FELINE CORONAVIRUS, FIP, AND THE GASTROINTESTINAL TRACT – DIANE ADDIE

Feline coronavirus can cause gastrointestinal signs in different ways. Gastrointestinal tract related clinical signs due to FCoV manifests in 4 main ways: 1. during primary infection: as small intestinal diarrhoea ± vomiting. 2. Persistently infected (FCoV carrier) cats can present with large intestinal diarrhoea. 3. Colonic form of non-effusive FIP causing thickening and lesions. 4. As enlarged mesenteric lymph nodes.

FCoV transmission is mainly indirect: from contaminated litter trays. To see a film of FCoV transmission: In English http://www.youtube.com/watch?v=rkqUjeQNEQs

In French http://www.youtube.com/watch?v=JrnopBFAr8A&feature=plcp

In German http://www.youtube.com/watch?v=职工l3e_2wfw

FCoV transmission is faecal-oral, not direct or transplacental. The majority of FCoV infection goes undetected: cats becomes infected, shed FCoV in the faeces from around 2 days post-infection, seroconvert around 3 weeks post-infection, shed virus for on average 2-3 months, stop shedding virus, then gradually become antibody negative. Recovered cats are then susceptible to re-infection by the same, or another, FCoV strain: immunity is very short-lived (likely IgA and cell-mediated immunity in the gut). Contrary to the results of experimental laboratory infections of cats, cats naturally infected in the field are most likely to develop FIP on their first encounter with the virus, rather than subsequent infections (so called antibody disease enhancement (ADE) is a laboratory artefact: this is an important fact in the Felocell FIP vaccine argument: Felocell FIP does NOT induce ADE).
**Diarrhoea, and occasionally vomiting, in primary feline coronavirus infection**

Diarrhoea, and occasionally vomiting, occurs in kittens and some adult cats at primary FCoV infection, the diarrhoea is small intestinal and usually self-limiting within a few weeks. However, occasionally the virus can be responsible for a severe acute or chronic course of vomiting or diarrhoea with weight loss, which may be unresponsive to treatment, continue for months and even result in death. Kipar et al, 1998 However, there are many other causes of diarrhoea in cats which require to be excluded before a diagnosis of FCoV diarrhoea can be made.

**Feline coronavirus as a cause of postweaning kitten diarrhoea with or without stunting**

In situations where FCoV is endemic, kittens will become infected as soon as maternally derived antibody (MDA) wanes. This phenomenon is commonly observed in breeding catteries as diarrhoea in 5-7 week old kittens. Sometimes the nictitating membranes also protrude. The kittens may or may not experience mild upper respiratory signs at the same time. Another significant clinical sign, pointing to FCoV as the cause of the diarrhoea, is that littermates tend to be of uneven sizes Addie & Jarrett, 1992 though this may not become apparent until the kittens are slightly older. However, there are many other causes of diarrhoea in cats which require to be considered before a diagnosis of FCoV diarrhoea can be made (for example Tritrichomonas foetus which tends to affect the same group of cats – young cats living in crowded multicat environments) or torovirus, which can also cause diarrhoea with protruding nictitating membranes. Muir et al, 1990

**FCoV infection as a cause of chronic diarrhoea in the carrier cat**

Persistently infected FCoV carrier cats usually appear to remain in adequate health, though some develop chronic large intestinal diarrhoea and faecal incontinence in older age. Again, there are many causes of chronic diarrhoea in the older cat, and FCoV carrier should be near the bottom of any list of differential diagnoses: it is uncommon. Detection of carrier cats requires positive faecal reverse transcriptase-polymerase chain reaction (RT-PCR) test results for nine months. FCoV carrier cats rarely develop FIP. Remarkably, the level of virus shedding remains incredibly constant: giving virtually identical Ct (cycle threshold) results month after month (though viral quantity decreases slightly as the cat ages).
Intestinal / Colonic FIP

Colonic FIP is a form of non-effusive FIP that usually presents as either diarrhoea, or, sometimes, as constipation, in addition to the usual clinical signs of non-effusive FIP: i.e. chronic weight loss, chronic mild pyrexia and anorexia. Lesions are most commonly found in the colon or ileo-caecocolic junction but may also be in the small intestine. Cats may have various clinical signs as a result of this lesion - usually constipation, chronic diarrhoea, or vomiting. Palpation of the abdomen often reveals a thickened intestine and raised mesenteric lymph nodes. A hematologic finding may be increased numbers of Heinz bodies, in addition to the lymphopenia and non-regenerative anaemia customary in FIP. Biochemical findings tend to be hyperglobulinaemia, raised bilirubin levels and raise alpha 1 acid glycoprotein (AGP).

