GUIDELINE for Feline Infectious Peritonitis

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The Feline Infectious Peritonitis guidelines were first published by D. Addie et al. in the Journal of Feline Medicine and Surgery (2009) 11, 594-604; the present update was drafted by Séverine Tasker et al.

A far more detailed review of this topic, following the same headings and including comprehensive cited references, is available HERE

Key points

- Feline coronavirus (FCoV) is a ubiquitous virus of domestic and large cats.

- Most FCoV-infected cats either stay healthy or show only mild enteritis.

- Only a small proportion of FCoV-infected cats goes on to develop feline infectious peritonitis (FIP).

- FCoV transmission is faecal-oral via litter trays and fomites.

- FCoV infection of monocytes is the key event in FIP pathogenesis.

- Most likely, internal mutations of FCoV (to mutants with a switch of cell tropism arising in an individual cat) are the reason for the development of highly pathogenic FIP-inducing FCoV (internal mutation theory).

- Coronaviral genomes possess a high level of genetic variation due to the error rate of RNA polymerase leading to different types of mutations.

- FIP disproportionately affects pedigree cats under two years old.

- Sampling the effusion, when present, is the most useful diagnostic step.

- The definitive diagnosis of FIP relies on consistent histopathological changes in affected tissues and this, together with FCoV antigen immunostaining, is considered the gold standard for diagnosis.

- Faecal RT-PCR is not useful for diagnosis of FIP but for identification of FCoV shedders within a cat colony.

- A positive FCoV antibody test is not confirmatory of FIP (it is not a „FIP-test") but absence of FCoV antibodies makes FIP less likely.

- Without treatment with new potentially curative anti-coronaviral drugs (not yet widely available), FIP has a very

poor prognosis.

- ABCD FIP diagnostic trees (please see the ABCD Tool "FIP diagnostic trees") provide information on how to reach a 'likely' diagnosis of FIP in cats to increase confidence in the use of antivirals.

- The ABCD considers the FIP vaccine to be non-core and it is not recommended in FCoV antibody-positive cats. However, FCoV antibody-negative kittens could potentially benefit from vaccination.

Agent properties

Feline Coronavirus (FCoV) is the causative agent of the serious disease of feline infectious peritonitis (FIP). FCoV is a large spherical enveloped virus with a single stranded RNA genome.Being an RNA virus, FCoV has a high level of genetic variation due to frequent errors during RNA replication. The hypothesis is that genetic variation and subsequent selection facilitates the switching of cell tropism from a mostly asymptomatic enteric FCoV infection to a FIP-associated FCoV. This switch occurs within an infected cat and FIP-associated FCoVs replicate efficiently within monocytes, lead to the serious disease of feline infectious peritonitis (FIP).

Type I and type II FCoVs are recognised, which differ based on antigenic and genomic properties, with type I FCoVs being most prevalent in most parts of the world. However, type I FCoVs, unlike type II FCoVs, are difficult to grow in cell culture and thus many *in vitro* studies are based on the less common type II FCoVs. Both types can cause FIP.

The FCoV genome comprises many genes including those encoding the spike [S], matrix [M], nucleocapsid [N] and envelope [E] proteins. The S protein is a particular focus of attention as the spike protein mediates entry into host cells and has both receptor binding and fusion functions. Specific mutations in the S gene were postulated to be specific to FIP-associated FCoV, but it is now thought that these mutations are associated with an ability of the FCoV to spread systemically rather than being *only* FIP-associated, and it is known that systemic FCoV infection can occur in the absence of FIP.

Epidemiology of FCoV & FIP

The major route of transmission of FCoV is faecal-oral as it is ingested orally and shed in the faeces, with litter boxes representing the principal source of infection in groups of cats. Transmission is often indirect, such as contact with objects (e.g. via litter trays, scoops, brushes, vacuum cleaners, shoes), handling at cat shows, shelters or in a veterinary practice. Kittens are often infected at a young age and shed virus in faeces within a week; they then continue to shed intermittently for weeks or months (or life-long) and immunity is short-lived meaning that cats, in the face of infection, can undergo multiple cycles of recurrent infections.

FCoV infection occurs worldwide and is very common, particularly in multi-cat households where antibody prevalence can reach almost 100% of cats. Fortunately, FIP arises in only a small percentage (5-10%) of FCoV-infected cats.

