Update on feline infectious peritonitis

Background: Feline coronavirus (FCoV) infection in cats is common, usually only causing mild intestinal signs, such as diarrhoea. It is highly infectious and found worldwide. A sequela of FCoV infection, feline infectious peritonitis (FIP), is a common cause of death in young cats, occurring in up to 10 per cent of cats infected with FCoV. Although suspicion of FIP is frequent in sick, particularly young, cats, obtaining a definitive diagnosis using non- or minimally-invasive approaches is difficult.

Aim of the article: This article provides an update regarding diagnosing cases of FIP and guidance on current treatment recommendations.

Epidemiology

Coronaviruses are relatively large, enveloped, positive-sense, single-stranded RNA viruses (Figs 1, 2). They exhibit a high rate of mutation during replication and therefore exist as clusters of genetically diverse populations. Cats have been found to be infected with feline coronavirus (FCoV) worldwide, with the exception of cats on a small number of isolated islands. Two serotypes of FCoV are recognised: Type 1, which represents the vast majority of field strains, and Type 2. The latter arises following recombination events between Type 1 FCoV and canine coronavirus. The two serotypes are distinguished primarily by differences in their transmembrane spike (S) glycoprotein. The S glycoprotein (Fig 2) mediates binding to and entry into host cells.

Infection with FCoV is very common – 35 per cent of the owned domestic cat population have detectable antibodies to FCoV, indicating exposure (combined data from the eight serological studies listed in Drechsler and others 2011). In single-cat households (combined data), seroprevalence reduces to 21 per cent, but correspondingly in multicat households it can be over 90 per cent (Addie and others 2000). Most infections are transient (although reinfection is common) with only a small percentage becoming persistent ‘carriers’ or ‘chronically shedding’ cats (Kipar and Meli 2014).

Transmission and pathogenesis

Transmission is primarily faeco-oral, with litter boxes representing the principal source of infection among cats within a household. In breeding catteries, kittens commonly become infected at a young age, mostly at five- to six-weeks-old (Addie and Jarrett 1992), as maternally derived antibodies have started to wane. Nose-to-nose contact is considered an uncommon route, and transplacental transmission is considered rare. Experimentally, infection has been transmitted by parenteral injection of virus derived from cats with feline infectious peritonitis (FIP).

Small intestinal villi enterocytes are the primary point of host cell entry and replication. In most cases, FCoV infection is subclinical or results in only mild gastrointestinal signs (eg, diarrhoea, vomiting). However, occasionally more severe gastrointestinal disease is seen. Subclinical FCoV infection was previously believed to be confined to the intestinal tract, but we now know that healthy FCoV-infected cats develop a detectable low-level viraemia during acute infection (Kipar and others 2014).
are also likely to be important for the development of mediating effective and sustained replication in per se (Barker and others 2017). Other viral factors without FIP with equal frequency, rather than FIP infection, occurring in FCoV viraemic cats with and that one of these sets of mutations, involving the gene influencing cell tropism (Kipar and Meli 2014). This has led to suggestions from clinically ‘healthy’ cats (Chang and others 2012, derived FCoVs, as compared to faecally shed FCoV been detected with increased frequency in FIP tissue-

Viral factors are important in the pathogenesis of FIP. As mentioned earlier, the S glycoprotein of FCoV mediates host cell entry, with mutations in the S gene influencing cell tropism (Kipar and Meli 2014). Mutations at different sites within the S gene have been detected with increased frequency in FIP tissue-derived FCoVs, as compared to faecally shed FCoV from clinically “healthy” cats (Chang and others 2012, Licitra and others 2013). This has led to suggestions that some of these mutations could be a useful target in differentiating cats with FIP from cats without.

Clinical signs associated with feline infectious peritonitis

The variability in the extent and distribution of both vasculitis and perivascular granulomata underlies one of the difficulties in diagnosing FIP. Clinical signs of FIP can change over time, warranting repeated clinical examinations to detect newly apparent pathology. Non-specific clinical signs (Table 1) – often waxing and waning – are attributable to the systemic inflammatory response and frequently occur in cats both with and without detectable effusions, with FIP a significant differential for pyrexia of unknown origin (Spencer and others 2017). However, it should be noted that the absence of these signs does not rule out FIP.

