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FELINE INFECTIOUS PERITONITIS (FIP) – WHAT'S NEW IN DIAGNOSIS AND TREATMENT

Rachel Korman

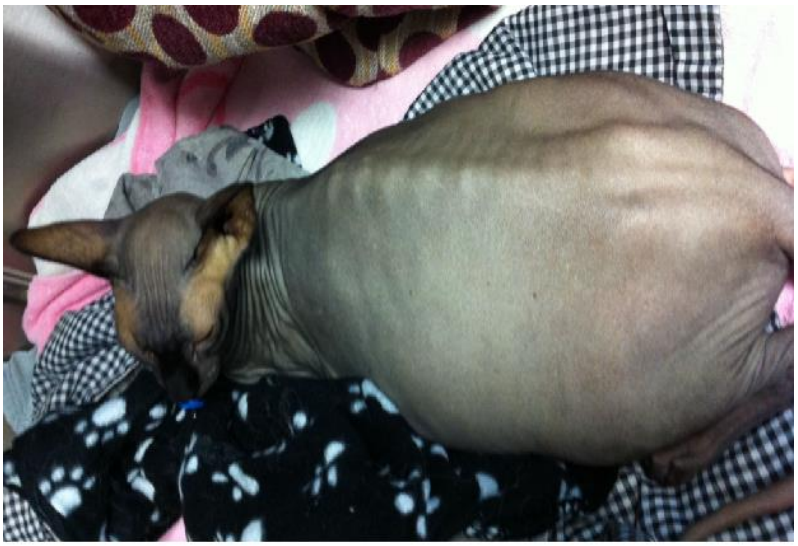
Feline Infectious Peritonitis (FIP) is a devastating syndrome caused by infection of cats with feline Coronavirus (FCoV) – a large, enveloped, positive-sense single stranded RNA virus. A spike protein mediates entry into host cells. Two serotypes are recognized. Type I is associated with most field strains and Type II formed from recombination events between FCoV and Canine Coronavirus. There are differences in transmembrane spike (S) gene and protein. Approximately 40% of cats are reported to be infected with FCoV with prevalence rates increasing to 90% within multicat households, although regional variation is expected.

Typical infection with FCoV results in mild intestinal signs. FCoV was thought to be confined to the intestine, however systemic FCoV infection has been demonstrated in healthy cats. Up to 10% of cats infected with FCoV will develop FIP.

Due to the high prevalence in many areas of FCoV, definitive diagnosis of FIP can be difficult. Making a definitive diagnosis is based on demonstrating appropriate signalment, history and examination findings and interpreting this together with laboratory data.

Cats are typically under 2 years of age and may be from multicat households. There is often a history of recent stress (e.g. neutering, rehoming etc), abdominal distension and dyspnoea. Physical examination findings include pyrexia, jaundice, effusions, uveitis and neurological changes. In a recent retrospective study of pyrexia in 106 cats from a referral centre, 20% of the cats had FIP.

A typical kitten with FIP demonstrating a distended abdomen and gereralised muscle wastage



Another cat with FIP demonstrating marked abdominal distension and jaundice

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Laboratory findings include but are not limited to:

- Lymphopenia (50-80%)
- Hyperglobulinemia (80%)
- Decreased A:G ratio
  - <0.4 FIP very possible
  - > 0.8 FIP very unlikely
- Hyperbilirubinemia (20-60%
  - More common in effusive FIP
  - ALT, ALKP often not markedly increased
- Increased a1-acid glycoprotein (AGP) in serum/effusion
- Pyogranulomatous change on cytology/biopsy.
-

Serology can be performed to assess antibody titres to FCoV but is often unhelpful. It only indicates infection with FCoV and seroconversion. Cats with FIP tend to have higher titres but there is a great deal of overlap with cats exposed to FCoV. Many healthy cats have high or very high titres and 10% of cats with FIP are seronegative. A study assessing the relationship between FCoV antibody titre and signalment in Australian cats found no association between health status and titre level. British Shorthair cats have high levels of antibody compared with domestic shorthairs and Persians demonstrated low level titres.

