

FIP DIAGNOSIS & TREATMENT UPDATE

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Introduction

Feline infectious peritonitis (FIP) is a fatal feline coronavirus (FCoV)-mediated disease posing a significant threat to cats worldwide, both domestic and wild. The acquisition of macrophage tropism remains the key feature distinguishing the highly pathogenic form - often referred to as FIP virus (FIPV) - from its more common, low-pathogenic and ubiquitous counterpart, feline enteric coronavirus (FECV). The pathogenic biotype possesses an enhanced capacity to infect and replicate within macrophages, facilitating systemic spread and provoking immune-mediated pyogranulomatous inflammation in affected tissues.

FIP can present in either an effusive (wet) or non-effusive (dry) form, with a diverse range of clinical signs. These phenotypes, however, likely represent a disease continuum, whereby a cat might start 'dry' then later develop effusion, and vice versa. Both 'wet' and 'dry' phenotypes can also have ophthalmic and/or neurologic involvement.

Treatment for FIP has advanced significantly, particularly with the use of nucleoside analogues and, in some instances, the addition of a protease inhibitor. With prompt antiviral treatment, long-term survival rates of 77-96% are now expected.¹⁻⁸ While some cats require initial supportive therapy, most show marked improvement within days. In severe cases, mortality may still occur despite commencing treatment, typically within the first week of starting antiviral therapy. Survival beyond the first week of treatment significantly improves the chance of achieving long-term remission. Relapse after three months post-treatment is rare when currently recommended dosages are implemented.

The FIP-related lectures presented during this conference aim to improve clinician confidence around diagnosis, treatment and management of refractory cases and comorbidities.

Diagnosis

Diagnosing FIP remains complex and is often first based on building the index of clinical suspicion with patient history, signalment, clinical presentation and routine diagnostics such as CBC and biochemistry. Diagnostic imaging, fluid analysis and biopsies are often then required collect samples from which to perform confirmatory testing such as immunofluorescence, immunohistochemistry, and RT-qPCR, while concurrently ruling out mimicking diseases with cytology, culture and histopathology.

Young purebred cats are often overrepresented, though it is important to acknowledge that 20-30% of cats will be over the age of two years when they are diagnosed and this disease can affect any breed, including domestics. FIP therefore needs to be on your radar for any

cat that is presenting unwell to your practice. Now that safe and effective treatment is available, it is vital we do not miss this disease as clinicians.

Common clinical features include (but are not limited to) pyrexia, icterus, poor BCS, abdominal or thoracic effusions, pericardial effusion, myocarditis, pneumonitis, uveitis, renomegaly, lymphadenopathy (abdominal and occasionally peripheral), intestinal mass lesions, and neurological signs affecting the brain or spinal cord. It is important to recognise, however, that FIP is a disease that wears many 'faces' and has been confirmed in just about every organ, including the skin.

Complete blood cell count (CBC) usually shows mild, nonregenerative anaemia, microcytosis, neutrophilia (with or without toxic changes), lymphopenia and thrombocytopenia or thrombocytosis. Serum biochemical findings often include hyperproteinaemia, hyperglobulinemia, hypoalbuminemia, increased liver enzyme activities, hyperbilirubinemia, and electrolyte imbalances. Low albumin:globulin ratio (A:G) further increases suspicion, with A:G ≤ 0.4 making FIP more likely. In one study an A:G of 0.5 had a positive predictive value of 89%, and an A:G of 1.0 had a negative predictive value of 91%.⁹ When hyperglobulinemia is detected, protein electrophoresis can be performed which usually shows polyclonal gammopathy with greatest increases in the gamma (γ)-globulin fractions.¹⁰ Acute phase proteins, mainly alpha1-acid glycoprotein and serum amyloid A are often increased in cats with FIP, but can also be increased with other inflammatory diseases. Measuring FCoV antibodies in cats with FIP is not very helpful due to the high number of seropositive cats after FECV infection and about 10% of cats with FIP have been reported to be seronegative. Similarly, FCoV PCR on blood is also not considered very helpful, due to the overlap with FECV.

