IMPORTANT NOTICE

Prior to even considering treatment for feline infectious peritonitis (FIP) you absolutely MUST ensure that the cat really does have FIP. At time of writing, FIP treatment is mainly immunosuppressive and immunosuppression of a cat with an infection other than FIP will kill the cat.

Do a FCoV antibody test: provided the test is sensitive enough, a negative result will rule out FIP. Addie et al, 2015 You can find out which FCoV antibody tests are recommended (and which ones are useless) at www.catvirus.com/FCoVantibody.htm.

A major differential of FIP is toxoplasmosis: run a toxoplasma antibody test in at-risk cats, for example those with access to outdoors or who are fed butcher meat. However a positive FCoV antibody test does NOT confirm FIP.

PREVENTION IS BETTER THAN CURE

It is my hope that by the time you have listened to this webinar you will have understood the complexity of the disease that is FIP. In many other diseases, the destruction of the invading pathogen, by antivirals or antibiotics, results in the cure of the patient, but FIP is a disease involving the very complex immune response of the cat. If we don’t completely understand the pathogenesis of FIP how can we hope to fix it? And the disease isn’t a fixed target, it changes, the pathology changes throughout the infection. FIP is slightly different in every individual so treatment needs to be tailored to that individual patient: it is not a case of one size fits all. Therefore it is my view that prevention of FCoV infection is preferable to an attempt to cure, and prevention can be achieved by hygiene and education.
**Pathogenesis of FIP**

Due to the slowness of my internet connection I am unable to incorporate some of my important videos into the lecture: please do watch them – they can be counted as CPD.

Please watch my animation of FCoV transmission on

http://www.youtube.com/watch?v=rkUjeQNEQs

Please watch my animation of FIP pathogenesis on

http://www.youtube.com/watch?v=6Ryl2Ll9R9Q&feature=related

In brief, feline infectious peritonitis (FIP) is the result of an excessive inflammatory response to infection with feline coronavirus (FCoV). FCoV transmission is indirect, from contact with virus in faeces, usually from a shared litter tray or via fomites on a litter scoop, brush, floor, etc. The virus is ingested, is believed to replicate first in the epithelial cells of the small intestine, it undergoes a brief viraemia, then is shed from the ileum and colon into the faeces. In around 90% of cats, virus shedding lasts for a few months in type I FCoV infection, and approximately 2 weeks in type II FCoV infection. In a minority of cats the virus is able to hijack the monocyte and replicate within it. Regardless of the pathogenicity of the coronavirus infecting it, the monocyte controls the amount of viral replication within it.

The key cell in the pathogenesis of FIP is the monocyte / macrophage. FCoV-infected monocytes/macrophages release matrix metalloproteinase (MMP) 9; tumour necrosis factor (TNF)-α; interleukin (IL) -1β and IL-6, -9 allows the extravasation of FCoV-infected monocytes. TNF-α is a major contributor to the inflammatory response and pathogenesis of FIP. TNF-α is very likely the cause of the lymphopenia seen in FIP. TNF-α upregulates fAPN (the receptor for type II FCoVs) and, along with GM-CSF and G-CSF which are also produced by FCoV-infected monocytes, is a neutrophil survival factor. In later infection, TNF-α production shifts from macrophages to lymphocytes.

Chronic over-production of TNF-α results in cachexia.

In early infection, IL-6 stimulates hepatocytes to release acute phase proteins (such as alpha-1 acid glycoprotein, AGP). Hepcidin is a type 2 acute-phase protein and iron regulatory hormone which inhibits iron export from the gut and macrophages by binding to ferroportin: hepcidin is produced mainly by the liver in response to IL-6. IL-6 causes B lymphocytes to proliferate and differentiate into plasma cells. It is likely that high IL-6 levels found in cats with FIP are the cause of hypergammaglobulinemia. IL-6 can be pro-inflammatory or anti-inflammatory.
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www.catviruses.com

From this brief synopsis, it is apparent that FIP treatments fall into one or more categories:

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Anti-virals</td>
<td>GC376</td>
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<tr>
<td></td>
<td>Feline interferon omega (Virbagen Omega, Virbac)</td>
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<td></td>
<td>Human interferon</td>
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<td></td>
<td>Cyclosporin A</td>
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<tr>
<td>Support the monocyte / immune system</td>
<td>Arginine: i.e. real meat daily</td>
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<tr>
<td></td>
<td>Feline interferon omega (Virbagen Omega, Virbac)</td>
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<td>Polyprenyl Immunostimulant (Sass and Sass)</td>
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<tr>
<td>Anti-inflammatories and immunosuppression</td>
<td>Corticosteroids e.g. prednisolone</td>
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<td>Meloxicam (Metacam, Boehringer Ingelheim)</td>
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<td></td>
<td>Cyclosporin A</td>
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<td>Thalidomide</td>
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<tr>
<td>Targeted modification of the immune response</td>
<td>Anti-TNF-α (metronidazole); anti-TNF-α antibodies (e.g. Infliximab)</td>
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<td>? Anti-IL-6 antibodies (e.g. Siltuximab)</td>
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<td>? Curcuma longa (turmeric)</td>
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<td></td>
<td>? anti-MMP-9 (e.g. doxycycline)</td>
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<tr>
<td>Counteract FIP anaemia</td>
<td>Erythropoietin</td>
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</table>

Erythropoietin was added to this list because non-regenerative anaemia is a consequence of FIP: see notes on anaemia below.

