. Therefore, histopathology is usually not performed

until post-mortem[12]. Histology or immunohistochemistry staining are currently the only tests that can confirm the diagnosis of FIP[6,9,10,13].

Treatment and Management Options:

A modified live, nonadjuvanted intranasal vaccination for FIP does exist, however, it is not recommended by the American Association of Feline Practitioners[3,5,9,10]. The efficacy of the vaccine is very questionable, as it is ineffective for cats that have already been exposed to FeCoV (the majority of cats)[1,3,9,10]. In addition, the vaccine cannot be given until after 16 weeks of age, by which time most kittens have already been exposed to the virus. Lastly, the vaccine will make the cat FeCoV positive if tested, making it nearly impossible to establish and control an FeCoV negative household or cattery[3,9,14]. Thus, this vaccine should not be used in an attempt to prevent FIP.

The only way to prevent FIP is to prevent infection with FeCoV[10]. Therefore, hygiene plays a key role. The transmission is fecal-oral and the FeCoV can survive for several days to weeks in dried feces in litter[1]. So, the litterbox should be cleaned daily, disinfected weekly, and kept away from food and water dishes. There should be an adequate number of litterboxes for the number of cats present (n+1) and the number of cats should be kept to a minimum (groups of 3 or fewer per room)[5,9,10]. FeCoV transfer from queen to kitten is common, so weaning kittens early at 5-6 weeks of age can help as well[9,14]. Any new cat(s) entering the environment should be antibody tested. If negative, they should then be quarantined for three weeks and retested. However, this should not be used for a "test and removal" program due to the low specificity[9,10]. If a cat in a multiple cat household develops and dies of FIP, the owners should wait a minimum of two months before introducing a new cat to the house[9,13]. Prevention can be provided through these cattery management strategies.

Diagnosing FIP is crucial, as it is nearly always fatal once clinical signs develop[9,10]. If the decision is made to attempt treatment, supportive and palliative care including a low stress environment, high quality diet, intravenous fluids, and drainage of effusion fluid should be provided[5,9,10]. High dose corticosteroids along with cytotoxic drugs such as chlorambucil or cyclophosphamide may be used to provide immunosuppression. In some cases, Pentoxyfylline, and Ozagrel hydrochloride have been beneficial in decreasing the vasculitis caused by FIP[1,6,7,10,13]. Antiviral treatments have been investigated, but many have met with limited success. The use of human interferon-α has been shown to have a direct antiviral effect against FIPV. Immune modulators (tylosin, interferon-α, etc) have been used in attempt to restore the compromised immune function[12]. An immunostimulant, Polyprenyl immunostimnulant (PPI) is the only available and approved product used to treat symptoms associated with feline rhinotracheitis (herpes) virus infection. It works by directing the adaptive immune response and upregulating innate immunity[5]. Recently it has been used in attempts to treat FIP cats. At the terminal stage of FIP, cats tend to have a severe depletion of CD4+ and CD8+ T-lymphocytes which are necessary for mounting a cell mediated immune response. PPI upregulates Th1 cytokines and enhances cell-mediated immunity[12]. In the pilot trial in 2006, 3 cats diagnosed with dry form FIP were given PPI, two of which survived at least 2 years after treatment. The study was resumed using 58 FIP cats in 2009; 22% lived for 6 months or longer, and 5% were alive at 1 year[12,14]. This success shows hope for the future treatment of FIP, however, no control group was used in this study making clear benefits of PPI unknown[13]. A prospective study using 42 cats confirmed to have either form of FIP had a median survival time of 9 days after diagnosis[13]. Some cats with the dry form, can temporarily respond with supportive care, and those without neurologic signs or anemia can survive for months with treatment[5]. However, due

to the low success rate and lack of available successful treatments, euthanasia should be considered if FIP has been confirmed or is highly suspected[9].

Expected Outcome and Prognosis

The prognosis for cats diagnosed with FIP is poor to grave. Survival times vary from 9-200 days' post infection[10]. This wide range may be due to the dry form acting more as a chronic disease allowing the cat to live slightly longer, while the wet form causes death within months. Once clinical disease is present however, approximately 95% of cats will succumb and die[9,10]. Poor prognostic indicators include: low platelet and lymphocyte counts, high bilirubin concentration, a large quantity of effusion fluid, and seizures. Cats that do not show improvement within 3 days of treatment, almost certainly will not benefit from any therapy and euthanasia should be considered. Remission from clinical signs and longer survival is rare[13].

Conclusion:

Feline Infectious Peritonitis is considered a fatal disease and can be difficult to detect. History, signalment, physical exam, and diagnostics can help guide this diagnosis. Nevertheless, only post-mortem samples can provide true confirmation. Without successful treatment available, management strategies are key in the prevention of this disease. FIP remains to be a major killer of young cats and is one of the last important feline infections for which we have no single diagnostic test, no effective vaccination, and no definitive pathogenesis. It remains one of the most researched infections of the feline species with hope for a cure one day[11,15].

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