Whilst cats of any breed or age can develop FIP, it is particularly seen in pedigree cats under 2 years of age. Different pedigree breeds are predisposed to FIP in different countries, suggesting a genetic rather than inherent breed effect. Males are also very slightly more likely to develop FIP than females. When considering FIP as a differential diagnosis in a cat, it is important to consider whether the signalment is consistent with factors known to be associated with FIP, especially the age of the cat, and whether or not there has been an opportunity for the cat to have become infected with FCoV previously. ABCD FIP diagnostic trees are available HERE that allow the vet to integrate risk factors for FIP and decide on the likelihood of FIP as a diagnosis.

Pathogenesis of FIP

FCoV infection occurs following ingestion of the virus (e.g. by grooming paws contaminated with faeces during litter tray use) and FCoV then replicates in the epithelial cells of the small intestinal villi, resulting in faecal shedding within a week. This enteric FCoV infection is often asymptomatic but can result in enteritis. FCoV is then found in the colon where the main site of viral replication is the ileo-

caecocolic junction. FCoV infection can then spread to the mesenteric lymph nodes followed by viraemia in the blood. Whilst low level FCoV viraemia in monocytes can occur in cats that do not go on to develop FIP, efficient and high FCoV replication in activated monocytes and macrophages (which are likely mediated by viral mutations) is believed to be a key event in FIP pathogenesis, alongside the nature of the immune response mounted by the cat in response to FCoV infection.

When FIP develops there is a reaction between replicating FCoV in monocytes and blood vessel walls, allowing extravasation of the monocytes, where they differentiate into macrophages. Breakdown of the endothelial tight junctions allows plasma to leak out of the vessels; this can appear clinically as an effusion in the abdominal, thoracic and/or pericardial cavities that usually develops quickly. In more chronic forms of FIP fewer blood vessels are affected, but larger perivascular pyogranulomata result on affected organs such as the liver, kidneys, intestine, lungs, brain and/or eyes.

Horizontal transmission of FIP, via a FIP-associated FCoV strain, is not believed to occur frequently.

Immunity to FCoV & FIP

Cats resistant to FIP are known to have strong cell-mediated immunity (CMI), which can be measured by high levels of the cytokine interferon gamma (IFN-γ) in the serum. However, CMI is also likely to be involved in the pathogenesis of FIP, albeit at a tissue level, as evidenced by high IFN-γ concentration in FIP effusions. Single nucleotide polymorphisms (SNPs) in the feline IFN-γ gene (fIFNG) have been found to be associated with the outcome of FCoV infection but the associations are not discriminatory enough to be beneficial to deduce to susceptibility in individual cats nor to guide breeding.

The role of humoral immunity in protecting against FIP is ambiguous. Maternally derived antibodies have been suggested to provide protection until about five to six weeks of age until they decline by six to eight weeks of age. Antibody production to FCoV takes 10-28 days post-infection. In cats with pre-existing antibodies, 'antibody dependent enhancement' (ADE) has been observed experimentally, resulting in a more rapid disease course and earlier death, and this has been problematic for vaccine development. However, in field studies, cats have developed FIP on first exposure to FCoV (and thus had not had pre-existing antibodies) and cats that experienced repeated infections by FCoV had not developed FIP, leading to the conclusion that ADE is not common in natural infection.

Clinical signs

FCoV infection

Cats with FCoV infection are usually asymptomatic, although occasionally enteritis, with diarrhoea and/or vomiting, are seen.

FIP

Cats that go on to develop FIP after FCoV infection present with varied clinical signs depending on the distribution of vasculitis (which can lead to effusions) and/or granulomatous lesions (which can lead to masses) in the body. Although effusive and non-effusive forms of FIP are often described, there is much overlap between these forms. Clinical signs of FIP can change over time, therefore repeated physical examinations are important to detect newly apparent clinical signs; for example, an effusion can develop or ocular changes can become visible on ophthalmoscopic examination. ABCD FIP diagnostic trees are available HERE that allow the vet to assess clinical signs for FIP and the likelihood of FIP as a diagnosis.

Non-specific clinical signs include lethargy, anorexia and weight loss (or failure to gain weight/stunted growth in kittens). A fever that is refractory to treatment is commonly present.