**FIRST STEP TO TREAT EFFUSIVE FIP: DRAW OFF THE EFFUSION!**

Abdomino- or thoraco-centesis will also physically remove virus-infected cells which are a source of pro-inflammatory cytokines. Drawing off the effusion will immediately make the cat more comfortable, especially in thoracic effusive FIP where the cat will be able to breathe better. Remember that the cat has an intact mediastinum, so you will need to draw effusion off from both sides of the thorax. While you have the needle in place you can administer feline interferon omega directly to the site of the virus infection. Effusion can often be removed with minimal restraint and without sedation: in fractious cats, clipnosis can be attempted: put bull clips or clothes pegs onto the scruff of the neck – the cat will often go limp for some minutes. Pozza et al., 2008

The effusion should be sent for FCoV RT-PCR to confirm the diagnosis of FIP.

**TREATMENT PROTOCOLS AND DOSES OF COMMONLY AVAILABLE DRUGS**

Remember to get clients to sign an informed consent form when using drugs off-label.
ANTI-VIRALS

INTERFERONS

Interferons work best administered as closely as possible to the site of infection.

Recombinant feline interferon omega (Virbagen Omega,® Virbac, France)

Feline interferon omega is an alpha interferon and can resist stomach acid. Once a vial is reconstituted, it will keep for up to 3 weeks at 4°C, or up to 6 months in a freezer.

**Dose for effusive FIP:** 1 MU*/kg every other day, and then twice a week for however long it takes until recovery is obtained or until death administered initially into the abdominal or thoracic cavity (i.e. the site of the effusion) or subcutaneously.

**Dose for non-effusive FIP:** 100,000 Units of feline interferon omega per day per os

Diluting Virbagen Omega

Virbagen Omega (VO) comes in vials of 10 million units. It should be reconstituted with 1ml of diluent. Using 10 x 1ml insulin syringes withdraw 0.1ml into each of ten 1ml syringes: you now have 1 MU of VO per syringe. Freeze 9 of the syringes in a baggie (they will last up to 6 months in the freezer).

Put 1 syringe content (0.1ml) of reconstituted VO IFN (which now has 1 million units of VO) into 4.9 mls of saline or water: this gives you 100,000 units per half ml. Give the cat 0.5 mls of the mixture daily on food, or gently squirted into the side of the mouth at the commissure of the lips, with the head gently tilted backwards to encourage swallowing. This diluted mixture will last up to 21 days at 4°C.

Human interferon alpha

Interferons are species specific which is why it’s better to use feline interferon than human interferon. However, the human one is all that’s available in some countries.

**Dose:** Non-effusive feline infectious peritonitis (FIP): 30 i.u./daily or for 7 days at alternate weeks given by mouth.

In effusive FIP 30 i.u./daily can be used, or larger doses of interferon can be given by intramuscular injection daily (104 –106 i.u. per day). By 6–7 weeks, if the cat is still alive, interferon will no longer work at this dose because the cat will make antibodies against it.

To obtain human interferon-alpha write a prescription for your local pharmacist. Obviously, in areas where feline interferon is available it is preferable as it is likely to have more effect than the human interferon.

GC376

Some cat guardians want to go beyond what is currently available and seek the newest possible treatments. At present, this usually manifests as a request for treatment of their pet with GC 376: at time

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* MU = Million units
of writing (February 2018) there are no clinical trials of this drug ongoing. Updates on its progress are available on www.sockfip.org.

**SUPPORT THE MONOCYTE / MACROPHAGE AND THE IMMUNE SYSTEM**

**FEED REAL MEAT TO GIVE THE CAT ARGinine**

**Key message: do NOT give L-lysine to a cat with FIP**

Arginine is an essential amino acid in the cat: necessary for effective function of both the urea cycle and the monocyte / macrophage. Give real meat daily to augment arginine levels: even just a tablespoonful a day will make a difference. Or regularly use commercially available real meat based cat foods such as Applaws & Almo Nature (available from the Zooplus website in Europe: use Zooplus link on the catvirus website links page to obtain a discount).