Although effusive FIP is regarded as being three to four times more common than non-effusive FIP (Kipar and Meli 2014, Riemer and others 2016), and the distinction between the two forms is important for diagnostic purposes, there is considerable overlap between them. Cases with effusive FIP often have pyogranulomatous lesions visible at postmortem examination, while many cats with non-effusive FIP go on to develop effusions. Effusive FIP is often acute in nature, progressing within a few days or weeks, whereas non-effusive FIP tends to be more chronic, progressing over a few weeks to months. In effusive FIP, effusions may form in one or more body cavity, with abdominal effusion leading to a clinical presentation of ascites and abdominal

In Practice: first published as 10.1136/inp.m3187 on 4 September 2020. Downloaded from http://inpractice.bmj.com/ on January 10, 2021 by guest. Protected by copyright.
Companion animals

Distension being the most common manifestation. Cats with pleural effusion often develop dyspnoea, whereas cats with pericardial effusion rarely show signs of cardiac tamponade. Occurring only rarely, scrotal effusion leads to scrotal enlargement in entire males. Non-effusive FIP is often more difficult to diagnose, particularly in the earlier stages of disease, as vague non-specific clinical signs may be all that can be seen. More specific signs depend on the organs affected by the granulomatous lesions, often the central nervous system (CNS), eyes, or abdominal organs (eg, liver, MLNs, kidney, gastrointestinal tract); however, any tissue can be affected and primary involvement of the lungs or skin have been described.

In sick cats, careful neurological and ocular examination may reveal changes that support a diagnosis of FIP, as well as indicating a potential source of samples for testing. Neurological signs associated with focal, multifocal or diffuse changes in the CNS may be seen in up to 30 per cent of cats with FIP, and for some these are the only signs noted (Fig 5); this makes FIP a common differential for neurological disease, particularly in young cats.

Commonly reported signs in FIP with neurological involvement include:

- Ataxia (with varying degrees of tetra- or paraparesis);
- Hyperaesthesia;
- Head tilt;
- Nystagmus;
- Seizures;
- Behavioural change;
- Mental state change;
- Cranial nerve deficits; and
- Postural reaction deficits.

However, differentiating subtle neurological signs from those exhibited by systemically unwell cats may not be possible. Similarly, FIP is a major

Table 1: Commonly encountered features of signalment, history and physical examination seen in cats with feline infectious peritonitis

| Features | Signalement | History | Physical examination |
|----------|-------------|---------|----------------------|
| Young (often <2 years); male; breed* | Background: recent stress (vaccination, rehoming, new cat, surgery); multicat household (current/historical) | Abdominal distention/fluud thrill test for ascites; palpable mass; uveitis; jaundice; pyrexia; restrictive dyspnoea with dull lung sounds (pleural effusion); neurological deficits; lymphadenopathy |
| | Health: weight loss/failure to thrive; inappetence/anorexia; lethargy; pyrexia of unknown origin (non-responsive to antibiotics; +/- fluctuating); behavioural change, ataxia, seizures |

* Non-pedigree cats make up the majority of cats presenting with FIP (85% in a recent study [Richards 1995]). However, various prevalence studies have identified increased incidence in certain pedigree breeds. The breeds identified of having increased risk vary from country to country, suggestive of either country-specific blood lines being more of a factor or reporting bias within the local pedigree cat communities.
Fig 6: Feline infectious peritonitis is a major differential for uveitis, manifestations of which include: changes in iris colour, thickness and texture; dyscoria (abnormal shape of the pupil); anisocoria (unequal pupil sizes); sudden loss of vision; hyphema; keratic precipitates ('mutton fat' deposits on the ventral corneal endothelium); chorioretinitis; retinal detachment; and aqueous/vitreous flare. These changes may be subtle and unilateral or bilateral and severe.

(a) Mild iridial changes, aqueous flare and keratic precipitates (white arrow) of the right eye in an eight-month-old chinchilla persian with pyrexia of unknown origin.

(b) Bilateral severe fibrinous, flocculent, aqueous flare limiting examination of the interior of the eye, where assessment of the retina is possible changes may be present there too.

(c) Severe bilateral chorioretinitis including haemorrhage and granulomata (pink and red arrows); aqueous flare and retinal oedema results in the image appearing to be out of focus.

In Practice: first published as 10.1136/inp.m3187 on 4 September 2020. Downloaded from http://inpractice.bmj.com/ on January 10, 2021 by guest. Protected by copyright.
## Companion animals