Effusions are common, especially in the abdomen, but pleural effusions and pericardial effusions are also seen, sometimes concurrently. When effusions are present, the disease progression is often quite fast, progressing within a few days or weeks. When effusions are not present, FIP is often more difficult to diagnose and it also tends to be more chronic, progressing over a few weeks to months. Additional signs of non-effusive FIP depend on the organs affected but can include the central nervous system (CNS), eyes and/or abdominal organs (such as the liver, abdominal lymph nodes, kidney [including renomegaly], pancreas, spleen and/or gastrointestinal tract including mesenterial lymph nodes). These signs can also be present in cats with effusions. Cats with FIP affecting the intestines usually have a history of vomiting and diarrhoea or constipation and an abdominal mass can also be present. Jaundice can occur, more commonly in cats with effusions, but the degree of hyperbilirubinaemia is often not high enough to result in clinical jaundice. Occasionally, cats with FIP show multiple non-pruritic or pruritic nodules or papules.

Neurological signs that can develop with FIP include ataxia (with varying degrees of tetra- or paraparesis), hyperaesthesia, nystagmus, seizures, behavioural and mental state changes and cranial nerve deficits. Central vestibular clinical signs can include head tilt, vestibular ataxia, nystagmus, obtunded appearance and postural reaction deficits. Fever was shown to be less common in cats with neurological FIP compared to those without neurological signs. FIP can also cause uveitis, which can be unilateral or bilateral in nature. Clinical signs include changes in iris colour, dyscoria or anisocoria secondary to iritis, sudden loss of vision and hyphaema. Keratic

precipitates can appear as 'mutton fat' deposits on the ventral corneal endothelium and aqueous flare can occur. On ophthalmoscopic examination, chorioretinitis, fluffy perivascular cuffing (representing retinal vasculitis), dull perivascular puffy areas of pyogranulomatous chorioretinitis, linear retinal detachment, vitreous flare and fluid blistering under the retina can all be seen.

Diagnosis

Diagnosis of FCoV infection

Diagnosis of FCoV infection in asymptomatic cats is not often indicated except sometimes when control of FCoV infection is being attempted by the household owner. When FCoV infection is suspected in young cats with vomiting and/or diarrhoea, diagnosis of FCoV infection can be achieved via reverse transcriptase polymerase chain reaction (RT-PCR) on faecal samples or rectal swabs. However, many other causes of enteritis exist in cats, which should be considered before making a definitive diagnosis of FCoV-associated enteritis.

Diagnosis of FIP

Diagnosis of FIP in sick cats showing clinical signs suggestive of FIP (as described above) is often challenging. A cat cannot develop FIP unless it has been infected with FCoV and demonstration of FCoV in tissues and effusions with features consistent with a diagnosis of FIP is helpful during diagnostic investigations of FIP. As mentioned above, FIP is more common in young cats (especially under two years old) and pedigree breeds, and male cats are at slightly higher risk of disease. Additionally, most cats that develop FIP have been housed in multi-cat households previously. A recent history of stress (e.g. adoption, being in a shelter, neutering, upper respiratory tract disease, vaccination) is common. ABCD FIP diagnostic trees are available HERE that allow the consideration of signalment in the diagnosis of FIP.

If an effusion is present, sampling the effusion is the single most useful diagnostic step because tests on effusions have a higher diagnostic value compared to those on blood samples (ABCD FIP diagnostic trees are available HERE that show an approach to the diagnosis of FIP when an effusion is present). Samples of effusion are often easy to obtain; imaging (especially ultrasonography) can be used to confirm, identify, localize and tap smaller volumes. FIP effusions are usually clear, viscous/sticky and straw-yellow in colour. Diagnosing FIP if no effusion is present is more challenging due to the large number of possible clinical signs and their non-specific nature (e.g. anorexia, lethargy, weight loss, pyrexia) and because biopsy collection *ante-mortem* can be very difficult due to, for example, problems accessing affected tissues, contra-indications (such as the need for general anaesthesia) for the invasiveness of taking biopsies from a sick cat and/or costs involved in tissue collection. Cases with neurological or ocular signs can be approached via sampling of cerebrospinal fluid (CSF) or aqueous humour (ABCD FIP diagnostic trees are available HERE that show an approach to the diagnosis of FIP when neurological or ocular signs are present). Currently, there is no non-invasive, *confirmatory* test available for cats with FIP that don't have effusions, although in some cases valuable supportive information can be gained through diagnostic investigations, including RT-PCR, and analysis of fine needle aspirate (FNA) samples collected from affected organs, if accessible, as described later.