**POLYPRENYL IMMUNOSTIMULANT – FOR TREATING NON-EFFUSIVE FIP ONLY**

There has been no placebo-controlled clinical trial of PPI in cats with FIP published, and a major problem with the recent publication by Prof. Legendre was that FIP was not diagnosed beyond reasonable doubt in the 60 cases described. I am keen to amass independent data on FIP treatment using PPI and would love to hear from veterinary surgeons using it: my email address is draddie@catvirus.com.

PPI is a treatment for non-effusive FIP; it is not recommended in effusive (wet) FIP. PPI is used off-label in FIP treatment.

Survival was better in cats not concurrently treated with systemic corticosteroids, but it is probably safe to use topical ophthalmic corticosteroid treatment along with PPI in cats with intra-ocular signs of non-effusive FIP. UK veterinary surgeons will need to apply to the VMD for special import permission.

To obtain PPI: email orders@vetimmune.com, or visit www.vetimmune.com.

**Dose:** 3.0 mg/kg orally of Polyprenyl Immunostimulant three times a week.

**ANTI-INFLAMMATORIES AND IMMUNOSUPPRESSION**

Cats receiving immunosuppressants should also receive antibiotic cover to protect them against secondary infections (see section below on Antibiotics). Do a toxoplasma antibody test to determine whether there is a risk of activating toxoplasmosis by immunosuppressing the cat: if so, use clindamycin for 4 weeks. Warn the cat’s guardian that latent FHV could also recrudesce.

**CORTICOSTEROIDS given to both effusive and non-effusive* FIP cases**

*unless the cat is being treated with Polyprenyl Immunostimulant (PPI). Systemic corticosteroids are contraindicated in non-effusive FIP cases being treated with PPI, although topical corticosteroids can be used in ophthalmic preparations.
**Prednisolone**

Prednisolone is the main anti-inflammatory / immunosuppressant used in feline infectious peritonitis therapy, though unfortunately it suppresses both the humoral and cell-mediated immune response. It is possible that we should be using an anti-inflammatory, rather than an immunosuppressive dose, especially in effusive FIP, whereas in non-effusive FIP the immunosuppressive dose makes more sense. 2 mg/kg/sid is the high end of an anti-inflammatory dose and low end of immunosuppressive dose. Trepanier, 2015

Prednisolone should never be used in cats with toxoplasmosis, or septic peritonitis or pleurisy, which is one reason why cytology of the effusion is a very important part of FIP diagnosis, as there will be many more white blood cells in the effusion of a cat with sepsis, and a good cytologist will detect the bacteria or fungi. If in doubt, send the effusion for bacterial culture.

**Dose:** 1-2 mg/kg/ sid given by mouth, halving the dose every 10-14 days, right down to 0.5 mg/kg every other day or until an optimal dose for that cat is found (this will be the dose at which alpha-1 acid glycoprotein (AGP) levels have reduced to, and remain at, normal. (See the section below on monitoring treatment.)

**Prednisone is not recommended in cats:** it is not as effective as prednisolone. Trepanier, 2015

**Dexamethasone / injectable corticosteroids**

Dexamethasone (or other injectable corticosteroids) can be used to kick start the immunosuppressive treatment (or for cats which cannot be pilled). It can also be administered directly to the site of inflammation in effusive FIP cases.

**Dose:** dexamethasone 1 mg/kg intrathoracic or intraperitoneal injection on one occasion or every 5 days.

**MELoxicam (M**etac**am, B**oehringer I**ngelheim)**

Provided kidney function and blood pressure are normal, consider using the non-steroidal anti-inflammatory meloxicam instead of corticosteroids. Meloxicam was used for 119 days, along with one month of metronidazole, in one FIP case report in a cat who survived 787 days. Hugo and Reading, 2015

**Dose:** 0.05 mg/kg BW, PO, q24h

**CycloSPORIN A**

Has anti-FCoV and immunosuppressant activity.

Use only in cats with toxoplasma antibody titres of zero or give concurrent clindamycin treatment.

**Warning:** if you give CsA to a FCoV-infected healthy, or diarrhoea-only, cat, you WILL induce FIP. Only use with extreme caution.

**Dose:** start at 75 mg/cat/day

reduce to 50 mg/cat/day

reduce to 25 mg/cat/day

**THALIDOMIDE**
The rationale of using thalidomide instead of corticosteroids in the treatment of feline infectious peritonitis is to reduce inflammation and the humoral immune response to feline coronavirus while leaving the cell mediated (anti-viral) immune response intact. Thalidomide is actually a very safe drug.

Be sure to obtain the owner's consent for using a drug not licensed for cats.