Ultrasound often confirms effusions in case of 'wet' FIP and abdominal lymphadenopathy, medullary rim sign and masses can be seen in both effusive and non-effusive FIP. Fluid analysis and cytology in cases of effusive FIP allows confirmatory testing to be performed. The effusions are mostly consistent with modified transudate or low cellularity exudate and is usually high in protein (≥ 35 g/L) and with low nucleated cell counts (< 5000 cells/ μ L). Mixed inflammatory cell populations of lymphocytes, macrophages, and neutrophils occur most commonly; neutrophils predominate in most cases, but in some cats, macrophages are the primary cell type seen. Measurement of protein concentrations in effusions and calculation of the Alb:Glob of the effusion can increase the suspicion of effusive FIP. It is important to remember to exclude alternative or comorbid pathologies, therefore, cytology and culture and sensitivity testing is also recommended.

Confirmatory tests

The globally accepted reference test (aka gold standard test) for diagnosis of FIP is supportive histopathology and positive FIP immunohistochemistry (IHC). FIP IHC detects FCoV antigen in macrophages by binding a visible stain to the virus, enabling it to be visualised within the cytoplasm of tissue macrophages. It requires formalin-fixed biopsies,

which commonly creates a barrier when dealing if debilitated young cats who may be too high a GA risk to undergo the procedures. FIP Immunocytochemistry utilises a similar method of detecting FCoV antigen with the macrophages that may be present within effusions. Immunocytochemistry via direct immunofluorescence can be used to detect feline coronavirus on cytology (eg. FNA) samples.

FCoV RNA can also be detected in fluid, tissue aspirates or biopsies by reverse transcriptase polymerase chain reaction (RT-PCR). The specificity and sensitivity of RT-PCR varies based on the test and sample used for diagnostics, with highest specificity being on pleural and peritoneal effusion as FCoV is unlikely to be in effusions from other causes. Approximately 10% of PCR's performed on tissue will yield false-positive results. In cases of neurological FIP, cerebrospinal fluid could be taken for analysis and RT-PCR. Cats with ocular involvement can undergo aqueocentesis and RT-PCR performed on aqueous humour.

In many cases, a presumptive diagnosis of FIP is made based on clinical and clinicopathologic findings, along with the exclusion of other potential causes of the presenting signs. When confirmatory testing is unsafe, cost-prohibitive, or yields negative results despite a strong clinical suspicion, an antiviral treatment trial may be considered. Where FIP is present, a rapid clinical improvement should be evident within seven days of initiating antiviral treatment. If the response is poor, clinicians must reassess alternative differential diagnoses, as prolonged antiviral therapy without clear justification may increase the risk of resistance and compromise patient welfare by delaying the appropriate diagnosis and treatment of an alternative disease.

Treatment

Nucleoside and nucleotide analogues are a versatile class of drugs, mainly used as antiviral and chemotherapeutic agents¹¹, and remain the cornerstone of FIP treatment. Remdesivir and GS-441524 form a nucleotide-to-nucleoside pairing, with remdesivir being metabolized into GS-441524 *in vivo*.¹² Similarly, molnupiravir is a prodrug that converts into the nucleoside analogue β -D-N4-hydroxycytidine (NHC or EIDD-1931). GS-441524 and NHC represent intermediate metabolites, with further hydrolysis into their respective pharmacologically active triphosphates occurring intracellularly. The mechanism of action for these nucleoside analogues differs slightly. Remdesivir and GS-441524 produce an adenosine analogue that disrupts viral replication by incorporating into viral RNA via RNA-dependent RNA polymerase, causing delayed chain termination.^{13,14} In contrast, molnupiravir and NHC act as mutagenic agents, creating various tautomers over subsequent rounds of RNA synthesis, increasing mutation frequencies beyond sustainable thresholds. This elevated mutation rate produces replication-incompetent genomes, leading to viral death via 'error catastrophe'.^{15,16}