Definitive diagnosis utilising laboratory techniques revolves around the use of non-invasive methods, confirmation via cytology and histopathology findings (e.g. pyogranulomatous change) and examination of effusion cytology and immunostaining for virus within macrophages. Examination of effusion and biopsy of gross lesions yields the most useful data. Effusions are typically clear, viscous, straw/yellow in colour and protein rich. They often have a thick eosinophilic or proteinaceous background and total protein > 35g/L which classifies them as an exudate, but they are cell poor (<5x10^9/L). Cell infiltrate is most often pyogranulomatous - macrophages, non-degenerate neutrophils and a few lymphocytes. AGP measured in fluid is often high (>1.55 mg/ml) but there is some overlap in cats without FIP.

Abdomina; effusion is typically straw coloured and has elevated protein concentration

A Rivalta's test can be performed to differentiate a transudate from an exudate. A tube is filled with distilled water and acetic acid. To this mixture one drop of effusion is added. The test is positive if the drop stays on the surface or retains its shape and floats to the bottom. The test is negative if the drop disappears. Unfortunately this is a somewhat subjective test. A positive test confirms that the fluid is an exudate, but is not specific for FIP. Positive results are seen with FIP, bacterial/septic peritonitis and lymphoma. If the Rivalta is negative, FIP is unlikely.
Recently, PCR testing has become commercially available for FCoV, however there are still many unanswered questions with this method and a positive test result does not necessarily mean the cat has FIP. Reverse transcriptase PCR (RT-PCR) amplifies FCoV RNA. As FCoV is an RNA virus, there is a high error rate in replication which can affect primer or probe binding and affects the sensitivity of the PCR. Ideally a laboratory would report the test result with sensitivity and specificity for the PCR in use, information regarding the primer binding site origin and also the cycle threshold (CT) value of the PCR. This is the number of cycles it takes to obtain a positive result. The lower the number, the more significant the result. It is often difficult to obtain this data. The advantage of PCR is that results are obtained rapidly.

Reverse transcriptase PCR can be performed on tissue (not formalin fixed) and FIP cats are more likely to be FCoV RT-PCR positive (90% compared with 8%) and cats with FIP had higher FCoV loads with quantitative RT-PCR (qRT-PCR) compared with non-FIP cats, however cats without FIP can still be positive for FCoV by RT-PCR. High levels (qRT-PCR) suggest FIP but are not definitive.

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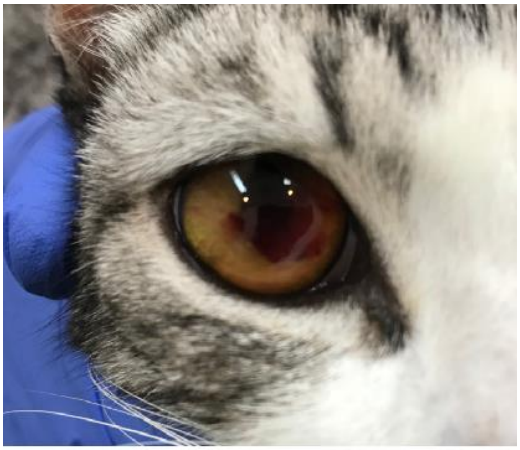
RT-PCR can also be performed on effusions. Most FIP cats (72-89%) have high levels of FCoV in effusion, however negative results can't exclude FIP and specificity is not perfect (a few false positives). RT-PCR is not useful on blood as most cats demonstrate a low level viraemia.



A patient with FIP demonstrating hyphaema and uveitis

RT-PCR appears useful on CSF and one study (Doenges 2016) reported a 100% specificity (i.e. no false positives) but had a low sensitivity (41.2%). Similar findings were identified in a later study (Barker 2017).
These results essentially mean that when performed in patients with appropriate signalment, clinical signs and laboratory data, a positive FCoV RT-PCR is SUGGESTIVE of FIP, but a negative FCoV RT-PCR does not exclude FIP.