### Table 2: Common differential diagnoses for feline infectious peritonitis

|                               | Non-specific signs | Jaundice | Effusion | Ocular | CNS | Mass lesion | Notes                                                                                                                                 |
|-------------------------------|-------------------|----------|----------|--------|-----|-------------|----------------------------------------------------------------------------------------------------------------------------------------|
| **Toxoplasmosis**              | ✔                 | ✔        | ✔        | ✔      | ✔   | ✔           | History: Fed raw diet or hunter (also vertical transmission in kittens)                                                                 |
|                               |                   |          |          |        |     |             | Differences: Hyperglobulinaemia uncommon                                                                                               |
|                               |                   |          |          |        |     |             | Diagnosis: Cytological identification of organisms on aspirates; PCR of aspirates or CSF; paired Toxoplasma serology (IgM and IgG)        |
| **Lymphocytic cholangitis**    | ✔                 | ✔        |          | ✔      |     | ✔           | History: Persians may be over-represented                                                                                               |
|                               |                   |          |          |        |     |             | Differences: Usually (not always) associated with increased hepatic enzyme activities (primarily cholestatic). Cats often relatively well and normothermic |
|                               |                   |          |          |        |     |             | Diagnosis: Liver biopsy                                                                                                                 |
| **Neoplasia (eg, lymphoma; carcinoma)** | ✔         | ✔        | ✔        | ✔      |     |             | Can affect cats of any age, particularly lymphoma. Jaundice may be present particularly with hepatic involvement                           |
|                               |                   |          |          |        |     |             | Diagnosis: Cytology of fluid or aspirates; biopsy                                                                                       |
| **Mycobacterial disease**      | ✔                 | ✔        | ✔        | ✔      |     | ✔           | History: Hunter or outdoor access (geographical variation), fed raw diet                                                                |
|                               |                   |          |          |        |     |             | Differences: Usually minimal to no effusions. Usually (not always) relatively well and normothermic                                     |
|                               |                   |          |          |        |     |             | Pulmonary signs (tachypnoea; cough) not uncommon                                                                                       |
|                               |                   |          |          |        |     |             | Diagnosis: Ziehl-Neelsen stain of aspirates or biopsy; interferon-γ release assay; mycobacterial PCR or culture of aspirate or biopsy |
| **Pancreatitis**               | ✔                 | ✔        | ✔        | ✔      |     | ✔           | Differences: Usually (not always) normothermic. Ascites, where present, usually small volume with high cellularity (non-degenerate neutrophils) |
|                               |                   |          |          |        |     |             | Diagnosis: Feline pancreatic lipase immunoreactivity; abdominal imaging                                                              |
| **FIV/FeLV**                   | ✔                 | ✔        | ✔        | ✔      |     | ✔           | History: Outdoor or ‘stray’; entire adult with unknown mating activity (especially FIV)                                             |
|                               |                   |          |          |        |     |             | Differences: Common differential for lymphadenopathy and/or uveitis. FeLV may be associated with neoplasia (especially lymphoma)       |
|                               |                   |          |          |        |     |             | Diagnosis: FIV antibody/FeLV antigen serology (positive results should be confirmed)                                               |
| **Sepsis**                     | ✔                 | ✔        | ✔        | ✔      |     | ✔           | Infection can involve different organ systems (eg, kidney, liver, uterus, heart) or body cavities (eg, pyothorax, septic peritonitis) |
|                               |                   |          |          |        |     |             | Cats are often very sick (eg, pyrexia may have progressed to hypothermia with onset of shock)                                          |
|                               |                   |          |          |        |     |             | Diagnosis: Haematology suggestive (leukocytosis or neutropenia; left shift and toxic change); hypoglycaemia may be present; imaging; |
|                               |                   |          |          |        |     |             | cytology (degenerate neutrophils; intracellular bacteria) and culture of fluid or aspirates*                                           |
| **Septic peritonitis**         | ✔                 | ✔        | ✔        | ✔      |     | ✔           | Pyrexia common. Most frequently associated with gastrointestinal or urinary tract perforation                                            |
|                               |                   |          |          |        |     |             | Differences: Ascites with high cellularity (degenerate neutrophils; intracellular bacteria)                                         |
|                               |                   |          |          |        |     |             | Diagnosis: Cytology and culture of fluid or aspirates*                                                                               |
| **Pyothorax**                  | ✔                 | ✔        | ✔        | ✔      |     | ✔           | Usually pyrexic                                                                                                                        |
|                               |                   |          |          |        |     |             | Differences: Pleural effusion with high cellularity (degenerate neutrophils; intracellular bacteria)                                 |
|                               |                   |          |          |        |     |             | Diagnosis: Cytology and culture of fluid or aspirates*                                                                               |
| **CHF**                       | ✔                 | ✔        | ✔        | ✔      |     | ✔           | History: Some breeds are predisposed to cardiomyopathy (eg, ragdoll, Maine coon) with increased risk of CHF at a young age. Heart mumur (non-jaundice) |
|                               |                   |          |          |        |     |             | (non-jaundice), gallop sounds, arrhythmia, jugular vein distention and pulse may be present. Differences: Low protein/low cellularity effusion. |
|                               |                   |          |          |        |     |             | Hypothermia and/or hypotension are common, Pyrexia, hyperglobulinaemia and jaundice are not features                                    |
|                               |                   |          |          |        |     |             | Diagnosis: Echocardiography                                                                                                             |

✔ = feature shared with feline infectious peritonitis (NB: absence does not rule it out as a differential); * NB: risk of false-negative if collected after antibiotics are administered

CHF Congestive heart failure, CNS Central nervous system, CSF Cerebrospinal fluid, FeLV Feline leukaemia virus, FIV Feline immunodeficiency virus, LN Lymph nodes
In practice | September 2020

27/08/2020 14:11

372-383 Barker.indd 377

used to make a diagnosis of FIP. However, imaging alone cannot be used to make a diagnosis of FIP.