The human licensed formulation of remdesivir (GS-5734; Veklury), is available by off-label prescription in the USA (though sometimes difficult for veterinarians to source) and compounded oral GS-441524 can now be prescribed as well in the USA. Confidence in the

efficacy of these oral formulations has grown, and most cases (including neurologic FIP) can now be treated exclusively with oral GS-441524, so long as the cat has a competent swallow reflex. Remdesivir is typically only used intravenously in critically ill cats for initial stabilization, transitioning to oral therapy as clinical signs improve. Currently recommended dosages for GS-441524 and remdesivir are displayed in Table 1.

Form of FIP	GS-441524 PO[^]	Remdesivir IV[*]/SC
Effusion(s) and without ocular or neurological signs	15 mg/kg q 24hr or split q 12hr [†]	10-15 mg/kg q 24hr
No effusion and without ocular or neurological signs	15 mg/kg q 24hr or split q 12hr [†]	12-15 mg/kg q 24hr
Ocular signs (+/-effusion)	20 mg/kg q 24hr or split q 12hr [†]	15 mg/kg q 24hr
Neurological signs (+/-effusion)	10 mg/kg q 12hr	20 mg/kg q 24hr

Table 1 - Currently recommended treatment protocols for GS-441524 and RDV by presenting the form of FIP.

*Slow IV (intravenously) – Give as CRI over 30mins-2h, can be diluted in saline.

[^]PO (orally) – Give fasted with water bolus or tbsp wet food, full meal 30mins later.

[†]Divided dose may improve plasma concentrations when using oral GS-441524 and is suggested as preferred by some. The author still considers SID dosing highly effective and appropriate, particularly where compliance may be an issue.

Standard treatment duration has historically been 84 days; however, emerging evidence suggests that shorter treatment courses of 42 days may be effective in less severe cases (mainly effusive cases) who demonstrate rapid normalization of clinicopathologic signs.¹ Individual patient assessment remains critical before discontinuing treatment. The author currently recommends antiviral treatment continue for 2 weeks beyond clinical resolution of signs referable to FIP. Adverse side effects appear to be rare. ALT elevations have been reported, though they do not appear to require specific treatment. Subcutaneous (SC) administration of remdesivir (or unlicensed SC administration of GS-441524) may produce pain and injection site reactions such as ulceration and focal alopecia. Feline injection site sarcomas (FISS) have been confirmed in a handful of cases collected by Dr Samantha Evans, Colorado State University, secondary to unlicensed injectable GS-441524 (Pers com, unpublished data). Urolithiasis has also been reported with the use of unlicensed GS-441524 but, to date, has not been seen with compounded formulations used at dosages described in these proceedings. Due to the poor regulation of unlicensed formulations,

often containing substantially more GS-441524 than disclosed, the emergence of uroliths is hypothesized to be due to inadvertent overdoses (exceeding 40mg/kg/day).

Molnupiravir (EIDD-2801) is another nucleoside analogue that inhibits viral replication and is metabolised into EIDD-1931 (NHC). In USA, molnupiravir and EIDD-1931 are available from compounding pharmacies. Initial use was as a second-line antiviral for cats that failed to respond to remdesivir / GS-441524. Recent studies suggest that it may be used as a primary treatment option. A prospective study assessing molnupiravir as monotherapy reported a 77% survival rate, with 11% of treated cats requiring dose escalation due to relapse. Safety concerns include a narrower therapeutic window, potential for neutropenia, elevated liver enzymes, gastrointestinal side effects, loss of hair and whiskers, folding of the ears, and teratogenic risks. Current recommendations suggest caution when exceeding 15 mg/kg every 12 hours. When considering the use of molnupiravir, it is also important to note its mutagenic and teratogenic properties, and the observation of viral resistance observed in COVID-19 cases. It is not recommended for human patients under 18 years of age or during pregnancy due to risks such as embryofetal lethality and teratogenicity seen in rats and reduced foetal body weights in rabbits. Therefore, staff/owners should wear gloves when administering this medication, and pregnant humans should avoid handling. For these reasons, the author recommends reserving molnupiravir and NHC as second-line antivirals. Currently recommended dosages for second-line MPV and NHC therapy are displayed in Table 2.