Routine haematological changes are not specific for FIP but common abnormalities seen include lymphopenia, neutrophilia, sometimes with a left shift, and a mild to moderate normocytic, normochromic anaemia. Serum biochemistry changes are also non-specific in cats with FIP, but certain abnormalities can be helpful in making FIP as a differential diagnosis more likely. These include hyperglobulinaemia, accompanied by hypoalbuminaemia or low to normal serum albumin, a low albumin to globulin (A:G) ratio of <0.4 (an A:G ratio of >0.8 makes FIP very unlikely). High bilirubin levels in the absence of both haemolysis and elevations of liver enzyme activity should raise the suspicion of FIP. Acute phase proteins (APPs) are produced in the liver in many inflammatory and non-inflammatory diseases and the major APP in cats is a1-acid glycoprotein (AGP) and moderately elevated serum AGP concentrations of >1.5 mg/ml are often seen with FIP. Another important APP in cats is serum amyloid A which is also markedly increased in cats with FIP.

FIP effusions are highly proteinaceous, with a total protein concentration >35 g/l, consistent with an exudate, but with relatively low cell counts of <5 x10^9/l cells, more consistent with a modified transudate; although sometimes cell counts are up to 20 x10^9/l cells. Cytology is pyogranulomatous with macrophages, non-degenerate neutrophils and few lymphocytes. Thick eosinophilic (pink-red) proteinaceous backgrounds on cytology slides are often described. If cytology reveals a septic neutrophilia (typically with degenerate neutrophils containing bacteria), neoplastic cells or a marked lymphocyte population, the effusion is more likely to be of another origin to FIP. Typical FIP effusions have low A:G ratios of <0.4 (values of >0.8 help rule out FIP).

The Rivalta's test is a crude point-of-care assay to identify proteinaceous inflammatory exudates, which occur with FIP but also septic peritonitis and lymphoma. If positive, effusion cytology can be helpful to discriminate between these causes. A negative Rivalta's test help rule out FIP. To perform the Rivalta's test, 8 ml of distilled water at room temperature and one drop of 98% acetic acid (white vinegar can be used instead) are mixed in a test tube, and then one drop of effusion is carefully placed or layered onto the surface of

the solution. A positive Rivalta's test is indicated by the drop staying attached to the surface of the liquid, retaining its shape with a connection to the surface, or floating slowly to the bottom of the tube as a drop or jellyfish-like. A negative test is indicated by the drop disappearing and the solution remaining clear. However, interpretation of results can be problematic due to subjectivity and difficulties in deciding whether a result is positive or negative. A video showing how to perform the test is available http://www.youtube.com/watch?v=XmOk2veunqA

No specific ultrasonographic or radiographic findings exist for FIP. However, ultrasonography or radiography can show the presence of effusions. Pneumonia due to FIP that is occasionally reported can be associated with radiographic changes. Ultrasonography can reveal abdominal lymphadenopathy and/or abnormalities of the liver, spleen, intestines and/or kidneys (which can include a medullary rim sign), depending on which organs are affected. Imaging can also be of use to direct sampling of abnormal tissues, e.g. FNA for cytology can be collected to reveal non-septic pyogranulomatous inflammation, or ultrasound-guided needle core (e.g. Tru-Cut) biopsies (TCB) can be collected and submitted for histopathology.

When a cat is showing neurological signs, imaging of the brain by MRI, if available, with contrast, can be useful to demonstrate neurological abnormalities due to FIP (such as obstructive hydrocephalus, syringomyelia, foramen magnum herniation and marked contrast enhancement of the meninges, third ventricle, mesencephalic aqueduct and brainstem). A description of CT findings in cats with neurological FIP has not been published but MRI is likely to be more sensitive in the detection of subtle intraparenchymal lesions.

CSF analysis can be helpful to diagnose FIP in cats with neurological signs, although care should be taken with cisternal CSF sampling as the risk of brain herniation is high and thus, ideally advanced imaging, such as CT or MRI, should be performed beforehand to assess the potential risk of herniation. This procedure might require referral or consultation with a neurologist for those unfamiliar with the technique. CSF samples from cats with FIP typically show elevated protein concentrations (of >0.3 g/l [>30 mg/dl] in cisternal samples, and >0.46 g/l [>46 mg/dl] in lumbar samples). CSF samples of cats with FIP often also have an increased cell count (>0.008 x 10^9/l [>8 cells/µl] in either lumbar and/or cisternal samples) and occasionally this pleocytosis is extremely marked in cats with FIP (cell counts of >1x 10^9/l [>1000 cells/µl]). CSF cytology is predominantly neutrophilic, mononuclear, mixed or pyogranulomatous. Some cats with neurological FIP have unremarkable CSF analysis results.