Much research has been focused on identification of a specific FIP mutation point within the FCoV. Unfortunately, sequencing is not always possible due to low levels of FCoV and sequence variability. A mutation in the spike protein (which facilitates FCoV attaching to cells) has gained great attention. S gene markers were found by comparing FCoV sequences in FIP tissues compared with faeces from healthy non-FIP FCoV strains. Unfortunately, the spike mutation has also been demonstrated in cats with systemic FCoV infection, not just with FIP (Tasker, Barker, Porter 2014, 2017) and a further study has found that additional testing for the spike mutation in tissue or fluid only increased specificity by 2%, so this may not add more useful information than a positive FCoV RT-PCR.

Histopathology often provides useful information. Appropriate tissue samples can be obtained by tru-cut, laparotomy or laparoscopy. The most appropriate technique depends on the individual patient and invasive procedures may not be appropriate in extremely ill cats. Kidney, liver, mesentery and lymph nodes are the most commonly affected organs and may demonstrate fibrinous serositis, nodular lesions and pyogranulomatous inflammation.

Advanced immunostaining techniques such as immunohistochemistry, immunocytochemistry and immunofluorescence can be performed. These tests examine antibody binding to host cell associated FCoV antigen resulting in an enzymatic reaction that causes a colour change that can be visualised. A positive test result is likely to confirm FIP, however a negative result doesn't exclude FIP as there may be variable distribution of FCoV in tissues.

Immunocytochemistry stains macrophages within effusions and has shown a variable sensitivity (57-100%). FIP effusions often have a low nucleated cell count, resulting in false negative results and additionally FCoV antigen can be masked by high amounts of FCoV antibody.

Treatment for cats with FIP remains limited and to date there are absolutely no curative treatments. Treatment involves the use of glucocorticoids although no studies have evaluated it's effiacy. Pentoxyfilline was not shown to be useful in one study of cats however it was only evaluated in cats with effusive FIP and it may still be useful in cats with dry FIP.

Polyprenyl immunostimulant (PPI) triggers innate celluar immunity (Th1) and may be useful in cats with dry FIP. Two studies have been performed which show that the drug is well tolerated. Cats receiving PPI had longer survival times compared with cats receiving both PPI and corticosteroids, however the inculsion criteria for diagnosis of FIP was questionable.

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Interferon alpha and feline IFN omega have also been used and appear effective invitro. FCoV may act as an IFN antagonist. No obvious evidence of a survival benefit has been identified.
Feline omega interferon (three times weekly) and mefloquine (10mg/kg once or twice weekly) has also been used in a small number of cats. Mefloquine has been demonstrated to be an effective anti-viral for FIPV in vitro with no toxic effects on cells. Appropriate treatment protocols are unknown and more research is required (and underway) to assess efficacy and safety in naturally infected cats.

Recently Pederson *et al* evaluated targeted antiviral drug therapy, mainly protease inhibitors that are based on drugs currently used to treat human diseases such as hepatitis C and HIV/AIDs. The studies performed to date are small field trials. The first study on a cohort of client owned cats tested safety and efficacy of the 3C-like protease inhibitor GC376. Doses changed throughout the study but 19/20 cats had clinical signs improve. 13/19 cats relapsed after 1-7 weeks, predominantly with the development of neurological signs. Younger cats were more likely to enter remission and 30% had long term survival.

A second study assessed safety and efficacy of the nucleoside analog GS-441524 in cats with naturally acquired FIP. 26/31 cats completed 12 weeks or more of treatment. Unfortunately neither of these medications are currently commercially available. There is a reported increase in sourcing of these medications via the “black market”. Hopefully private veterinary pharmaceutical companies will realise the importance of such medication.
Recently, Remdesivir (GS-5734) was developed by the same company that had developed the GS-441524 as a treatment for SARS-CoV2 during the Covid-19 pandemic. Remdesivir has been shown to have efficacy *in vivo* against Feline Coronavirus and there are anecdotal reports of its use in cats with FIP with success.