Feline infectious peritonitis of the mesenteric lymph node

FIP presenting as an enlarged mesenteric lymph node, with few other clinical signs other than weight loss, malaise and fever, has been reported in the cat Kipar et al, 1999 and is the form of FIP most commonly seen in the ferret. The major differential diagnoses are neoplasia, toxoplasmosis, and other pyogranuloma inducing infections.

<table>
<thead>
<tr>
<th>Primary FCoV infection</th>
<th>Clinical signs</th>
<th>Population affected</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• usually asymptomatic</td>
<td>• usually pedigree kittens 5-7 weeks of age</td>
<td>• FCoV RT-PCR on faeces</td>
<td>• FCoV RT-PCR on faeces over several months</td>
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<tr>
<td>• small intestinal diarrhoea</td>
<td>• cats and kittens in multicat environment such as shelter</td>
<td>• FCoV serology from 21 days post infection</td>
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<tr>
<td>• ± vomiting</td>
<td>• any age</td>
<td>• requires consistently positive FCoV RT-PCR on faeces</td>
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<tr>
<td>• ± third eyelid protrusion</td>
<td>• any breed but pedigree over-represented</td>
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<tr>
<td>• may be short duration or chronic</td>
<td>• FCoV RT-PCR on cleaned gut biopsy</td>
<td></td>
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<tr>
<td>• weight loss</td>
<td>• IHC on gut biopsy</td>
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<tr>
<td>• failure to gain weight/runty kittens</td>
<td>• FCoV RT-PCR on FNA or biopsy of mes lymph node</td>
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**Diagnosis**

In this section, only the diagnosis of FCoV-related gastrointestinal signs will be addressed, since FIP diagnosis has been covered in the FIP diagnosis webinar notes. The most recent FIP/FCoV diagnosis algorithms can always be found on the www.catvirus.com website.

**Primary feline coronavirus infection in adult and kitten gastrointestinal signs**

No specific tests exist for coronaviral enteritis, and FCoV can only be assumed to be the cause of gastrointestinal clinical signs in FCoV-seropositive or RT-PCR fecal-positive cats in which all other possible causes have been carefully eliminated. Even biopsy is of limited use because the histopathologic features of villous tip ulceration, stunting, and fusion, or pyogranulomatous inflammation, are nonspecific. FCoV infection may only be confirmed if immunohistochemical (IHC) or immunofluorescent staining of gut biopsies is available (recommended laboratory for IHC in the UK is Liverpool Vet School. If using another laboratory ask whether they will perform a non-FCoV antibody control on every section of tissue – cat tissue is very sticky, leading to false positive results if the laboratory has not performed adequate controls.).

Exclusion of FCoV as a cause of GI signs is easier than diagnosing FCoV as the cause. Although serologic testing has limitations, it is clear that seronegative cats - as determined by a reliably sensitive * FCoV antibody test - do not have clinical signs related to FCoV infection. The only exception to this will be in initial FCoV infection, before the kitten or cat has had time to seroconvert (antibodies generally appear 18 – 21 days post infection) and in this case, an RT-PCR on faeces will be useful – a negative result will exclude FCoV definitively (provided the test is sensitive enough), but a positive result will simply indicate that FCoV is one of many possible causes of the GI signs –
other parasitic, protozoal, dietary, bacterial and viral causes will require to be excluded, as well as conditions such as intususception, foreign body (commonly trichobezoar), inflammatory bowel disease, tumour, etc. etc.

*A comparison of FCoV antibody tests was published by Addie et al (2015) and can also be found on catvirus.com.

**Key message:** a negative FCoV antibody test rules out FCoV as a cause of diarrhoea in kittens and cats over 10 weeks of age

However, a positive antibody test only indicates that FCoV is a possible diagnosis: other possible causes MUST be excluded before making a diagnosis of FCoV

**Persistent FCoV infection as a cause of chronic diarrhea**

Detection of carrier cats requires positive faecal reverse transcriptase-polymerase chain reaction (RT-PCR) test results once a month for nine months. A single negative FCoV antibody test rules out FCoV as a diagnosis.

Other causes (e.g. hyperthyroidism, inflammatory bowel disease, intestinal lymphoma or other neoplasia, pancreatitis, intestinal parasites, protozoa, etc) need to be investigated fully and eliminated before a diagnosis of FCoV diarrhoea can be arrived at.