Form of FIP	Molnupiravir (EIDD-2801) PO dosage	NHC (EIDD-1931) PO dosage
Effusion(s) and without ocular or neurological signs	10-15 mg/kg q12hr	15 mg/kg q12hr*
No effusion and without ocular or neurological signs	15 mg/kg q 12hr	15 mg/kg q12hr*
Ocular signs (+/-effusion)	15 mg/kg q 12hr	15 mg/kg q12hr*
Neurological signs (+/-effusion)	15-20 mg/kg q 12hr	20 mg/kg q 12hr*

Table 2 - Recommended dosages for MPV and its metabolite NHC.

*These dosages are currently recommended for relapses; for first line therapy lower dosages may be considered, more studies are needed to provide better guidance on dosing of NHC. The molecular weights of MPV and NHC are 329.31 g/mol 259.22 g/mol respectively, therefore, if there is complete hydrolysis from MPV into NHC, it is expected to get 0.78% the dosage of MPV administered (e.g. 10mg/kg MPV would equal 7.8mg/kg NHC).

Monitoring with nucleoside analogue treatment requires a case-dependent approach based on severity and comorbidities. Initial rechecks should occur within 1-2 weeks to ensure a positive clinical response. Subsequent rechecks are typically scheduled at 4, 6-8, and 10-12 weeks. Rechecks should include physical exams (particularly weight and temperature), CBC, and chemistry panels. Expected response timelines include fever and inappetence resolving within 1-5 days, effusion within 2-3 weeks (though scant effusion may remain for weeks to months), WBC abnormalities and total bilirubin within 2-3 weeks, hyperglobulinemia within 4-8 weeks, and low albumin to globulin ratio (improved to > 0.6) within 6-10 weeks. If abnormalities persist beyond these times, or new signs referable for FIP develop during treatment, consider a dosage increase of 5 mg/kg/day. Dose increases should be followed by rechecks within 1-2 weeks. If an adequate response is not observed, consider switching to molnupiravir/NHC or adding a protease inhibitor (see below). Depending on the level of certainty of the original FIP diagnosis, it may also be necessary to continue diagnostic investigation for alternate or comorbid disease process if adequate response to antiviral therapy is not observed with these strategies (unfortunately some cats are unlucky enough to have FIP and lymphoma or other diseases alongside their FIP). If treatment extends beyond 84 days, rechecks should be performed every 2 weeks until remission is achieved. Post-treatment rechecks should occur one month, three months, and then every 6-12 months. In cases of suspected relapse, thorough diagnostic investigation and confirmation, such as by PCR, are essential. This is because other inflammatory or neoplastic conditions, including gastrointestinal disease, pancreatitis, cholangitis, or lymphoma, can closely resemble the clinical presentation of FIP. Accurate diagnosis is critical to ensure these cats receive appropriate treatment. If FIP relapse is confirmed (or is most likely), a repeat course of GS-441524 may be commenced at 5-10mg/kg/day higher than the primary course. Alternatively the cat could be switched to molnupiravir/NHC, with or without the addition of a protease inhibitor (see next).

Protease inhibitors, such as GC376 and nirmatrelvir (Paxlovid), have shown promise as adjunctive therapies, particularly for refractory cases or in efforts to reduce treatment duration. GC376 has demonstrated efficacy in experimental FIP models and is undergoing FDA approval. Combination antiviral therapy has been explored, with a prospective study showing that combination of GS-441524 and GC376 produced treatment success with four weeks of therapy, though a GS-441524 monotherapy control group was not included in this study.¹⁷ GC376 is not currently available, though the patent company Anivive have initiated FDA registration. Unlicensed formulations marketed as GC376 have not been formally evaluated for content and purity.