Table 3: Commonly encountered changes on routine clinicopathological analysis seen in cats with feline infectious peritonitis

| Clinicopathological analysis | Changes seen |
|-----------------------------|--------------|
| **Haematology**             |              |
| • Anaemia (often mild and non-regenerative) |
| • Microcytosis              |              |
| • Lymphopenia               |              |
| • Neutrophilia (+/- left shift) |
| **Serum biochemistry**      |              |
| • Hyperglobulinaemia (often polyclonal gammopathy) |
| • Hypoalbuminaemia (secondary to acute phase protein response; compensatory for hyperglobulinaemia) |
| • Low albumin to globulin ratio |
| • Increased liver enzyme activities (primarily hepatocellular, especially aspartate transaminase) |

To provide a definitive diagnosis of FIP, cytological or histopathological changes consistent with FIP (ie, pyogranulomatous inflammation) should be identified and subsequently co-localised with FCoV antigen, using immunostaining for viral antigen. More recently RT-PCRs have also been used to support a diagnosis of FIP (Box 1).

**Analysis of effusions**

In effusive FIP, sampling the effusion is the single most useful diagnostic step in confirming a diagnosis. For this reason, where effusions are not evident on initial evaluation, repeated ultrasonography to identify any small volume effusion is recommended (Fig 4) and may facilitate sampling of small pockets of fluid. FIP effusions (Fig 8) are usually clear, poorly cellular (total nucleated cell count <5 x 10^9/l), yellow, viscous, protein-rich (with a total protein concentration of >35 g/l), have a low albumin to globulin ratio, and have a positive Rivalta test (Box 2). However, in some cats the effusions might be cloudy, of slightly lower protein levels (eg, in cats that were not originally markedly hyperproteinanaemic, or following repeated abdominoencestesis), or contain much higher cell counts (up to 20 x 10^9/l). Cytological examination usually reveals pyogranulomatous inflammation with macrophages, non-degenerate neutrophils and few lymphocytes. Effusion AGP concentrations may also be useful in supporting a diagnosis of FIP, potentially affording greater sensitivity and specificity than AGP (Duthie and others 1997, Hazuchova 2007, Hazuchova and others 2017). Other APPs, serum amyloid A and haptoglobin, have been assessed in the diagnosis of FIP but were both less sensitive and specific than AGP (Duthie and others 1997, Paltrinieri and others 2017). Overall, increased AGP (or other APPs) in serum, despite supporting a diagnosis of FIP, is not confirmatory and may be limited by cost, availability and turnaround time.

Clinicians vary as to whether they perform FCoV serology or not in suspected cases. Although a positive result indicates exposure to FCoV, many clinically healthy cats have positive, often high, antibody titres, while a small proportion of cats with both effusive and non-effusive FIP are seronegative. Diagnosis of FIP should never be made based upon positive serology alone. Faecal RT-qPCR has replaced serology in monitoring the effect of control measures in the management of FCoV infection within a breeding cattery.

**Imaging**

Imaging (Figs 4, 5) can be useful, in that it can often identify areas of pathology (eg, mass lesion, effusion) that may prove useful to sample as well as guiding sample acquisition (eg, ultrasound-guided needle biopsy). However, imaging alone cannot be used to make a diagnosis of FIP.

Fig 7: Flow diagram showing the diagnostic approach to cats with suspected feline infectious peritonitis. CBC Complete blood count, CSF Cerebrospinal fluid, FCoV Feline coronavirus, FIP Feline infectious peritonitis, FNA Fine-needle aspiration.
Feline coronavirus (FCoV) RT-PCR, when designed appropriately, is a very sensitive and specific assay for the detection of FCoV within samples, and is generally more sensitive than immunostaining for FCoV antigen in tissues (Barker and others 2017). However, it cannot co-localise virus to cytological/histological lesions, merely to the samples in which those changes are present. Following intestinal infection with FCoV, most cats develop a viraemic, disseminating virus throughout the body. Therefore, cats without feline infectious peritonitis (FIP) can have detectable virus within blood, effusions and tissues – albeit at a lower frequency and viral copy number. Due to low circulating levels of viraemia, use of RT-PCR of whole blood in cats with suspected FIP is not recommended (Emmler and others 2020).