**Dose:** 50-100mg at night. DO NOT USE IN PREGNANT CATS as it is teratogenic.

**ANTIBIOTICS**

Antibiotic cover is essential when immunosuppressing a cat, with either high dose corticosteroids, cyclosporin A or anti-TNF-alpha antibodies. Your choice of antibiotics will largely depend on what your major differential diagnoses are, given the presenting clinical signs. For example, if you are awaiting FIP confirmation from your laboratory and your major differential diagnoses are toxoplasmosis, or bacterial peritonitis / pleurisy, then clindamycin (Antirobe) will be your antibiotic of choice because it covers both aerobic and anaerobic infections; if your major differential is infectious anaemia, then doxycycline or oxytetracycline will be your choice. Sub-antimicrobial doses of tetracyclines have anti-MMP activity, which means that they might be a good choice in early effusive FIP treatment. However, doxycycline should not be used in healthy FCoV carrier cats, at least until further information becomes available, because doxycycline inhibits interferon-beta and was shown to increase shedding of the pig coronavirus, transmissible gastroenteritis virus, in vitro. 

The most commonly used antibiotic in cats in the UK is cefovecin (Convenia, Pfizer) because of difficulty in administering pills to cats. Cefovecin may be a good choice but I have not found any publications on its effect on the immune system, although there is a record of it having been used, along with many other drugs, in FIP in one case report. It has the advantages of being administered by a veterinary surgeon, so there is no problem with owner compliance/ability to dose the cat, and there is no risk to the oesophagus.

A few studies reported that amoxicillin/clavulanic acid (Synulox) can decrease IFN gamma, which is essential for FIP survival, although those studies were based on laboratory experiments. A study in healthy human volunteers showed no interference with IFN gamma.

Metronidazole is effective against anaerobic organisms, so is a good choice where bacterial pleurisy is a differential diagnosis. It inhibits TNF-alpha—i.e. is anti-inflammatory—and was used for one month, along with meloxicam, in one FIP case who survived 787 days. However, it is horrible to taste and can be difficult to administer to cats.

Where antibiotics are used, probiotics should also be given to replenish the microbiome and avoid overgrowth by pathogenic gut bacteria: my choice is Swanson's *Lactococcus rhamnosus* - one capsule per day mixed into food or drink. We have cultured capsules of these in our laboratory at Glasgow and verified that they contain what is claimed. The Protexin from Australia is also very good but unfortunately not very palatable:

ERYTHROPOIETIN

When a cat with FIP has a decreasing rbc count with no evidence of regeneration, then use erythropoietin, preferably while the Hct is still in the twenties: when it gets lower than 20, it may be too late.

**Dose:** A 0.2 ml darbepoetin s.c. injection (0.5 micrograms/kg) given twice weekly to be gradually reduced, depending on PCV.

This is based on Chalhoub's paper quoting a weekly dose of 1 microgram/kg/week. Chalhoub et al, 2012

FIP PROGNOSIS

Cats with effusive FIP usually die more quickly than those with non-effusive FIP: the median survival time for 33 cats with effusive FIP was 21 days (± 20 days) in one study, Tsai et al, 2011 and 9 days in another study of 36 cats. Ritz et al, 2007 The cats in the latter study were subjected to biopsy and the additional stress may have adversely affected their survival time. Ritz et al, 2007 They also received amoxycillin/clavulanic acid which was reported to decrease interferon-gamma: a key cytokine in FCoV/FIP survival. In addition the authors of that study surmised that their failure to taper the immunosuppressive doses of corticosteroids predisposed to secondary infections which led to the deaths of 5 cats. Ritz et al, 2007 Concurrent systemic corticosteroid administration was also noticed to decrease the survival of cats in a PPI study. Legendre et al, 2017

Cats with thoracic effusion seem to fare better than cats with an abdominal effusion. Cats treated with Virbagen Omega have been documented as surviving 18 months or more. Ishida et al, 2004; Gunn-Moore & McCann, 2004

In a recent therapeutic study of 60 cats with a presumptive diagnosis of non-effusive FIP, 20% survived over 200 days: survival varied with sub-type of disease, the most severe being neurological signs, where mean survival was 38.8 days. Legendre et al, 2017 The manifestation of non-effusive FIP with the best prognosis appears to be mesenteric lymph node adenopathy as the key clinical finding.

Staging for effusive FIP prognosis to help you to assess whether treatment has a chance of helping or not

In this staging system shown in the table below the severity of effusive FIP can be worked out, which will give you an idea of whether or not it is worth obtaining special drugs to treat, or whether it is worthwhile continuing treating a case. Look at the parameter in the left hand column, then look at where the result of your case falls in the range, then put the score for that parameter into the next free column in the grey shaded cells. Finally work out the total score for your case. An excel file of this table can be downloaded at http://www.catvirus.com/downloads.html: the total score will automatically fill in the cell at the bottom. A video of using this table can be found at https://youtu.be/F6FXcWgEZxU.