Aqueous humour analysis can be helpful to diagnose FIP in cats with ocular signs. However, this procedure might require referral or consultation with an ophthalmologist for those unfamiliar with the collection technique. Aqueous humour samples show cytological features consistent with FIP similar to CSF, i.e. mixed inflammation with the presence of neutrophils with or without macrophages.

Immunostaining exploits the binding of antibodies to host cell-associated FCoV antigens, which are subsequently visualised by enzymatic or immunofluorescent reactions producing a colour change in a process called immunohistochemistry (IHC) on biopsies or immunocytochemistry (ICC) or immunofluorescence (IF) on cytology samples (including effusion and FNA samples).

The definitive diagnosis of FIP relies on consistent histopathological changes in affected tissues in addition to FCoV antigen immunostaining by IHC; this is considered the gold standard for diagnosis.

Histopathological and cytological changes associated with FIP are typically pyogranulomatous in nature. Differential diagnoses for pyogranulomatous inflammation include other infections (mycobacteria, *Actinomyces*, *Nocardia*, *Rhodococcus*, *Bartonella*, *Pseudomonas* and fungal) as well as idiopathic sterile pyogranulomatous disease cases which can present with mass lesions such as in the lymph nodes or skin. Positive FCoV antigen immunostaining in macrophages in samples with pathology consistent with FIP can be used to confirm the diagnosis.

- Which samples can be submitted for immunostaining?

Biopsy samples of affected tissues (e.g. liver, kidney, spleen, mesenteric lymph nodes) can be collected by laparotomy, laparoscopy or ultrasound-guided TCB for histopathology and immunostaining whereas effusions, FNAs, CSF and aqueous humour samples can be collected for cytology and immunostaining. The sample sites most likely to be useful are those that are affected by the FIP changes, and inference of this can be gained from the clinical signs as well as results of diagnostic testing (e.g. ascites, neurological signs, imaging results, pyogranulomatous inflammation on FNA cytology).

- IHC on tissues

Positive FCoV antigen IHC in tissues with histopathological changes consistent with FIP is 100% specific and reliable when performed properly with appropriate controls. However, a negative result does not exclude FIP, as FCoV antigens can be variably distributed within lesions and might not be detected in all histopathological sections prepared from FIP-affected tissues. If unexpected negative IHC results are obtained, it is worth requesting additional sections of biopsies to be cut and examined by the pathologist.

- ICC or IF on cytology samples (effusions, FNAs, CSF, aqueous humour)

FCoV immunostaining (ICC or IF) of effusion samples shows variable sensitivity, ranging from 57 to 100% as false negative results can occur if the effusion is cell-poor and/or the FCoV antigen is masked by FCoV antibodies already in the effusion. However, immunostaining on effusions is usually specific, although occasionally false positive results are obtained. To increase sensitivity on effusion samples, some laboratories prefer to do immunostaining on cell pellets prepared from centrifuged effusion samples to prepare formalin-fixed, paraffin embedded samples that can then be treated like a tissue sample for FCoV antigen IHC. Ease of collecting FNA samples make this a technique worth considering in cats with pyogranulomatous inflammation where positive results would be very consistent with FIP. Positive FCoV immunostaining in CSF, or aqueous humour, samples also indicates likely FIP in cats with pyogranulomatous inflammation in samples and neurological, or ocular, clinical signs respectively. It is wise to consult the diagnostic laboratory before submitting samples for ICC or IF as their preferences for how samples should be prepared before sending vary.

FCoV RT-PCR assays can be used to detect FCoV RNA in blood, effusion, tissue (including samples obtained by FNAs), CSF, or aqueous humour samples. The RT-PCR assays should be quantitative (i.e. the q in RT-qPCR) and report the FCoV load (amount) present in the analysed sample. This is helpful because the systemic FCoV infection that can occur in healthy cats and cats without FIP is associated with lower FCoV viral loads than in cats with FIP; thus, a positive FCoV RT-PCR result on a sample is not specific for FIP, but positive results with a high FCoV load are very supportive of a diagnosis of FIP.

- RT-PCR on blood samples

Studies evaluating RT-PCR on blood samples have shown varying results; many have shown blood samples to be infrequently positive in cats with FIP, whilst newer ones have shown positive results to be quite common (sometimes with the same RT-PCR assays). Further investigation into the reasons for these differing results is required but it may be that blood samples should be revisited as a diagnostic sample to support a diagnosis of FIP.