In a recent large study, all but one cat of 57 (98%) with FIP had at least one tissue positive for FCoV by quantitative RT-PCR, as compared to 12 of 45 cats without FIP (Barker and others 2017); viral copy numbers were also significantly higher in the positive samples from cats with FIP than those without FIP. Further investigation of the single cat with FIP and a negative RT-PCR result revealed the FCoV present to have multiple mutations in the sequence normally detected by the RT-PCR assay, resulting in its failure. None of the cats without FIP (including those with a positive RT-PCR result) had histopathological evidence of granulomatous disease or positive immunostaining.

RT-PCR has been applied to cytological samples. Most (72–100%) effusions from cats with FIP are RT-PCR positive, compared to only two false-positives out of 76 samples from cats without FIP across three studies (Barker and others 2017, Felten and others 2017c, Stranieri and others 2018). Most (18 of 20; 90%) mesenteric lymph node aspirates from cats with non-effusive FIP are RT-PCR positive (Dunbar and others 2018); however, one false-positive result (out of 20 cats) did occur in a cat seropositive for FCoV. Detection of FCoV in cerebrospinal fluid (CSF) by RT-PCR from cats with FIP is variable, ranging from 21% to 86% (Foley and others 1998, Doenges and others 2003; Dunbar and others 2018), whereas RT-PCR was negative in all control cats. Detection of FCoV in aqueous humour from cats with FIP was poor (25%), and no control cats were tested (Emmler and others 2020).

Additional analysis has been applied to RT-PCR-positive samples to determine whether the FCoV present carries genetic mutations that have been said to be associated with FIP. The use of Spike gene mutation analysis has been most frequently studied for this purpose, albeit using different techniques, different sample types and with different conclusions. Where a highly sensitive method (pyrosequencing) was employed to evaluate the Spike gene, mutations were detected in FCoV-positive tissue from 15 of 17 (88%) samples from cats without FIP as compared to 202 of 206 (98%) samples from cats with FIP (Barker and others 2017). Other techniques (eg, allelic discrimination) that require a relatively high viral copy number in the sample to generate a result (often not present in cats without FIP), and consider a result where sequencing has failed to be negative, will increase the test specificity by a modest amount by reducing, but not eliminating, the number of false-positives; however, the detection of true-positives results in cats with FIP (ie, the test sensitivity) is more markedly reduced (Emmler and others 2020, Felten and others 2017a).

In conclusion, although a positive RT-PCR result on fluid, effusions, aspirates and tissue can provide strong support for a diagnosis of FIP (particularly for CSF), both false positives and false negatives occur such that RT-PCR should not be solely relied upon to make a diagnosis. Furthermore, Spike gene analysis is either of little benefit over RT-PCR at removing false-positives (ie, when pyrosequencing is used), or markedly increases the number of false-negatives (ie, when allelic discrimination is used) and may inadvertently cast doubt on a diagnosis of FIP in a cat with FIP, potentially delaying treatment. Note that RT-PCR of faeces is not a test for FIP, it is a test for FCoV shedding (which can be intermittent). Most cats that have a positive faecal FCoV result will not go on to develop FIP, and only two in every three cats with FIP are shedding FCoV at time of euthanasia (Barker and others 2017). It is only of use in special circumstances (eg, attempting to identify shedders within a multicat household).

In conclusion, although a positive RT-PCR result on fluid, effusions, aspirates and tissue can provide strong support for a diagnosis of FIP (particularly for CSF), both false positives and false negatives occur such that RT-PCR should not be solely relied upon to make a diagnosis. Furthermore, Spike gene analysis is either of little benefit over RT-PCR at removing false-positives (ie, when pyrosequencing is used), or markedly increases the number of false-negatives (ie, when allelic discrimination is used) and may inadvertently cast doubt on a diagnosis of FIP in a cat with FIP, potentially delaying treatment. Note that RT-PCR of faeces is not a test for FIP, it is a test for FCoV shedding (which can be intermittent). Most cats that have a positive faecal FCoV result will not go on to develop FIP, and only two in every three cats with FIP are shedding FCoV at time of euthanasia (Barker and others 2017). It is only of use in special circumstances (eg, attempting to identify shedders within a multicat household).
practice. Cytology typically reveals non-septic pyogranulomatous to granulomatous inflammation; however, this is only documented in 42 to 82 per cent of cats with FIP, and up to 30 per cent of samples from cats without FIP (Giordano and others 2005, Gruendl and others 2017, Felten and others 2018). Positive immunostaining for FCoV antigen can provide further support for FIP. However, as with cytological analysis alone, false-negatives occur in more than 15 per cent of samples from cats without FIP (Felten and others 2018), and 11 to 53 per cent of tissue aspirates (Giordano and others 2005, Felten and others 2019) from cats with FIP, with false-positives reported in around 20 per cent of samples from cats without FIP, including those with neoplasia or vascular disease.

