is feline coronavirus, there is the potential for the development of FIP. Following recommendations of the Coronavirus Study Group, in this chapter the virus will be called FCoV and the disease FIP.

Any age of cat can develop FIP, but fifty percent of cats with FIP are younger than 2 years old. FIP typically occurs some weeks to months after a stress in the cat’s life and can appear as effusive (or ‘wet’) or non-effusive (or ‘dry’). In the former, fluid collects in the abdomen and/or thorax, in the latter there is no fluid, but the cat loses weight, is anorexic, pyrexic, lymphopenic and shows clinical signs according to which organs are affected, the eyes, liver and brain being most commonly affected.

Cats from multicat environments, for example pedigree and rescue cats, are most at risk of developing FIP for several reasons:
- increased chance of becoming infected with feline coronavirus
- increased dose of FCoV
- increased stress (cats are naturally solitary animals)
- increased probability of concurrent disease, lowering immune function

### Aetiology

- Family: Coronaviridae
- Genus: Nidovirales
- Feline coronavirus (FCoV)
- RNA enveloped virus
- Fragile virus, but resistant in environment for 3 to 7 weeks when protected by protein (faecal material)
- Susceptible to sodium hypochlorite (common household bleach)

(Photo 1) Electron micrograph of feline coronavirus showing (arrow) the spikes or ‘corona’ from which it derives its name.

### Transmission

The majority of cats infected with FCoV do not develop FIP but become infected, shed virus in their faeces from 2-3 days post-infection, seroconvert at 18-21 days, stop shedding virus after 2-3 months to 7 months, then lose their antibodies. 13% of infected cats become lifelong carriers, continually shedding FCoV in their faeces and maintaining a high antibody titre.
Transmission is mainly indirect - not transplacental, and rarely direct. Virus is shed in the faeces continuously (sometimes intermittently towards the end of infection). Virus is only found in saliva very early in infection and then just for a matter of hours to 1–2 days (Addie and Jarrett, 2001).

Viral Excretion of FCoV

- Viral excretion begins from 2 days post-infection in faeces (Pedersen et al., 2004)
- Only found in saliva in very early infection (first days) (Addie and Jarrett, 2001)
- Transient shedders (usually < 3 months) (Addie and Jarrett, 2001)
- Intermittent shedders (Addie and Jarrett, 2001)
- Carriers cats (for their lifespan) (Addie and Jarrett, 2001)
- Resistant cats (3%) (Addie and Jarrett, 2001)

Detection of virus has become more accessible in recent years using Polymerase Chain Reaction (PCR). Because FCoV is an RNA virus, a DNA copy of the genome has to first be made using the enzyme reverse transcriptase (RT), thus FCoV detection is by RT-PCR. As with any test, not all tests are equal, and as with other tests, one should try to access a laboratory whose tests regularly feature in refereed scientific and veterinary papers. Uses of RT-PCR are shown in table 1.

Pathogenesis

FIP is a vasculitis

The exact pathogenesis of FIP is not fully understood. We know that FCoV-infected monocytes adhere to endothelial cells, extravasate and differentiate into macrophages, setting up an inflammatory phlebitis and perivasculitis (Kipar et al., 2005) (photo 2). The clinical signs are a consequence of the vascular damage – extensive vascular damage and leaking of plasma results in effusions in the body cavities. The earliest FIP occurs is around 28 days post-infection and there is usually a history of stress, such as having been rehomed, or neutered. Effusive, or wet FIP is the acute form, occurring 4–6 weeks post-stress, and non-effusive, or dry FIP is the chronic form and can occur months to years after infection. In effusive FIP many blood vessels are damaged, in non-effusive FIP, the immune response has been partly successful, walling off the infected vessels with pyogranulomata which can become quite large (in abdominal palpation and gross post mortem they can be mistaken for tumours).

Why one cat will go down with FIP, while its household companions, infected with the same virus, remain perfectly healthy, is a matter for speculation. One theory is that a mutation (more accurately a deletion, Vennema et al., 1998) occurs in otherwise harmless FCoVs (sometimes called ‘feline enteric coronavirus’) which changes viral tropism from enterocytes to macrophages. However, replicating FCoV has also been found in the macrophages of healthy cats (Simons et al., 2005).
Clinical Signs and Diagnostic Approach to FIP

See algorithm - diagnostic approach to FIP (on page beside).