Interpreting the total score for your case:

- 0-4: survival time more than 2 weeks
- 5-11: survival time less than 2 weeks
- over 12: survival time less than 3 days

While this isn’t an absolutely exact predictor, it does give a ballpark indicator of prognosis.

Remember that even giving the cat a few more days can help the cat’s guardian come to terms with the imminent demise of their pet: corticosteroids don’t cost much and will help ease those last days. Draw off the effusion to make the pet more comfortable. FIP doesn’t seem to be a painful condition.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
<th>Score</th>
<th>Your case date</th>
<th>Your case date</th>
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<tbody>
<tr>
<td>PCV (%)</td>
<td>&gt;26</td>
<td>0</td>
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<td></td>
<td>20 – 26</td>
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<td>&lt;20</td>
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<td>AST (U/L)</td>
<td>&lt;150</td>
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<td>150 – 300</td>
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<td>Total bilirubin</td>
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<td>(mg/dl)</td>
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<td>[9 – 38]</td>
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<td>(&gt; 2.2)</td>
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<td>[&gt;38]</td>
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<tr>
<td>Potassium (mmol/L)</td>
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<td></td>
<td>3.0 – 3.9</td>
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<td>&lt; 3.0</td>
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<tr>
<td>Sodium (mmol/L)</td>
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<td>Total</td>
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This table is adapted from that of Tsai et al, 2011. It can be downloaded from the catvirus.com Downloads page and I hope to have a video of using it in the FIP treatment page of the website and it can be seen here: [https://youtu.be/F6FXcWgEZxU](https://youtu.be/F6FXcWgEZxU).

**FIP AND ANAEMIA**

For FIP treatment to be effective, the causes of the anaemia associated with FIP need to be elucidated and treated. Commonly two types of anaemia are observed in FIP cases: non-regenerative anaemia, assumed to be that of chronic disease, and acute haemolytic anaemia: the latter causing the death of many cats with FIP. Riemer *et al* 2016 documented anaemia (defined as a packed cell volume less than 30%) in 106 of 200 cats with FIP, with 21 having a Hct of 20% or less. Tanaka *et al* 2015 cited anaemia
as the cause of death in 2 of 3 cats treated with Cyclosporin A. Tsai et al 2011 noted that a fall in Hct heralded the imminent demise of the patient. Anaemia has been reported as a side effect of interferon treatment in humans, but Tsai et al 2011 found that anaemia occurred equally in groups of cats treated and not treated with interferon.

Non-regenerative anaemia of chronic inflammation

I believe that FCoV/FIP could be one of the unrecognised and under-diagnosed causes of severe non-regenerative anaemia and haemolytic anaemia in FeLV-negative cats. In a retrospective study of 180 cats with anaemia, FIP was diagnosed in only 17 Korman et al, 2013 but likely was not tested for in most cases (S. Tasker, personal communication). The reason that the anaemia of FIP has not been given more than a passing comment previously might be because feline red blood cells circulate for approximately 73 days, White & Reine, 2009 which is longer than most cats with effusive FIP survive. Few reported cases survive beyond the two-month time-point and the reason for this could be that cats with FIP simply run out of erythrocytes as a consequence of FIP-induced erythroid bone marrow suppression. The survival of many cats with FIP might be increased if the bone marrow suppression could be reversed. Tanaka et al 2015 described one case, treated with Cyclosporin A, where a single treatment with erythropoietin at around day 60 post-diagnosis reversed the trend of declining Hct and the cat survived another 200 days, by which time she was 15 years old.

In many cases of FIP there are many pyogranulomata in the kidney cortex, thus another mechanism which may be involved in the anaemia of FIP could be lack of erythropoietin causing erythroid hypoplasia/aplasia. Chalhoub et al 2012 treated a cat by kidney transplant and darbopoietin: the cat survived another year, although it was unclear whether FIP was the cause of the kidney failure or if it developed due to the immunosuppression following transplant.

The simple inability to synthesise red blood cells does not seem to fully explain FIP-associated anaemia. White and Reine 2009 stated “Cats tend to develop anaemia of inflammatory disease within two to three days of the onset of the inflammatory process, and the haematocrit drops by an average of 8%.” The feline erythrocyte lasts around 73 days, so with non-regenerative anaemia one would expect Hct to fall by approximately 10% in a week: if it falls more than that in a FIP case, check a blood smear for signs of immune-mediated haemolytic anaemia: acanthocytes and schistocytes which suggest a degree of mechanical trauma to red cells. Check for rising bilirubin levels although normal bilirubin levels have been reported in cats with immune-mediated haemolytic anaemia. Swann et al, 2016