Until recently, histopathology alone (ie, in the absence of immunostaining) was the reference standard for the diagnosis of FIP; however, histopathology can be equivocal or misleading in some cases (Giordano and others 2005, Pedersen 2009, Giuliano and others 2020), particularly where needle-core samples are collected blind. Many now consider the demonstration of FCoV antigen within granuloma-associated macrophages by immunostaining as the reference standard, but it is subject to the similar limitations to histology, albeit with 100 per cent specificity. In a recent large study, only 62 per cent of tissue samples from cats with FIP revealed FCoV-positive lesions (Barker and others 2017). However, it should be noted that all the samples in this study were collected postmortem, visibly normal tissues were frequently sampled in addition to grossly abnormal tissues, and at least one tissue sample per cat was diagnostic for FIP. Wherever possible, grossly abnormal tissue should be sampled to maximise the likelihood of achieving a diagnosis.

Often, and especially in non-effusive FIP, collection of biopsies from tissues with gross lesions is necessary to achieve a definitive diagnosis. In the absence of a definitive diagnosis, or pending confirmatory tests, available results form the basis of discussion as to whether further, invasive investigation is likely to change treatment options and whether to start treatment. This can be frustrated by the geographical restriction (outside the UK) of some tests (eg, AGP, immunocytochemistry, immunohistochemistry, and RT-PCR) that would otherwise be strongly supportive of a diagnosis of FIP. If euthanasia is performed without a definitive diagnosis, postmortem examination is strongly recommended to assess whether gross findings (with histopathology if funds allow) are consistent with a diagnosis of FIP.

**Treatment and prognosis**

Potential alternative diagnoses, such as toxoplasmosis and mycobacterial infection, should be ruled out and a definitive diagnosis of FIP made before considering treatment. However, the reality is that treatment is often started when as close to a definitive diagnosis of FIP as possible has been achieved, taking into account the overall clinical picture alongside owner preferences and finances. A lack of definitive diagnosis makes it impossible to know whether a treatment response indicates efficacy against FIP, or a missed alternative diagnosis. Treatments administered may also interfere with the sensitivity and specificity of future diagnostic test results. A paucity of placebo- or ‘current best-treatment’-controlled clinical trials of cats with definitively confirmed FIP limits treatment recommendations. Currently, no licensed drug is available that has proved effective in curing FIP.

Prognosis for cats with effusive disease is grave, with death or euthanasia within days to occasionally weeks in most cases. The prognosis for cats with non-effusive disease is also poor, with death or euthanasia within weeks to months in most cases. However, it is not necessary to euthanase immediately if the cat still has a reasonable quality of life. It is possible to maintain palliative treatment for as long as weight and activity are maintained. Rarely, some individuals have survived for months to sometimes years, often with supportive treatment, but it is unclear as to whether the treatment administered influenced survival.

**Supportive care**

Treatment is currently limited to supportive care. Cats, once anorexic, can quickly become dehydrated; therefore, simple fluid therapy, correction of electrolyte disturbances, and encouraging them to eat can be extremely useful at improving their quality of life. The value of removing fluid effusions in cats with FIP has been debated. Thoracocentesis is indicated where effusion has resulted in dyspnoea. Abdominocentesis is controversial and may be

---

**BOX 2: RIVALTA TEST**

The Rivalta test is a simple, inexpensive, point-of-care test to differentiate a transudate from an inflammatory effusion. It does not replace more advanced analysis in-house or at external laboratories, but it can facilitate decision-making, particularly in financially constrained settings and where tests to quantify effusion protein concentrations are not available.

The Rivalta test is more useful at ruling out feline infectious peritonitis than ruling it in: over 90% of FIP effusions are Rivalta test positive (Hartmann and others 2003, Fischer and others 2012); positive results are also seen with bacterial peritonitis and neoplastic exudates; and low protein, non-inflammatory effusion (such as those seen with cardiac failure or hypoproteinaemia) are typically negative.

**Method:** Mix 10 ml distilled water with 2 to 3 drops of white vinegar in a test tube or universal container; one drop of effusion is added carefully to the top.

Positive result = the drop of effusion retains its shape and floats slowly to the bottom of the tube or sits on the surface of the water.

Negative result = dispersion of the drop of effusion.

---
**Companion animals**

Detrimental due to exacerbation of dehydration, although some authors have described fluid drainage followed by intracavitary corticosteroid administration.

**Immune-mediated treatment**

Given that FIP has a significant immune-mediated component, treatment to either suppress or modify the immune response can be considered. Corticosteroids are the most frequently used medication, and some cats receive benefit from them, particularly in terms of quality of life. However, there are no controlled studies to prove beneficial effect, only anecdotal reports, and they appear to do very little for the viral infection itself. Doses are empirical (prednisolone 2 to 4 mg/kg/day orally) and can be tapered slowly to response.