There is no single diagnostic test for FIP; diagnosis can only be confirmed by histopathology.

FIP is one of the most difficult diseases to diagnose in the living animal, because it can present with almost any clinical signs. The clinical signs in FIP reflect the vascular damage which has occurred. In effusive FIP, damage to many blood vessels leads to leakage of essentially plasma into the abdominal or thoracic cavities (or both). Presenting signs are therefore abdominal distension or dyspnoea. The effusion is modified transudate, has the same consistency as plasma and clots on exposure to air; the amount varies from a few ml to several hundred ml in the worst cases (photos 3 & 4). A thorough analysis of the effusion can lead to a presumptive diagnosis of FIP (see algorithm). The fluid should have > 35 g/l total protein, an albumin/globulin ratio of less than 0.8. There should be few nucleated cells (less than 2 x 10^9/l) and they should be mainly neutrophils and macrophages, not lymphocytes. The effusion should be sterile. One major differential diagnosis is bacterial peritonitis and pleurisy, where there are vast numbers of white blood cells in the effusion and bacteria present. Alpha 1 acid glycoprotein (AGP) is a useful adjunct to diagnosis, being extremely raised in FIP (> 1500 μg/ml) but normal in cardiomyopathy or tumour, which are the major differential diagnoses. However, AGP does also rise after trauma/surgery and with bacterial infections. FCoV serology is useful, since most cats with FIP have a very high antibody titre (though occasionally cats with effusive FIP have a low antibody titre due to antibody being attached to the vast amount of virus present, and therefore unavailable for the coronavirus antibody test). Detection of replicating virus in the effusion by RT-PCR is indicative of FIP, as is detection of FCoV in macrophages by immunofluorescence. In theory, effusion from a non-FIP FCoV-infected cat, suffering from some other condition, could co-incidentally have virus which had leaked into it from the blood; however, in practice, if FCoV is found in an effusion, the chances are very high that the cat is suffering from FIP. The same cannot be said for either blood or faeces – a positive RT-PCR reaction on either of those is not diagnostic of FIP; many healthy cats and cats with diseases other than FIP will give positive results.
Haematology reveals lymphopenia (Paltrinieri et al., 2001) and a non-regenerative anaemia (haematocrit usually less than 30%). Biochemistry shows hypergammaglobulinaemia (polyclonal) and either normal or slightly low albumin levels, giving a low albumin:globulin ratio. Albumin:globulin ratio was more useful in diagnosis than either total protein or gammaglobulin measurements (Hartmann et al., 2003). An A:G ratio over 0.8 rules out FIP whereas less than 0.4 strongly suggests FIP. Between 0.4 and 0.8 other parameters need to be considered. Bilirubin is often raised. AGP levels are greater than normal, but not as high as in effusive FIP (Addie, unpublished data). FCoV antibody titres are usually very high.

The course of non-effusive FIP is chronic, with the cats frequently surviving weeks to months on treatment. Neurological signs (nystagmus, ataxia, seizures, paralysis) can be due to meningitis, pyogranuloma impinging on nerves, or hydrocephalus. Once neurological signs begin then death rapidly ensues.

FIP Treatment

Until the recent introduction of recombinant feline omega interferon (rFeIFN-ω) FIP was deemed incurable and a diagnosis of FIP was usually followed by euthanasia of the cat. In the first published report of rFeIFN-ω and prednisolone treatment of FIP, 4 cats of 12 completely recovered and 2 survived 4 and 5 months (Ishida et al., 2004). Although effusive and non-effusive FIP are not distinct diseases, but rather are gradations of the same process, at time of writing we have two protocols for FIP treatment (see table 2).

 interferon omega is a monomeric glycoprotein related to interferon alpha and beta (but not gamma). It is secreted by virus-infected leucocytes and has antiviral and anti-inflammatory properties. IFN omega stimulates natural killer cell activity and enhances expression of MHC class I but not class II antigens. It is not cross-reactive with IFN-alpha, so cats which have been treated with, and have made antibodies against IFN alpha will not neutralise IFN omega. IFN omega is acid resistant, so can be given orally. As with any interferon, it is most effective at the site of the infection.

