University of Veterinary Medicine Budapest
Department of Pathology

Feline infectious peritonitis: Literature review

Lina Haas

Supervisor: Dr. Szilasi Anna
Senior Lecturer

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Summary

Feline infectious peritonitis is a pathogenic mutation of the highly contagious feline enteric coronavirus and is usually fatal. FIP is considered to be a complex and devastating disease of cats with few effective treatment options, and it still lacks an appropriate diagnostic approach, as our current diagnostic methods and techniques are neither specific nor sensitive enough. Over the years, several treatment protocols, both supportive and symptomatic, have been tested to combat FIP but none of them have shown promising results. One exception is the new nucleoside analogue GS-441524, cats treated with this compound have shown promising results in several studies. However, GS-441524 has not been approved for the use in veterinary medicine in most of the countries and is not currently licensed or legally available on the market.

To evaluate the use of GS-441524 as a possible therapeutic approach for the treatment of FIP, this study reviews the available literature.

Összefoglalás

A macskák fertőző hashártyagyulladása (feline infectious peritonitis, FIP) a macska enterális coronavírusának egy mutációja, és legtöbbször fatális kimenetelű. A FIP a macskák összetett és pusztító betegségének számít, amelynek kevés hatékony kezelési lehetősége van, és még mindig nincs megfelelő diagnosztikai megközelítés sem, mivel a jelenlegi diagnosztikai módszereink se nem elég specifikusak, se nem elég érzékenyek. Az évek során számos támogató és tüneti kezelési protokollt teszteltek a FIP leküzdésére, de egyik sem mutatott ígéretes eredményt. Az egyik kivétel az új nukleozid analóg GS-441524, az ezzel a vegyülettel kezelt macskák több vizsgálatban is ígéretes túlélési eredményeket mutattak. A GS-441524-et azonban az állatgyógyászatban még nagyon kevés országban engedélyezték csak, így jelenleg nem elérhető legálisan a piacon legtöbbünk számára.

Ez a szakdolgozat áttekintést nyújt a macskák enterális coronavírusáról, különös tekintettel a GS-441524 FIP kezelésében való lehetséges terápiás megközelítéséről.

Table of content

List of abbreviations

AFAST	Abdominal focused assessment with sonography for trauma, triage and tracking
AGP	Alpha-1-acid glycoprotein
CBC	Complete blood count
CCoV	Canine Coronavirus
CSF	Cerebrospinal fluid
DC-SIGN	Lectin dendritic cell-specific intracellular adhesion molecule-3-grapping non-integrin
FCoV	Feline Coronavirus
FECV	Feline Enteric Coronavirus
FIP	Feline Infectious Peritonitis
FIPV	Feline Infectious Peritonitis Virus
FISS	Feline Infection Site Sarcoma
GS	GS-441524
HCoV-229E	Human Coronavirus 229E
HCoV-NL63	Human Coronavirus NL63
IBD	Inflammatory Bowel Disease
IFN-alpha	Human interferon alpha
IL-1 beta	Interleukin 1 beta
LR	Likelihood ratio
NPV	Negative test result
ORF	Open Reading Frame
PEDV	Porcine Epidemic Diarrhea Virus
PI	Post Infection
PM	Post Mortem
POCUS	Point of care Ultrasound

RT-PCR	Real time reverse Transcriptase – Polymerase Chain Reaction
RTCA	1-beta-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide
TCB	True Cut Biopsy
TFAST	Thoracic focused assessment with sonography for trauma, triage and tracking
TGEV	Transmissible gastroenteritis virus

List of figures

1 Introduction – description of the disease and its significance

Feline infectious peritonitis (FIP) is a perplexing and often devastating challenge to feline health. While the enigmatic nature of the disease has hindered our understanding, it is in the area of treatment that our greatest concerns lie. FIP, caused by a specific variant of the feline coronavirus (FCoV), remains a formidable adversary for veterinarians and cat owners alike. The focus of this thesis is to explore and review various treatment strategies with an emphasis on new developments in antiviral drugs. By exploring the origins and clinical manifestations of FIP and evaluating new treatment modalities, we aim to provide valuable insights for veterinary professionals and concerned pet owners seeking improved therapeutic options.