Macrophages are widely distributed in peripheral tissues where they play a crucial role in the defence against pathogens. This is achieved, at least partially, through the control of intracellular iron availability, which limits pathogen growth. Gan et al, 2017 Macrophages also play a key role in body iron homeostasis by recovering iron from effete red blood cells and returning it to the circulation. Gan et al, 2017 M1 polarised macrophages, deal directly with microbes at sites of infection and are pro-inflammatory, releasing high levels of tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). Retention of iron in M1 macrophages reduces circulating iron levels and thus the availability of this essential nutrient for extracellular microbes. This also limits the amount of iron available for erythropoiesis, a mechanism involved in anaemia of inflammatory disease. Gene expression analysis of M1 macrophages showed a high level of ferritin, associated with iron storage, and a low level of ferroportin, associated with iron
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export. Compared to unstimulated macrophages, transcriptional changes were also noted in hepcidin and transferrin receptors, both iron regulators which favour iron sequestration in the reticuloendothelial system. In contrast to M1 cells, M2 polarised macrophages are anti-inflammatory and have an iron-release phenotype mediated through an elevated expression of ferroportin. Microcytosis, which occurs in iron deficiency, was noted in 35% of 188 cats with FIP, of which many were not yet anaemic. Macrophages loaded with iron lose their ability to kill intracellular pathogens such as Salmonella, Mycobacterium, Chlamydia, and Legionella by IFN-γ-mediated pathways. Presumably, their ability to deal with intra-cellular coronaviruses is similarly inhibited, thus sequestration of iron in macrophages is doubly hazardous for the cat with FIP, both leading to anaemia and reducing the macrophage’s ability to destroy the virus.

Immune-mediated haemolytic anaemia

The second type of anaemia seen in FIP, acute haemolytic anaemia, is less common but more acutely fatal. Norris et al. reported 2 of 42 cats with FIP dying of acute haemolytic anaemia and an acute anaemic crisis leading to euthanasia 7 weeks post-diagnosis has been encountered previously in a FIP case treated with adipose stem cell therapy (Andy Armitage, personal communication) and in a non-effusive FIP cat within 4 weeks of onset of clinical signs. Three (2.8%) of 107 cats with immune-mediated haemolytic anaemia (IMHA) had FIP, 35 of 107 cases had secondary IMHA and 3 of those cats had FIP, thus 8.6% of secondary IMHA was due to FIP (J. Swann, personal communication). Tsai et al. noted that all of 51 cats with FIP were moderately to severely anaemic prior to death. Falling Hct, rising bilirubin and AST were found to be adverse prognostic signs, all being parameters indicative of intravascular haemolysis. However, Riemer et al. found that only 38 of 109 cats (35%) with hyperbilirubinaemia, but without raised liver enzymes, were anaemic. Raised bilirubin occurred in 91 of 134 (68%) of cats with effusion and 15/35 (43%) of cats with non-effusive FIP. The authors explained this phenomenon as indicative of increased erythrocyte fragility in FIP. Erythrophagocytosis was seen in 17 of 28 FIP effusions.

Haemolytic anaemia has been reported in other viral infections such as African Swine Fever, Epstein-Barr virus, Human Influenza virus, and Parvovirus B19. In contrast, in cats haemolytic anaemia is most frequently associated with infection with feline leukaemia virus or the haemotropic mycoplasma bacterium. The pathogenesis of immune-mediated haemolytic anaemia is difficult to explain, and may be different in each infection. One possible explanation for the haemolytic anaemia of FIP might be that IL-6 causes the activation of auto-reactive plasma cells. Ironically, bilirubin inhibits the expression of TNF-α related endothelial adhesion molecules E-selectin and VCAM-1 which contribute to the pathogenesis of FIP phlebitis by enabling monocyte attachment and extravasation.

Monitoring treatment and the cat’s progress

In my experience, the most efficient measure of a treatment working is when AGP level reduces, especially if it reduces to normal levels (up to 500 μg/ml). Haematocrit (Hct) should be monitored continuously to assess anaemia.
WHEN TO ANNOUNCE RECOVERY AND DISCONTINUE TREATMENT

When a cat is eating well, regained normal weight and temperature, and AGP, globulin levels, Hct and lymphocyte count have all returned to normal, the question will arise whether or not it is safe to discontinue treatment. Cessation of virus shedding in faeces does not always indicate that the virus has been eliminated from the entire body.

To be absolutely certain that the cat has recovered, as opposed to being in remission, the FCoV antibody titre should have reduced to zero using a sensitive FCoV antibody test.

WHEN TO STOP TREATMENT AND EUTHANASE

1. If the cat develops neurological signs.
2. If the cat develops non-regenerative anaemia, haematocrit below 20%, with no response to erythropoietin.
3. If the cat develops immune-mediated haemolytic anaemia: don’t try a transfusion, it is unlikely to work.

TARGETED MODIFICATION OF THE IMMUNE RESPONSE: POSSIBLE FUTURE THERAPIES

If you do go down the route of using a drug off-label, make sure that your practice has a well-drafted consent form which absolves you of any legal liability, and ensure that the client signs it. Take time to explain any possible risks of side effects to your client.