Before treating the cat, it is absolutely essential that every effort has been made to ensure a correct diagnosis. Since FIP is an immune-mediated disease, treatment is directed at suppressing the inappropriate immune response, usually using corticosteroids, which could be disastrous in a lookalike condition of infectious aetiology (e.g. septic peritonitis or pleurisy).

In the first days of treating humans with hepatitis C infection, only 6% of patients...
Ten years later, with refinements to the protocol, over 60% of patients respond (Marian Horzinek, personal communication). At time of writing, we are still in the very early days of using interferon omega to treat FIP; hopefully as the protocols are modified, we shall see a larger percentage of cases recover. Updates on FIP treatment are available on the internet (www.catvirus.com).

Possible modifications of the treatment protocol are offered here. Most have never been used to treat FIP, or have only been used in a few cats.

- **Thromboxane synthetase inhibitors** (used in humans with asthma) cured one cat and gave remission for 8 months in a second effusive FIP (Watari et al., 1998).
  - dose: ozagrel hydrochloride 5-10 mg/kg bid and prednisolone at 2mg/kg/day

- **Epoxalin** (Zubrin, Schering-Plough) is also a thromboxane synthetase inhibitor, its use in cats with FIP has never been evaluated.

- **Dehydroepiandrosterone** (DHEA) is a natural steroid hormone and precursor of the sexual hormones, 7-b-estradiol and 5-a-dihydrotestosterone. DHEA administration can downregulate endothelial adhesion molecules and reduce neutrophils extravasation (Barkhausen et al, 2006).
  - suggested dose: 40mg/cat/day

- **TNF-alpha inhibitors** – antibodies against TNF alpha (infliximab) – are used in humans with rheumatoid arthritis and Crohn’s disease. TNF-alpha levels are also raised in FIP and contribute to the inflammatory response. Chronic over-production of TNF-alpha results in cachexia, therefore it is likely that TNF-alpha inhibitors could be used to treat non-effusive, as well as effusive, FIP.
  - dose: unknown

- **Cimetidine** stimulates cell-mediated immunity (Lin et al, 2004). In FIP there is a shift from cell-mediated (Th1) to humoral (Th2) immunity, there is also lymphopenia. Cimetidine could possibly reverse these changes.
  - dose: 50 mg once a day

- **Thalidomide** has anti-inflammatory properties and pushes immune response from Th2 to Th1. Non-toxic, but difficult to source.
  - dose: 50-100 mg once a day in the evening

- **Salvianolic acid B** is a matrix metalloproteinase 9 (MMP 9) inhibitor. Monocytes in FIP have been shown to excrete MMP 9 (Kipar et al, 2005). Matrix metalloproteinases are

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**Table 2. Treatment protocols for effusive and non-effusive FIP**

<table>
<thead>
<tr>
<th>Effusive FIP</th>
<th>Non-effusive FIP</th>
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</thead>
<tbody>
<tr>
<td><strong>Glucocorticoids:</strong></td>
<td><strong>Glucocorticoids:</strong></td>
</tr>
<tr>
<td>Dexamethasone 1 mg/kg intrathoracic or intraperitoneal injection once only, AND:</td>
<td>Prednisolone sliding dose:</td>
</tr>
<tr>
<td>4 mg/kg/day for 10-14 days reducing to 2 mg/kg/day for 10-14 days, then 1 mg/kg/day for 10-14 days, then 0.25 mg/kg/day for 10-14 days, then 0.25 mg/kg/day for 10-14 days, then 0.25 mg/kg/e.o.d. …… and so on</td>
<td>4 mg/kg/day for 10-14 days reducing to 2 mg/kg/day for 10-14 days, then 1 mg/kg/day for 10-14 days, then 0.25 mg/kg/day for 10-14 days, then 0.25 mg/kg/e.o.d. …… and so on</td>
</tr>
<tr>
<td>ceasing after complete remission of clinical signs</td>
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</tr>
<tr>
<td>If, at any point, the cat’s condition regresses, go back to the previous dose.</td>
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</tr>
<tr>
<td>Feline omega interferon:</td>
<td>In addition, for FIP-related uveitis, topical corticosteroids will be used.</td>
</tr>
<tr>
<td>1 MU/kg s/c e.o.d reducing to once weekly if remission occurs</td>
<td>Feline omega interferon:</td>
</tr>
<tr>
<td>50,000 U per cat orally s.i.d until globulins, Hct, lymphocyte count and clinical signs return to normal.</td>
<td></td>
</tr>
<tr>
<td>Diluting feline omega interferon (see diagram p.143):</td>
<td></td>
</tr>
<tr>
<td>Feline omega interferon comes in vials of 10 million units. It is reconstituted with 1ml of its diluent, 10 aliquots of 0.1 mL each are prepared in insulin syringes (i.e. 1 MU per syringe). 9 syringes out of 10 are kept in the freezer (can be stored up to 6 months). The 10th syringe is diluted with 19.9 mL of sterile saline solution (NaCl 0.9%) in order to obtain 20 mL of solution containing 1 MU of feline omega interferon in total (50,000 U/ml). This 20 mL are allocated into 20 syringes of 1 mL. These syringes are stored in the fridge at +4°C (not stable enough in the freezer because of dilution). Everyday, the cat is administrated 1 mL of this diluted solution (containing 0.05 MU) by the oral route, using the syringe without the needle.</td>
<td></td>
</tr>
</tbody>
</table>