Nirmatrelvir has also been evaluated in refractory cases, with preliminary data suggesting clinical benefit. Paxlovid®, Pfizer's antiviral combination for SARS-CoV-2, has received variable approval worldwide. It is available to veterinarians via off-label prescription in the US. Paxlovid® consists of two different tablets: nirmatrelvir, a 3CLpro protease inhibitor with a short half-life, and ritonavir, a pharmacokinetic booster that inhibits cytochrome P450 to delay nirmatrelvir metabolism. Nirmatrelvir has shown *in vitro* efficacy against FIPV I and II, with enhanced effectiveness when combined with other antivirals.¹⁸ Paxlovid® is under investigation for FIP treatment and has been used anecdotally with a nucleoside analogue in highly refractory cases. The author's colleague (Dr. Sally Coggins) reports 14 cases where this combination achieved remission, though this data is unpublished and anecdotal. Its use remains experimental, but for non-responding cats with confirmed FIP, a dose of nirmatrelvir 75mg/cat with ritonavir 25mg/cat BID PO, alongside continued nucleoside analogue treatment, could be considered. Always combine with a nucleoside analogue. Clinicians also need to be aware that given ritonavir inhibits cytochrome P450, it may delay the metabolism of other medications processed by this pathway (e.g. fluoxetine).

Even though global access to legally prescribable antiviral compounds for FIP continues to expand, unlicensed (black market) manufacturing persists, and by anecdotal reports, continues to thrive. Whilst this remains the only available option in many countries, sale and distribution of these unlicensed formulations appears to remain robust within countries where legal avenues now exist. It is important for practitioners to be aware of this as owners frequently continue to be either intentionally or inadvertently directed to groups on the internet with financial motivations to sell products and advise on protocols outside of veterinary medical institutions, sometimes with negative consequences for the patient or owner. Owners also remain open to criminal and financial prosecution if found to be importing unregistered drugs for veterinary use.

Ongoing research continues to refine the treatment protocols presented here. Clinicians should consider individual patient response, comorbidities such as immune-mediated haemolytic anaemia (IMHA) and sepsis, and the potential impact of emerging antiviral resistance. Immune-mediated hemolytic anemia arises due to immune-mediated erythrocyte destruction and can be non-associative or associative with disease processes such as FIP. If associative IMHA is suspected, these cats should have positive saline agglutination test or Coombs' test when performed and ideally be also tested for retroviral infections and *Mycoplasma hemofelis*. Cats with associative IMHA often have moderate to severe anemia and require corticosteroid therapy (~1-2mg/kg/day prednisolone with a fast taper as anemia is resolving) and the author (Dr. Cerna) also recommends starting clopidogrel for these patients (18.75mg PO once a day). If IMHA is diagnosed and treated early these cats usually achieve remission as any other FIP cat.

As more cats are being treated with antiviral drugs instead of being euthanized, new disease processes that may be associated with FIP are being recognized. This includes the development myocarditis and myocardial injury, which have also been documented in

humans and animals with SARS-CoV-2. Cats with FIP can present with elevations in cardiac troponin and wall thickening, both of which could be suggestive of myocarditis and/or myocardial injury; however, antiviral therapy may reduce active myocarditis in cats with FIP and most of these cats have normal troponin levels at the end of the therapy.

Despite the continued evolution of treatment strategies, nucleoside analogues remain the preferred first-line therapy, with protease inhibitors serving as adjuncts for refractory or severe cases. As global access to legal antiviral formulations expands, the prognosis for FIP has improved dramatically, transitioning from an invariably fatal disease to one with a high likelihood of long-term survival.

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