**Medical treatment**

Many different drugs have been considered for the treatment of FIP. Cyclophosphamide, ciclesporin A, and anti-TNF-α antibodies have been anecdotally used to prolong survival, but no controlled studies have been performed. Pentoxifylline has also been anecdotally used to manage the vasculitis; however, in a placebo-controlled trial of the related drug, propentofylline, no benefit was found (Fischer and others 2011). Interferons are also commonly used, on the basis of positive anecdotal reports; however, a placebo-controlled clinical trial failed to demonstrate a clinically relevant benefit (Ritz and others 2007). Polyprenyl immunostimulant has limited data to support its use and also has significant limitations (including lack of control treatment group and limited diagnostic criteria for FIP) (Legendre and others 2017); however, it is possible that it may improve survival times in the milder forms of non-ffective FIP without detrimental impact on the patient. Herbal medication has also been suggested for cats with FIP, often with no scientific data to support its use.

**Future treatments**

Recently described promising new, but as yet unlicensed, drugs comprise viral protease inhibitors and nucleoside analogs. FCoVs produce large viral proteins (e.g., the gene encoding polyprotein 1 forms a large component of the FCoV genome; Fig 1) that are cleaved into smaller functioning units by proteases. Therefore, inhibitors of these proteases affect viral production. The protease inhibitor GC376 has produced remarkable responses in both experimentally induced and naturally occurring FIP, with six of eight cats with experimentally induced FIP alive at eight months and 19 of 20 cats with naturally occurring FIP showing a positive response, which was sustained in seven cats (Kim and others 2015, Pedersen and others 2018). The nucleoside analog GS-441524 acts as an alternative substrate and RNA-chain terminator of the viral RNA polymerase, thus interfering with FCoV replication. It too has produced remarkable responses in both experimentally induced and naturally occurring FIP, with all 10 cats with experimentally induced FIP alive at eight months and 26 of 31 cats with naturally occurring FIP having a positive response, which was sustained in 25 cats (Murphy and others 2018, Pedersen and others 2019). Unfortunately, both the protease inhibitor GC376 and the nucleoside analog GS-441524 appear to poorly penetrate the blood-brain and blood-eye barriers, likely accounting for increased likelihood of relapses involving the nervous system or lack of initial response to treatment in study cats presenting with neurological or ocular signs of FIP. The use of higher than previously reported doses of these agents, along with extended courses, have been suggested for cases of neurological or ocular FIP; however, more studies are warranted.

We are aware that, in the absence of commercially available licensed products, some UK cat owners have obtained black-market forms of both GS-441524 and GC376 via the internet for the treatment of FIP in their pet. By their nature, these black-market products are of unknown quality, efficacy, toxicity and longevity, and therefore cannot be prescribed by veterinary surgeons for their patients.

**Supplements**

A ‘nutritional supplement’ (Mutian; Nantong Mutian Biotechnology) containing a novel adenosine nucleoside analogue (Mutian Xraphcnn [Nantong Mutian Biotechnology]; reported to be different to GS-441524) has been marketed worldwide, primarily at cat owners, for the treatment of FIP (Addie and others 2020a). However, there is only limited published research describing its use to stop faecal shedding of virus (Addie and others 2020a). There is currently no peer-reviewed evidence based upon which to recommend its use in cats with FIP. Furthermore, according to both the Veterinary Medicines Directorate (UK) and the Food and Drug Administration (USA), nutritional supplements may not be presented with medicinal claims (e.g., ‘the ability to cure cats of FIP’), otherwise they would be considered as a veterinary medication requiring authorisation.

**Prevention and in-contact cats**

One of the most frequent questions from owners following the diagnosis of FIP in one of their cats is what do with the other cats in the household. For the major considerations see Box 3. As spread of FCoV is most of a concern among large groups, reduction in environmental viral load through improved hygiene is key. Appropriate care in cleaning and use of disinfectants (see Addie and others 2015 for more information) to reduce environmental, including fomites, contamination is
BOX 3: WHEN ONE CAT GETS FELINE INFECTIOUS PERITONITIS, WHAT DO YOU DO WITH THE OTHER CAT(S) IN THE HOUSEHOLD?

- Where more than one cat is being considered (ie, the one with feline infectious peritonitis (FIP) and any in-contact cats), an accurate diagnosis becomes more important in order to guide advice.
- In-contact cats will be at slightly increased risk compared to the general population, particularly if they are direct siblings (estimated 2x risk), due to shared viral, environmental and possibly genetic factors – but none of these can be changed at the time of diagnosis.
- Although cats can pass feline coronavirus (FCoV) that causes intestinal infection between each other, they are not thought to be able to horizontally pass the mutated FCoV that directly causes FIP between themselves (ie, the mutation is a spontaneous event that happens within individuals). Given that the cat with FIP would have had historical intestinal infection with FCoV, it is likely that the other cat(s) in the household would have been infected historically too.
- Removal or isolation of a cat with (suspected/proven) FIP from a household is not indicated, and would likely negatively impact on the sick cat.
- As the household environment (including fomites) is likely contaminated with FCoV (particularly if there are five or more cats in the household, to maintain continuous infection), improved hygiene (particularly regarding the litter tray) is strongly recommended.