- RT-PCR on effusion samples

RT-PCR analysis of effusion samples in cats with FIP is often positive (72-100% of samples) for FCoV RNA and cats without FIP are usually RT-PCR negative although false positive and false negative results occur; however, presence of FCoV RNA, particularly in high levels, in an effusion that also has cytological and biochemical features suggestive of FIP, is highly supportive of a diagnosis of FIP.

- RT-PCR on tissue or FNA samples

Whilst tissue biopsy samples obtained from affected tissues in cats with FIP usually show high levels of FCoV RNA in them by RT-PCR, such samples should be submitted for histopathology and IHC, as this allows for a definitive diagnosis of FIP. Cats without FIP can also be positive for FCoV RNA by RT-PCR in tissues due to systemic FCoV infection in the absence of FIP, although positive results in cats without FIP are uncommon and when they are obtained the FCoV levels are usually very low. FNAs, such as obtained by ultrasound guidance, are a good alternative sample type for FCoV RT-PCR, with the advantage of relatively easy collection. The sample site should be guided by where pathology is likely based on clinical signs and other diagnostic investigations. Studies have shown promising results on FNAs collected from mesenteric lymph nodes from cats with FIP that did not have effusions.

- RT-PCR on CSF samples

Studies suggest that CSF FCoV RT-PCR appears to be a useful additional test in cats with neurological signs, as a positive result highly supports a diagnosis of FIP, but a negative result does not rule out FIP. Around 83% of CSF samples are positive for FCoV RT-PCR in cats with FIP-associated neurological signs.

- RT-PCR on aqueous humour samples

Studies with limited number of cats with ocular signs have shown that positive FCoV RT-PCR results on aqueous humour samples in cats with FIP are very supportive of a diagnosis, although sensitivity is poor (35.5% in one study). Larger studies are needed in cats with ocular signs.

- RT-PCR on faeces

RT-PCR on faeces is primarily used to identify cats that are shedding FCoV for the management of infection in a multi-cat household. It is not useful to diagnose FIP, as it is known that many healthy cats without FIP shed FCoV.

Following detection of FCoV RNA in a sample by RT-PCR, as described above, varied molecular techniques can be used to derive S gene

sequence data for the FCoV present. Available molecular techniques comprise of sequencing methods, such as pyrosequencing and Sanger sequencing of FCoVs, most often used in research, and methods designed to detect and quantify specific FCoV mutation sequences, such as PCR with allelic discrimination, which is available commercially for the diagnosis of FIP in some laboratories. Such techniques are only successful when high loads of FCoV RNA are present, so successful S gene mutation analysis at least suggests that the sample contained high levels of FCoV RNA. Published data have found that detection of S gene mutations alone cannot be regarded as being confirmative for FIP, and they have little benefit over RT-PCR.

Serum FCoV antibody tests, performed on blood, are usually enzyme-linked immunosorbent assays (ELISA), indirect immunofluorescence antibody tests or rapid immunomigration tests. A positive FCoV antibody test indicates that the cat has had contact with FCoV and has developed antibodies; this typically occurs around 10-28 days following natural infection (or vaccination). Although cats with FIP tend to have higher FCoV antibody titres than cats without FIP, there is much overlap, so there is little value in an individual cat in performing serum FCoV antibody testing. In addition, negative serum FCoV antibody results cannot rule out FIP, as cats with confirmed FIP have been found to be FCoV antibody negative. There is no 'FIP antibody test'; all that can be measured is antibody against FCoV. FCoV antibody tests can also be performed on effusion and CSF samples, but this is also of limited value.

Management of in-contact and hospitalized cats following a diagnosis of FIP

In-contact cats have likely been exposed already to the same FCoV isolate(s) that originally infected the cat that has FIP. However, in the cat that has developed FIP, these FCoV isolate(s) have undergone changes including *de novo* mutations to result in FIP-associated FCoV strains. The current understanding is that horizontal transmission of FIP, via a FIP-associated FCoV strain, is not believed to occur frequently, if at all. Therefore, based on the current knowledge, it is likely to be relatively safe to take a cat with FIP back into a household with cats that have already been in contact with it, as these cats are likely to already be FCoV-infected. In households where a cat with FIP has been euthanised, with no remaining cats in the household, it is recommended that the owner waits for two months before obtaining new cats, as it has been suggested that FCoV preserves its infectivity for days to a few weeks, depending on environmental conditions, such as in desiccated faeces.