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**Feline Infectious Perosinitis Disease**

Glucocorticoids:

- Dexamethasone 1 mg/kg intrathoracic or intraperitoneal injection once only, AND:
  - Prednisolone sliding dose:
    - 4 mg/kg/day for 10-14 days reducing to 2 mg/kg/day for 10-14 days, then 1 mg/kg/day for 10-14 days, then 0.25 mg/kg/day for 10-14 days, then 0.25 mg/kg/day for 10-14 days, then 0.25 mg/kg/e.o.d. …… and so on
  - ceasing after complete remission of clinical signs
  - If, at any point, the cat’s condition regresses, go back to the previous dose.
  - Feline omega interferon:
    - 1 MU/kg s/c e.o.d reducing to once weekly if remission occurs

---

Glucocorticoids:

- Prednisolone sliding dose:
  - 4 mg/kg/day for 10-14 days reducing to 2 mg/kg/day for 10-14 days, then 1 mg/kg/day for 10-14 days, then 0.25 mg/kg/day for 10-14 days, then 0.25 mg/kg/e.o.d. …… and so on
  - ceasing after complete remission of clinical signs
  - If, at any point, the cat’s condition regresses, go back to the previous dose.
  - Feline omega interferon:
    - 1 MU/kg s/c e.o.d reducing to once weekly if remission occurs

---

Diluting feline omega interferon (see diagram p.143):

Feline omega interferon comes in vials of 10 million units. It is reconstituted with 1ml of its diluent, 10 aliquots of 0.1 mL each are prepared in insulin syringes (i.e. 1 MU per syringe). 9 syringes out of 10 are kept in the freezer (can be stored up to 6 months). The 10th syringe is diluted with 19.9 mL of sterile saline solution (NaCl 0.9%) in order to obtain 20 mL of solution containing 1 MU of feline omega interferon in total (50,000 U/ml). This 20 mL are allocated into 20 syringes of 1 mL. These syringes are stored in the fridge at +4°C (not stable enough in the freezer because of dilution). Everyday, the cat is administrated 1 mL of this diluted solution (containing 0.05 MU) by the oral route, using the syringe without the needle.
zinc-dependent endopeptidases capable of breaking down extracellular matrix proteins, it is probably MMP 9 which is responsible for the leakiness of the blood vessels in effusive FIP. MMP 9 inhibitors may be useful in early effusive FIP but are unlikely to be useful in non-effusive FIP.
- suggested dose: 10 mg/kg once a day

- **Tropisetron** is a 5-hydroxytryptamine (3) receptor antagonist, bringing about a reduction of TNF, IL-1 beta, IL-6 and prostaglandins (Muller et al, 2006).
- suggested dose: 300 mg/kg once a day

- **Anti-coronavirus drugs**, not yet available commercially. The 3c-like protease of the coronavirus has been well-characterised and prototype drugs have been developed for use against human coronaviruses. It is likely that when these drugs become available that they could be useful in cats in the early stages of FIP.

- **In addition**, cats should be supported by good nutrition, fluids if dehydrated, and nursing.