**Intestinal / Colonic FIP**

Definitive diagnosis of intestinal FIP is by immunohistochemistry of a full thickness biopsy of the intestine. RT-PCR of faeces to detect FCoV will likely be positive, but since it is also positive in so many cats who do not have FIP, a positive result is of limited value. However a negative faecal FCoV RT-PCR, or RT-PCR on a FNA of the lesion, would be likely to rule out colonic FIP as would a negative FCoV antibody test.

In addition, cats with intestinal FIP would be expected to have elevated AGP levels; lymphopenia; hypergammaglobulinaemia and a non-regenerative anaemia with Heinz bodies.
Feline infectious peritonitis of the mesenteric lymph node

Viral detection on a fine needle aspirate (FNA) from enlarged mesenteric lymph nodes is a very useful method of diagnosing FIP, since histopathology of an enlarged lymph node is often vague, only describing pyogranulomatous inflammation. Quantitative (real time or Taqman) RT-PCR tests can give an idea of the amount of virus present, which will be high in cats with mesenteric lymph node FIP. FCoV RT-PCR and can be performed at the University of Glasgow Veterinary Diagnostic Services laboratory: send the FNA in 0.25ml of saline in a plain tube.

Treatment

Updates on FIP/FCoV treatment can always be found on the www.catvirus.com website.

Coronavirus enteritis in initial infection in kittens, adults and carrier cats

Treatment is symptomatic and supportive: use of fluid-electrolyte replacement and restricted caloric oral diet with living natural yogurt or with probiotics (e.g. Protexin, International Animal Health Products (IAHP), Australia and New Zealand) may be useful. Any cat with diarrhoea should receive weekly vitamin B12 injections. Applaws (MPM products, Cheshire) and Almo Nature chicken and pumpkin tinned cat foods are remarkably useful in controlling diarrhoea. Addie personal observation Some persistently infected carrier cats with diarrhoea respond to low doses of prednisolone (0.5 to 1 mg/day per cat) but remember that you MUST have established that they really are a carrier cat, otherwise immunosuppressing a non-carrier FCoV infected cat could result in FIP.

No specific antiviral treatment has yet been demonstrated to cure FCoV diarrhea although interferon omega (Virbagen Omega, Virbac, France) has been shown to reduce FCoV shedding. Gil et al, 2013 Gil et al (2013) gave 1 million units/kg recombinant feline interferon omega subcutaneously for 5 daily injections beginning at day 0, 14, and 60 to 16 shelter cats co-infected with FCoV and FeLV or FIV. Two cats didn’t shed FCoV at all, thus the FCoV group was actually 14 cats: FCoV shedding appeared to reduce but not statistically significantly and unfortunately there was no control group, nor was it determined whether it was type I or type II FCoV in the shelter (type II FCoV is only shed for a couple of weeks; though the shelter virus was probably type I). Overall clinical scores improved and 13 cats shedding feline calicivirus stopped shedding virus. Diarrhoea was only noted in two cats, mostly the faeces of the FCoV infected cats were reported as normal.
Presumably when / if the 3C-like protease inhibitor described by Kim et al (2016) becomes commercially available it will be the treatment of choice for FCoV-associated diarrhoea.

**Colonic and mesenteric lymph node FIP**

Since FIP is immune mediated, treatment aims at diminishing the immune reaction, usually using quite high doses of prednisolone, as a sliding dose (i.e. 2mg/kg/day for 10-14 days, reducing to 1 mg/kg/day for 10-14 days, then 0.5 mg/kg/day .... and so on). Until recently, FIP was incurable and most so-called "recovered" cats were probably simply misdiagnosed. However, recombinant feline interferon omega (reFIFNΩ) (Virbagen Omega,® Virbac, France) has been introduced which, according to one paper, effected a cure in around 25% of cats and remission in others, but in another controlled study no benefits were found. Nevertheless, in these cases, this author believes that reFIFNΩ given at doses of 100,000 units per day per os will give remission to some of these cats. To obtain this dose, reconstitute a 10 million unit vial, withdraw ten 0.1ml aliquots and freeze 9 of them (Virbagen Omega can last for months in the freezer). Put the remaining 0.1ml into 4.9 mls of water and give 0.5 ml to the cat per day. Store the diluted reFIFNΩ in the fridge, where it will last for 3 weeks.