CURCUMIN

Curcumin is the principal curuminoid chemical of turmeric (Curcuma longa) rhizomes which are increasingly available in organic, health food, and Asian shops. This chemical has been shown to possess anti-inflammatory, anti-viral and antioxidant properties and is available as a herbal supplement. Compared with prednisolone, curcumin had superior activity in suppressing two key pro-inflammatory cytokines implicated in FIP development, TNF-α and IL-6. Curcumin has previously been used in cats resulting in a reduction in the level of the acute phase protein AGP. Curcuma longa rhizomes are not associated with some of the drawbacks of turmeric powder, which often contains unknown preservatives and fillers and the cat is exquisitely sensitive to many chemicals. However, in one case of FIP treated with curcumin in which we have monitored AGP, neither prednisolone nor curcumin were able to reverse the adverse effects of IL-6, since AGP remained elevated throughout.

Dose: instruct the cat’s guardian to liquidise a 1cm long piece of fresh C. longa rhizome in omega-3 rich oil every 3 days, store the mixture at 4°C and administer 0.5mL daily. Alternatively, use ¼ teaspoon of ground organic turmeric, but be aware that turmeric powder is often mixed with other substances, which may be toxic to cats.
Addie: Feline infectious peritonitis treatment
www.catvirus.com

**ANTI-TNF-ALPHA ANTIBODIES (E.G. INFliximab)**

Dr Ishida and I postulated the use of anti-TNF-α antibodies as a possible treatment for FIP in 2008. Doki et al, 2016 used anti-feline TNF-α antibodies synthesised in their own laboratory to prevent FIP development in 2 of 3 cats experimentally infected with a strain of FCoV known for its virulence. Infliximab is a monoclonal antibody that binds human TNF-α and is used to treat autoimmune diseases in humans. As TNF-α is highly conserved at a protein level amongst mammalian species infliximab it is likely to also bind feline TNF-α. I have experience of using it in only one cat and unfortunately he developed iritis and we lost him to immune-mediated haemolytic anaemia.

TNF-α is essential for an effective immune response against bacteria and suppressing it in a bacterial peritonitis or pleurisy would be catastrophic.

**Dose:** one administration of 4mg/kg given in a 0.9% saline infusion over a four-hour period.

**ANTI-IL-6 ANTIBODIES (Siltuximab)**

Antibody against IL-6 siltuximab (Sylvant) has not yet been tried in any FIP case. IL-6 can be pro-inflammatory or anti-inflammatory so that the effect of inhibiting its action is not known. However, in a cat who is going to die of immune-mediated haemolytic anaemia, it might be worth trying.

**ADIPOSE STEM CELL THERAPY**

We have attempted treatment of two cats with FIP with adipose stem cell therapy: unfortunately both cats died. The UK expert on Adipose Stem Cell Therapy is Dr Andy Armitage of Greenside Veterinary Practice. [www.greensidevetpractice.co.uk](http://www.greensidevetpractice.co.uk).

**Plasmapheresis**

Antibodies have a key role in the development of FIP so plasmapheresis to remove them might help cats with FIP.

**Prevention IS better than cure**

By now you will have realised the enormous complexity of unravelling the immune reaction which is at the heart of the development of FIP. Furthermore, you would have to work out precisely what was happening in each individual cat before you would know whether it is best to use antivirals, or to inhibit MMP-9, or TNF-alpha, or IL-6. How could you shift M1 macrophages to M2 macrophages and would you heal or kill the cat by doing so? How will you reverse the anaemia which the case likely has?

Preventing FIP is more feasible than curing it, and will be the subject of the next webinar in this series.
## Survival of Cats in Recent Studies Which Treated Naturally Occurring FIP (and Two Experimental Infections)