In order to understand the underlying issues in the management of FIP, we must first focus on the difficulties posed by its aetiology. FIP belongs to the genus *Coronaviridae*, the feline coronavirus, which can be divided into two strains. FIP is a pathogenic mutation of the mostly asymptomatic feline enteric coronavirus (FECV). FECV is mainly shed in the faeces and infects rapidly by the faecal-oral, nasal or transplacental route. Due to the mutation of the predominant pathotype FECV, FIP develops and can occur in different forms (wet and dry) and causes severe systemic infections and changes in many organs (most commonly the peritoneum). Immunosuppression and overcrowding can predispose cats to the highly fatal disease.

The diagnosis of FIP can be considered challenging as there are many differential diagnoses that fit the clinical signs and history of FIP. There are several tests that can be used to diagnose feline infectious peritonitis, but they are not able to provide a direct diagnosis of FIP.

The management and treatment of the disease can also be challenging as there are no approved drugs on the current veterinary market. There have been several different treatment protocols over the years, but none have shown successful results. There is currently an antiviral drug, the nucleoside analogue GS-441524, being developed by Gilead Sciences®. Years of studies have shown promising results. Unfortunately, the drug has not been approved by the FDA, which is why many owners buy it illegally from the internet.

The aim of this thesis is to gain a better understanding about the disease, its diagnostic techniques and treatment approaches.

2 Aetiology

Feline infectious peritonitis virus (FIPV) belongs to the genera *alpha-Coronavirus,* which is closely related to other coronaviruses such as porcine transmissible gastroenteritis virus (TGEV), canine coronaviruses (CCoVs) and some more remotely related species such as porcine epidemic diarrhea virus (PEDV), human coronavirus 229E (HCoV-299E), human coronavirus NL63 (HCoV-NL63) [13]. Feline coronavirus is a positive single-stranded RNA virus that consists of two different serotypes, serotype 1 FCoV, which is more common in Europe and America and serotype 2 FCoV, which is less common in Europe and America but has mostly been observed in Asia [13]. The FCoV genome varies in over 29000 nucleotides and 11 open reading frames (ORFs) which are encoding for structural, non-structural and accessory genes [10]. The crown-like shape of the coronavirus is due to the protrusion of the peplomers from the viral surface and leads to the name coronavirus [3]. A complementary ligand on the spike or surface protein "S" is required for coronaviruses to attach to specific cell receptors. Once attached to the specific cell receptors, the CoV fuses with the cell membrane. Two heptad regions belong to a special fusion peptide which is located in a separate fusion domain makes fusion possible [10].

Cats can become infected with the CCoV through contact with infected dog faeces. Antibodies to CCoV can neutralise FCoV serotype 2, but they cannot neutralise FCoV serotype 1, because the FCoV is genetically more closely related to CCV [3]. Feline coronaviruses can be diversified into two separate biotypes based on their pathogenicity: Feline enteric coronavirus and Feline infectious peritonitis virus, and both of them exist in serotype 1 and 2 [13].

2.1 FECV

Feline enteric coronavirus (FECV) causes infections in wild and domestic *Felidae* worldwide. The seropositivity rates in domestic cats are about 20–60%. In animal shelters and in multi-cat households the seropositivity rates may be as high as 90% [13]. FECV is the enteric biotype of FCoV, also known as the avirulent pathotype, and exists in both serotypes 1 and 2. It infects the enterocytes and can cause mild but usually self-limiting infections [7]. Feline enteric coronavirus spreads by the oral-faecal route. Oral infection in young kittens results in a reduction in maternal antibodies, which can lead to severe enteritis, possibly catarrhal or haemorrhagic. Oral infection in older cats usually results in only mild clinical signs such as transient anorexia [13].

2.2 FIPV

Feline infectious peritonitis, like FECV, exists in both serotypes 1 and 2. Serotype 1 consists of a distinct feline spike protein, whereas serotype 2 is a recombination of the canine and the feline spike proteins of coronaviruses. The FIPV is a mutation of the harmless enteric FCoV that occurs during RNA replication. The feline coronavirus mutation occurs mainly in the intestinal tract of young and immunocompromised cats, leading to infection and replication in macrophages and monocytes. Macrophages transport the mutated coronavirus to its target organs such as the pleura, peritoneum, nervous system, kidneys, and the uvea. This leads to immune-mediated vasculitis, exudative fibrinous polyserositis and perivascular pyogranulomatous inflammation. These processes occur as a result of the cat's immune response to the virus [9][12].