### Monitoring Treatment

Good indicators of treatment success or failure are globulin levels, albumin:globulin ratio, **alpha 1 acid glycoprotein (AGP)** levels, haematocrit and lymphocyte count. If the treatment is working, globulin levels should return to normal, A:G ratio should increase, AGP levels fall to normal (500 µg/ml or less), haematocrit level should stay above 20% and lymphocyte count should return to normal. Measuring FCoV antibody titre is less useful in the shorter term (weeks) since it will tend to remain high, but over a period of months, its fall to zero indicates a full recovery and that it is safe to discontinue treatment. Weight gain is a useful indication of recovery in a non-effusive FIP case, but is less useful in effusive FIP because it may simply indicate that the amount of effusion has increased.

### Storage of Feline Omega Interferon:

(See diagram page 143)

### Management of Multicat Houses

- **Main source of infection:** faeces

The main mode of FCoV transmission is indirect - uninfected cats coming into contact with the faeces of infected cats, usually by sharing a litter tray, and also by microscopic...
### Feline Infectious Peritonitis, Disease

**Fomite transmission, for example on poop scoops.** Thus **good hygiene practices** are the single best way of controlling FCoV infection. There should be adequate numbers of litter trays for the number of cats in a household: preferably one for each cat. Site litter trays away from food areas. Covered or flushing litter trays are the best design to minimise infectious particles of litter being blown about and choose a non-tracking cat litter (such as World’s Best) and consider using specialised mats which further reduce cat litter tracking. Litter trays should be declumped at least once daily and cleaned and disinfected with household bleach at least once a week.

> **Prevent infection of uninfected cats by testing before introduction/mating**

Cats can be kept FCoV free only by preventing them coming into contact with faecal matter from FCoV infected cats. Once a cat is FCoV antibody negative, any new cat should be antibody tested BEFORE being introduced. FCoV antibody positive pedigree cats can still be mated but should only be mated with other FCoV seropositive cats and their kittens should be early weaned and isolated to prevent them becoming infected (see below). A free register of FCoV tested cats is available on the internet on www.catvirus.com.

FCoV-free households should be quarantined and rested every 3-4 months until they become seronegative. For these measures to be effective, it is essential that a reliable FCoV antibody test be used, and that the first dilution used by the laboratory is around 1:10, laboratories using a cutoff of 1:100 will miss some cats shedding FCoV. Detection of virus in faeces of healthy cats by RT-PCR may be used as an adjunct to FCoV serology (Addie and Jarrett, 2001).

> **Maternally derived antibodies protect kittens until 5-6 weeks old**

Kittens of FCoV antibody positive cats are protected by maternally derived antibody until they are 5-6 weeks old. Pregnant FCoV antibody positive queens should be isolated 1-3 weeks before kitting (3 weeks if they have concurrent feline herpesvirus infection). The queen and her kittens should be kept isolated from other cats in the house. At 5-6 weeks, the kittens should be removed to a clean room (free of cats for over a week, well vacuumed, and with a clean, disinfected litter tray). Kittens should be antibody tested when they are 10 weeks of age or older and rehomed as soon as possible if seronegative. Antibody positive kittens can be restected every 4-6 weeks until they are seronegative, then homed.

> **Vaccination of cats before first exposure to feline coronavirus**

There is only one vaccine against FIP available: Primucell (Pfizer). It is a temperature-sensitive mutant coronavirus which can only replicate in the cooler nares (and cannot replicate systemically). It is administered intra-nasally; the first dose being given at 16 weeks of age, or later; and the second dose 3 weeks later. All FCoV-naïve cats going into potentially high-risk environment, for example a rescue, boarding or breeding cattery, should receive this vaccine. Primucell will not prevent FIP in cats already viraeic with FCoV (Fehr et al, 1997).

**Selected references**


**Further reading**

FCoV/FIP WEBITES:

www.catvirus.com
- FCoV/FIP website with the latest information for veterinary surgeons and information for cat owners and breeders.

- National Institutes of Health website with search facility for finding the latest scientific and veterinary publications on FCoV and FIP.

www.felinecoronavirus.com
- The website for FCoV/FIP symposia news.

www.orionfoundation.com
- A website for cat guardians, with a section for memorials for cats who have died of FIP which can be very useful as part of the grieving process for some owners.