Cats with FIP in a veterinary practice or clinic should be handled and housed like any other cat, as any cat is a potential source of FCoV infection, and routine hygiene measures should be taken. Thus, there is no benefit in isolating the cat with FIP and it is not necessary to keep cats with FIP in infectious disease isolation wards.

Treatment of FIP

Historically, no effective treatment was available for FIP, so every cat with confirmed FIP died or was euthanized, as FIP has a very poor prognosis. If an effusion is present, some cats benefit from removal of the effusion, particularly if pleural effusions are resulting in dyspnoea. Immune-suppressive or anti-inflammatory drugs, such as prednisolone, were used to try to slow down disease progression, but their effect has not been substantiated in controlled studies. Interferons and polyprenyl immunostimulant (PPI) have also been frequently used in cats with FIP as immunomodulators but conclusive evidence for their efficacy in curing FIP is lacking.

Currently, no drugs licensed in cats for the treatment of FIP are available but newer antivirals (mainly GS-441524) show much promise for effective treatment of FIP and are becoming increasingly used successfully in cats. Although only illegal products have been available, in late 2020 and 2021 legal 'special'[1] formulations of antivirals became available for purchase in some countries, such as Australia and the UK, although treatment with antivirals is very costly.

[1] A veterinary 'special' is a drug formulation especially prepared for the treatment of a specific animal. Such formulations are also known as extemporaneous preparations or compounded medicines. In the UK, specials can be prepared by a vet or a pharmacist. As well as representing modified formulations of licensed medicines, in the UK specials can also be prepared by manufacturers that have authorisation from the Veterinary Medicines Directorate (VMD) to manufacture unlicensed (unauthorised) veterinary medicines for use under the UK's prescribing laws of Cascade.

Treatment (or euthanasia) of cats with suspected FIP should only be considered after every effort has been made to obtain a diagnosis, since the wrong treatment can be detrimental for a cat. However, now that antiviral treatments are available in some countries, such as GS-441524, a balance between the costs of diagnostic testing and treatment should be made, with treatment started whilst awaiting results to confirm or be highly suspicious of a diagnosis of FIP (ABCD FIP diagnostic trees are available HERE that show an approach to having a diagnosis of FIP confirmed as well as being very likely). Some clinicians are using a rapid and sustained positive response to antiviral treatment as a means of supporting a diagnosis of FIP. Ideally, clinicians should be confident that FIP is a very likely diagnosis before starting antivirals, due to the cost and length of treatment required. The ABCD diagnostic trees HERE provide information on how to reach a 'likely' diagnosis of FIP in cats to increase confidence in the use of antivirals. If a sustained response to antivirals is not

maintained in a treated cat, the clinician should re-evaluate the original diagnosis of FIP.

The antiviral treatments which have shown the most promise in published studies on both experimentally and naturally induced FIP are the 3C-like protease inhibitor, **GC376**, and the nucleoside analogue, **GS-441524**, with GS-441524 showing the better success rates. Both of these drugs have only been available from illegal suppliers online and thus have not been able to be prescribed or used by vets in most countries of the world. This has led to owners needing to source the agents online and administer them to their cats themselves, usually in the absence of veterinary care due to the products being illegal. Both GC376 and GS-441524 can be given as daily injections but the injections do sting and can be difficult to administer, especially for owners, from a compliance point of view. Oral formulations of GS-441524 then became available, making administration easier, and these were also associated with cure rates of over 80-90% and recently up to 100% in cats treated for at least 12 weeks. Cats with ocular and neurological signs require higher dosages of GS-441524 than cats without such signs. However, accurate dosage recommendations are difficult to make based on the use of illegally obtained formulations as manufacturers do not report on quality control nor the concentration or identity of the active ingredient contained in the formulation. No serious adverse effects are seen with oral GS-441524 treatment, with only a mild increase in liver enzymes noted in some cats, together with a lymphocytosis and eosinophilia in others. No renal side effects are reported. Of note is the likely importance of intensive veterinary supportive care (e.g. intravenous fluids, appetite stimulants, anti-emetics, analgesia) during the first week of treatment in cats that are particularly sick. A legal 'special' formulation of GS-441524 is available in Australia and the UK for use in cats; costs of treatment vary based on the type of FIP being treated and the weight of the cat but are often at least £5,000-£10,000 (in 2021) per 12-week course for the drug alone, showing that treatment is costly.