3 Transmission

The FECV and FIP are a worldwide problem in multi-cat households, animal shelters, catteries, and pet shops, all places where cats are kept in a confined space. Due to the changes in domestic cat management and the introduction of litter boxes, cats are increasingly kept indoors, resulting in increased exposure to FCoV [3].

Feline coronavirus is highly infectious but largely asymptomatic despite systemic infection. Transmission of the mutated FCoV that causes FIP is improbable under natural conditions. However, transmission may occur iatrogenically or under experimental conditions [3].

Indirect fomite transmission is also possible via clothing, toys, and grooming equipment. Rarely, transmission can also occur via other excretions such as saliva, respiratory secretions, and urine. Transplacental transmission is possible; the virus has been found in 4-day-old, stillborn and weak newborn kittens [3].

Direct transmission of feline infectious peritonitis virus (FIPV) occurred in a Taiwanese shelter where 5 kittens were introduced into a shelter with no history of FIP before [16]. Type 2 FIPV was detected in all of the FIP cats that died. This suggests that horizontal transmission of the mutated FIPV is possible [16].

3.1 Infection

Infection generally occurs via the faecal-oral route and the virus mainly infects enterocytes [5]. It can also occur nasally or transplacentally. Cats become infected with non-pathogenic FCoV through the shedding of FCoV-containing faeces. The main source of the infection is

litter boxes used by both infected and uninfected cats, which can lead to continuous re-infection of the cats [3].

3.2 Shedding

The shedding of FCoV mainly takes place with the faeces [5]. During the early infection, the FCoV is shed in saliva and respiratory secretions due to the virus replication in the tonsils. The virus can also be shed in the urine. Shedding of FECV begins within a week and can be transient, persistent, recurrent, or chronic over months to years [9]. This is the source of reinfection in cats.

Initial infection with FCoV in a multi-cat household results in infection of all cats and the development of antibodies against the virus. The correlation between the shedding frequency and intensity of shedding and high antibody titers is well established [5]. One third of FCoV antibody positive cats shed the virus and antibody negative cats do not shed the virus [3].

4 Pathogenesis

FCoV replicates in the cytoplasm of enterocytes and causes destruction of intestinal epithelial cells. It usually causes asymptomatic infection or mild diarrhea. The mutated FCoV replicates in the monocytes and macrophages and can lead to FIP.

The infection of FCoV happens through the oronasal route and the replication takes place in the tonsils and the small intestine of the body, causing viremia, leading to mild enteritis with or without clinical signs. Infectious outcome is dependent on virulence and virus dosage. High virulence or a mutant virus load of five percent or more results in cell-attached viremia in monocytes and macrophages, leading to systemic infection. A weak T-cell immunity but a strong antibody response leads to the acute, effusive, wet FIP, resulting in type 3 hypersensitivity due to immune complexes. These immune complexes develop via Ig Fc receptors and lead to apoptosis of activated T-cells and release of vasoactive molecules (virokins). Moderate T-cell immunity within the cell-attached viremia leads to the non-effusive, dry FIP, which belongs to the type 4 hypersensitivity, which is cell-mediated with a low antibody response. If the viral load is low and no mutation is identified, clinical recovery occurs through a strong local or T-cell immunity, resulting either in virus elimination (95% of reported cases) with a healthy and virus free cat, or in a persistent infected but otherwise healthy cat (5% of reported cases). Persistently infected felines are at risk of developing FIP through mutation. T-cells are white blood cells involved in both adaptive and innate cell-mediated immunity in naturally occurring FIP. When infected with FIPV, cats show a rapid depletion of T-cells in the spleen, blood, and mesenteric lymph

nodes. It is thought that the innate immune system is less able to attack the virus due to the depletion of the T-cells and NK cells [10].