Human interferon is not recommended because interferon is fairly species specific and cats develop antibodies to human interferon after 6 weeks, although if that is all that is available to you, then it is better than nothing. Human interferon can be given orally to cats.

Polyprenyl Immunostimulant (Sass & Sass, Inc, Oak Ridge, TN 37830, USA) is a mixture of phosphorylated, linear isoprenols which upregulates biosynthesis of Th-1 cytokine mRNAs. It was used successfully in three cats with non-effusive FIP, with survival times of 14 months, over 26 and 27 months, but had no beneficial effect on cats with effusive FIP. Legendre & Bartges, 2009 However, Legendre presented at AAHA that 22% of 58 cats with FIP were alive at 6 months, and only 5% at one year. The dose of 3mg/kg orally is given three times a week until cure or death. The effect of PPI on FCoV associated diarrhoea, or FCoV shedding, has never been reported. For the latest on PPI availability in Europe and further information on FIP treatment visit the FIP treatment page of my catvirus website. One needs permission from the VMD to import it into the UK and it can be purchased from the Vetimmune website. PPI should not be given with steroids.
Nutrition

Many of the larger cat food companies uses poor quality, cereal based, protein in their foods. Excessive amounts of omega 6 polyunsaturated fatty acids, such as are found in cereal based diets, promote chronic inflammation. In this author’s opinion, feeding as varied and natural a diet as possible to cats with FCoV infection and FIP is essential, avoiding highly processed commercial foods. The aim should be to source a high protein food with adequate levels of omega 3 oils, especially eicosapentaenoic acid (EPA): EPA supplementation has been shown to reduce monocyte adhesiveness to blood vessel walls. EPA is found in salmon, amongst other things. Fish oil, rich in omega 3 fatty acids, may be helpful in treating humans with ulcerative colitis and could help cats with FCoV infection, though one has to be wary that in cats too much vitamin A will cause excessive bone to be laid down in joints, so this avenue of treatment must only be pursued with caution.

Unlike humans, cats are unable to synthesize arginine: it is an essential amino acid in the cat. Arginine deficiency impairs the capacity of T cells to proliferate and to produce interferon gamma. Arginine is found naturally in meat.

The author is aware of two commercially available cat foods in Europe which contain high quality ingredients and are not full of additives: Applaws (MPM products, Cheshire, UK www.mpmproducts.co.uk) and Almo Nature (Italy, www.almonature.com) – no doubt there are others. In this author’s experience, a natural tinned food containing chicken and pumpkin (Applaws, MPM products, UK) stops diarrhoea in some cats without need for further medication. In addition, these natural foods are highly palatable, reducing or eliminating the need to use appetite stimulants.
**Appeal for samples**

We are looking for fine needle aspirates (FNA) of mesenteric lymph nodes from FCoV antibody or RT-PCR positive cats without FIP (i.e. healthy or suffering from a non-FIP disease). Please send the FNA in 0.25ml saline in a plain tube, plus a blood sample (or the FCoV antibody result) by first class post (no need for ice) to:

FAO Dawn Dunbar Veterinary Diagnostic Services Bearsden Rd Glasgow G61 1QH UK

Please put in a cover letter or sample submission form requesting FCoV RT-PCR on the FNA and FCoV antibodies tested on the blood sample. Please contact me at draddie@catvirus.com so that I can tell you how the tests can be done for free.

**Work with me on a FCoV elimination project**

If you have a FCoV infected household with an owner who is keen to eliminate FCoV and who would be interested in participating in a research study, please contact me at draddie@catvirus.com to discuss participation. I am a veterinary surgeon: everything you tell me about your patients will be kept absolutely confidential.

**Acknowledgements**

Diane is deeply grateful to all the veterinary surgeons and guardians who have supplied samples from naturally infected cats for almost three decades, helping her to avoid laboratory experiments on cats.

**No conflicts of interest**

Diane holds no shares or directorships in any of the products mentioned. However, if you use the Zooplus link on her catvirus website to buy pet supplies, not only will you receive a discount, but she will receive an affiliate fee and she profits from sales of her book “FIP and Coronavirus” available as e-books from her website and in print from Amazon in English and Spanish.
References, further reading and useful websites

Diane Addie’s FCoV and FIP website: www.catvirus.com

Jody Gookin’s website on Tritrichomonas foetus: www.cvm.ncsu.edu/docs/personnel/gookin_jody.html

Applaws food: www.Applaws.co.uk To source Applaws or Almo Nature in Europe: www.zooplus.com


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