Remdesivir, GS-5734, a prodrug of GS-441524, has been licensed as treatment for Covid-19 in humans in some countries and has been used for FIP treatment in cats, but the safety and efficacy of remdesivir for FIP in cats has not been established in peer-reviewed publications. Reports on the treatment of field FIP cases in Australia and the UK, using a 'special' formulation of injectable remdesivir legally available for cats in those countries, suggest that injectable remdesivir is effective although comparative studies with GS-441524 are not available. In other countries, human-licensed preparations of remdesivir can be used in cats if available. The cost of a full 12-week treatment course of remdesivir might be prohibitive, as it is more costly than oral GS-441524, but protocols including dosages (see below), based largely on the experience of vets in Australia who have treated over 800 cases, have been established and are available HERE. Oral mefloquine, an antimalarial agent licensed for humans, also has been used by vets in Australia to treat cats with FIP when finances prohibit the use of a full course or increased dosages of GS-441524 or remdesivir because mefloquine is cheap and shows some encouraging efficacy as adjunct treatment.

Drug resistance is relatively common for antiviral agents, especially with prolonged drug exposure, and although it has been suggested that only a small percentage of cats (~ 3%) is resistant to antivirals used to treat FIP, resistance is a real threat and has to be avoided. Concerns regarding antiviral resistance are behind the recommendation not to use antivirals in healthy FCoV infected cats.

Vaccination for FIP

Although an intranasal vaccine for FIP is available in some countries for cats aged 16 weeks or over, it is only indicated in cats that have not yet encountered FCoV infection, its efficacy is questionable. and its use is not recommended.

Control of FCoV and FIP

FIP is especially a problem of cats kept in larger groups, particularly in breeding catteries and rescue situations, and usually arises as a sporadic disease. Very occasionally an unusually high number of cats (>10%) develop FIP within a multi-cat environment as a "mini-outbreak". Factors that might contribute to "mini-outbreaks" include involvement of FCoVs that have a high chance of becoming FIP-associated FCoVs, high viral replication and thus viral loads in the environment and spread of these FCoV within a highly susceptible cat population. Stress in a multi-cat environment may also be a factor.

Reducing FCoV transmission and subsequent FIP

As FCoV is transmitted predominantly via the faecal–oral route, hygiene is the mainstay of FIP control. FCoV infection is maintained in a household by continual cycles of infection and re-infection and is less of a problem amongst cats leading an indoor–outdoor lifestyle or in stray cats that bury their faeces outside. The goal in every cat household must be to reduce the FCoV infection pressure and risk of transmission. This can be achieved by keeping not more than three well-adapted cats per room (and keeping such cat groups stable), keeping strict hygiene, and providing outdoor access if possible. If outside access is not possible, enough litter boxes should be provided (one more than the number of cats). Litter trays should be positioned in different rooms, away from food and water bowls. They should have faeces removed at least twice a day, and litter tray utensils should be cleaned daily. Litter trays should be completely emptied at least weekly and cleaned using detergent. Although FCoV is only rarely shed in saliva, food and water bowls should be cleaned daily using detergent or in a dishwasher at a cycle of at least 60°C, because of the risk of fomite contamination. Being an enveloped virus, FCoV is readily inactivated by most disinfectants, steam and washing at 60°C. It has been suggested it preserves its

infectivity from days to a few weeks, depending on environmental conditions.

In breeding catteries, identification of cats that are persistently shedding a high FCoV load, and their separation from low shedders and non-shedders (faecal RT-PCR-negative cats), has been suggested for reducing transmission rates. Minimisation of stress and avoidance of secondary infections are important features of prevention of the development of FIP in FCoV-infected cats.

Eliminating FCoV transmission and subsequent FIP

The use of nucleoside analogue antivirals to eliminate FCoV shedding (with shedding cats identified by positive faecal RT-qPCR), from healthy cats in households in which a case of FIP has occurred, has been described. in part this has been done to try and prevent re-infection of a successfully treated and recovered FIP cat by other cats in the household. However, maintaining a FCoV-free household thereafter is difficult because FCoV is so common in cat populations and can be carried on fomites. Additionally, it is highly unlikely that treatment leads to more permanent prevention of re-infection than natural infection. Finally, as mentioned above, the use of antivirals should strictly be preserved only for the treatment of cats with FIP, in view of the potential for resistance to develop.

Acknowledgement