<table>
<thead>
<tr>
<th>Definitions of survivors by authors</th>
<th>Survival</th>
<th>Number of cats</th>
<th>FIP type</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>11.2 months post treatment</td>
<td>6 or 7 of 20</td>
<td>6 effusive 1 non- effusive</td>
<td>GC376: a 3C like protease inhibitor</td>
</tr>
<tr>
<td>Recovery</td>
<td>up to 8 months</td>
<td>6 of 8</td>
<td>effusive (experimental infections)</td>
<td>GC376: a 3C like protease inhibitor</td>
</tr>
<tr>
<td>Remission</td>
<td>&gt; 2 years</td>
<td>4 of 12</td>
<td>effusive</td>
<td>fIFN omega</td>
</tr>
<tr>
<td>Partial remission</td>
<td>2-5 months</td>
<td>4 of 12</td>
<td>effusive</td>
<td>fIFN omega</td>
</tr>
<tr>
<td>Very short term</td>
<td>&lt; 7 days</td>
<td>8 of 21</td>
<td>effusive</td>
<td>fIFN omega and prednisolone</td>
</tr>
<tr>
<td>Short term</td>
<td>7-21 days</td>
<td>10 of 21</td>
<td>effusive</td>
<td>fIFN omega and prednisolone</td>
</tr>
<tr>
<td>Medium term</td>
<td>21 days to 3 months</td>
<td>2 of 21</td>
<td>effusive</td>
<td>fIFN omega and prednisolone</td>
</tr>
<tr>
<td>Long term</td>
<td>&gt; 3 months (180 days)</td>
<td>1 of 21</td>
<td>effusive</td>
<td>fIFN omega and prednisolone</td>
</tr>
<tr>
<td>Remission</td>
<td>264 days</td>
<td>1 of 1</td>
<td>effusive</td>
<td>Cyclosporin A, IFN alpha, erythropoietin</td>
</tr>
<tr>
<td>Remission</td>
<td>14 months</td>
<td>1 of 3</td>
<td>non-effusive</td>
<td>PPI</td>
</tr>
<tr>
<td>Remission?</td>
<td>over 2 years</td>
<td>2 of 3</td>
<td>non-effusive</td>
<td>PPI</td>
</tr>
<tr>
<td>Survival</td>
<td>&lt;100 days &gt;100 days &gt;200 days &gt;300 days &gt;900 days &gt;1,829 days</td>
<td>29/60 16/60 8 4 2 1</td>
<td>non-effusive FIP presumed</td>
<td>PPI</td>
</tr>
<tr>
<td>Very short term</td>
<td>&lt; 7 days</td>
<td>8 of 16</td>
<td>effusive</td>
<td>prednisolone only</td>
</tr>
<tr>
<td>Short term</td>
<td>7-21 days</td>
<td>4 of 16</td>
<td>effusive</td>
<td>prednisolone only</td>
</tr>
<tr>
<td>Medium term</td>
<td>21 days to 3 months</td>
<td>4 of 16</td>
<td>effusive</td>
<td>prednisolone only</td>
</tr>
<tr>
<td>Long term</td>
<td>&gt; 3 months</td>
<td>0 of 16</td>
<td>effusive</td>
<td>prednisolone only</td>
</tr>
<tr>
<td>Survived</td>
<td>65 days</td>
<td>2 of 3</td>
<td>effusive</td>
<td>anti-TNF-alpha MAb</td>
</tr>
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<td>-------------</td>
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<td>---------------------------------------</td>
</tr>
<tr>
<td>Remission</td>
<td>12 months</td>
<td>1 of 1</td>
<td>non-effusive FIP suspected</td>
<td>Darbepoietin, immunosuppressants and kidney transplant</td>
</tr>
<tr>
<td>Prolonged survival</td>
<td>787 days</td>
<td>1 of 1</td>
<td>effusive / MLN FIP confirmed</td>
<td>meloxicam, metronidazole, cefovecin, amoxicillin-clavulanic acid, tramadol hydrochloride</td>
</tr>
</tbody>
</table>

IFN = interferon  
PPI = polyprenyl immunostimulant

**FURTHER INFORMATION WEBSITES**

FIP website by D. Addie: [www.catvirus.com](http://www.catvirus.com). You will find more extensive notes there, plus the FIP prognosis excel file.

YouTube channel: [www.youtube.com/user/DrDianeDAddie](http://www.youtube.com/user/DrDianeDAddie)

Webinarvet previous FIP webinars: [www.thewebinarvet.com/speaker/diane-addie](http://www.thewebinarvet.com/speaker/diane-addie)

University of Glasgow Veterinary Diagnostic Laboratory: [www.gla.ac.uk/schools/vet/cad/](http://www.gla.ac.uk/schools/vet/cad/)

The book for cat guardians, veterinary nurses and students, *FIP and Coronavirus* by Diane D. Addie, is available from Amazon.

To contact me: email draddie@catvirus.com. Please consider becoming a veterinary subscriber to catvirus.com to be kept informed of my latest research.

**ACKNOWLEDGEMENTS**

I am eternally grateful to the guardians of cats with FIP and with FCoV infection: these grief-stricken souls have been beyond generous in allowing me to use their stories and photographs and many have gone on to financially support my work. I also profoundly thank the veterinary surgeons of these cats, who have gone beyond the call of duty in sharing information. My work woulsd not have been possible without these people, since I refused to use laboratory cats for my research. I sincerely thank donors to my research, and the catvirus.com subscribers who support me personally.

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**DECLARATION OF LACK OF VESTED INTERESTS**

Apart from a fee from Webinarvet and occasional locum employment at VDS, I have no vested interests in any of the products mentioned in this webinar: I hold no shares or directorships of any companies and
no other kind of benefit will come to me as a result of mentioning any specific products: I am completely independent.

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