Although achievement of a FCoV-free household or kittens (eg, via early weaning) is technically possible, it is not without significant cost and potential welfare concerns – more information can be found in the latest European Advisory Board on Cat Diseases (ABCD) guidelines on FIP (www.abcdcatsvets.org/feline-infectious-peritonitis).

Minimising host risk factors, particularly relating to stress of conflict or overcrowding, is also recommended. Furthermore, in breeding situations where particular sire and queen combinations have resulted in cases of FIP across multiple litters, retiring one or both cats from the breeding programme should be considered in case they are conferring increased genetic risk of FIP.

The FIP vaccine (Felocell FIP; Zoetis), where available, is not recommended for use in cats under 16 weeks age, nor is it considered to be of benefit to cats that are already FCoV antibody-positive cats. Therefore, it is of limited usefulness as initial exposure to FCoV is considered to be much earlier than 16 weeks in most cases. Furthermore, as current serological tests are unable to differentiate vaccinated from naturally exposed cats, it is of no benefit if trying to maintain a FCoV-free household. The FIP vaccine is either ‘not recommended’ or considered ‘non-core’ under current American Association of Feline Practitioners, ABCD, and World Small Animal Veterinary Association vaccination guidelines (and not even discussed in the British Small Animal Veterinary Association’s vaccination guidelines).

Summary

FIP is a common differential for disease in cats, particularly younger animals. Obtaining a definitive diagnosis by minimally invasive means can be difficult, and a balance of probability might need to be used to guide further testing. Although currently treatment is limited, novel antiviral agents show real promise for the future.

References

ADDIE, D., HOUÉ, L., MAITLAND, K., PASSANTINO, G. & DECARD, N. (2020b) Effect of cat litters on feline coronavirus infection of cell culture and cats. Journal of Feline Medicine and Surgery 22, 350-357
ADDIE, D. D., BOUCRAUT-BARALON, C., EGBERINK, H., FRYMUS, T.,
### SELF-ASSESSMENT: UPDATE ON FELINE INFECTIOUS PERITONITIS

In Practice partners with BMJ OnExamination to host self-assessment quizzes for each clinical article. These can be completed online at inpractice.bmj.com

| Question                                                                 | Answer |
|--------------------------------------------------------------------------|--------|
| 1. Feline infectious peritonitis (FIP) is caused by systemic infection with which agent? | a) Aspergillus felis  
   b) Feline calicivirus  
   c) Feline coronavirus  
   d) Feline hepadnavirus |
| 2. Following initial infection with feline coronavirus, what is the most commonly encountered clinical sign to be reported by owners? | a) Abdominal distention (ascites)  
   b) Mild gastrointestinal signs  
   c) Inappetence and weight loss  
   d) Severe lethargy |
| 3. A definitive diagnosis of feline infectious peritonitis can be made based on which clinicopathological result? | a) A positive feline coronavirus RT-qPCR result on a lymph node aspirate  
   b) A severe hyperglobulinaemia due to a polyclonal gammopathy (confirmed by serum protein electrophoresis)  
   c) Positive feline coronavirus antigen immunostaining within granuloma-associated macrophages  
   d) Any of the above |
| 4. Pleural effusion is not an uncommon presentation of FIP. One alternative diagnosis for pleural effusion is congestive heart failure (CHF). Fluid analysis can be very useful in rapidly differentiating between the two. What in-house fluid analysis result would be supportive of FIP rather than CHF? | a) Low cellularity (eg, <5 x10⁹/l)  
   b) High protein concentration (eg, >35 g/l or positive Rivalta test)  
   c) Cloudy appearance on gross appearance  
   d) Normal glucose levels |
| 5. The nucleoside analog GS-441524 has recently been shown to be highly effective in the treatment of FIP. What is its mechanism of action? | a) Prevention of cleavage of the polyprotein into its functional constituents  
   b) Interference with the binding of spike glycoprotein to host cell receptors  
   c) Interference with viral RNA transcriptase, preventing viral replication  
   d) Immune-suppression, via effects on host lymphocyte replication |

---

**Companion animals**

#### Further reading and useful resources

Tasker, S. (2018) Diagnosis of feline infectious peritonitis: update on evidence supporting available tests. *Journal of Feline Medicine and Surgery* 20, 228-243

The most up to date version of the ABCD guidelines on Feline Infectious Peritonitis are available at: [www.abcdatcvs.org](http://www.abcdatcvs.org)

Feline infectious peritonitis