Around 5 to 10 percent of FCoV infections results in feline infectious peritonitis, infected cats start shedding the virus two days post infection. Initial viral shedding does not always lead to seroconversion: If patients do not seroconvert, studies show that viral shedding decreases over time. At one-month post-infection, shedding ceased in about 58% rising to up to 95 percent after nine months. 13 percent of the infected cats remain carriers for their whole life, while 4 percent gain full resistance. Seropositivity can be reported in 5-12% of infected cats, usually around month 4-8 [10].

4.1 FECV

Feline enteric coronavirus is highly contagious and is transmitted horizontally via the faecal-oral route. It most commonly infects young kittens through the litter and faeces of their FECV-infected mother [3][13].

Cats ingest the virus, and it replicates in the villous epithelial cells of the small intestine. FECV infection is usually asymptomatic or causes mild enteritis, rarely severe enteritis or even death. It usually goes undetected. A symptomless persistent infection resembles natural infection and the virus can be detected in faeces a few days post-infection (PI) [13]. In addition to detection in faeces, viral RNA can be detected in the blood. Seroconversion occurs within 10 days after infection.

Acute infections with feline enteric coronavirus consist of a tropism for the apical epithelium of intestinal villi from the lower part of the small intestine to the caecum. The lower part of the gastrointestinal tract is the main site of viral replication, although coronaviruses have been detected in blood, tissues, and throughout the gastrointestinal tract. Feline enteric coronavirus is associated with the intestinal tract, but can also infect monocytes and therefor spread throughout the whole body [13]. This phenomenon makes the diagnostic approach more difficult differentiating FCoV and FIPV infection.

Aminopeptidase-N is found in the intestinal brush border and is an enzyme of the specific receptors for FCoV 1 [13]. This enzyme is a cell surface metalloprotease that acts as a cellular receptor for the FCoV and is mainly assigned to the S protein [13][9]. FCoV may block the aminopeptidase-N and therefore prevents the virus to attach to the cells but enhances the virus uptake by macrophages [9].

4.2 FIPV

Feline infectious peritonitis virus is a sporadic, non-infectious disease that affects 5–10% of cats of certain breeds and ages that are persistently infected with FECV [3]. While FECV infection has a high incident in cats of various ages and breeds, FIP is a relatively rare finding with disastrous consequences for patients. FIP does not focus on singular organs instead affecting multiple organ systems, inducing a fatal immunopathologic disease [1].

The working theory regarding the FECVs shift in tropism, losing affinity for enterocytes and in turn gaining affinity for macrophages, postulates that the location inside the infected individual where the mutation occurs is not yet known and can only be theorised. A possible place for an intermediate location where this shift in tropism could take place would have to be between the former affected location, the intestine (enterocytes), and the new affected location, the macrophages. As blood macrophages and monocytes can be infected during FECV infection, they could provide the missing link between the intestinal wall and soft tissues. Since FIP has an affinity for the endothelium and is typically not generalised but focused on multiple lesions, the target cells for FIP, cannot be general macrophages but instead precursors with a high affinity for these target locations [10].

Based on the molecular pathogenesis we can determine the difference between FECV and FIPV is that FIP is associated with mutations within the accessory genes, most commonly the 3c and 7a/b genes, and the S gene of FCoV [13]. FECVs always contain an intact 3c gene, studies have shown [10]. More than two thirds of 3c sequences enclose deletions or point mutations. These mutations were thought to be the virulence markers of FIP. This hypothesis is confirmed by more recent studies. Virus isolation differs between FECV and FIPV. FECV is isolated from the gut and FIPV is isolated from the gut, organ lesions and effusions [13]. For the viral replication within the gut, it is necessary to have an intact 3c gene but for the systemic viral replication of FIP it is not necessary to have an intact 3c gene. The surface spike or protein is responsible for the specific receptor binding and entry of coronaviruses. If the S gene contains a mutation it can contribute to a biotype switching and target cell tropism [1][13]. Mutations of the S genome can occur alone or in combination. The identification of two point mutations within the S genome has been demonstrated in studies analysing 11 FECV and 11 FIPV genomes [1]. The mutation results in changes in amino acid position, (M1085L) means a Met to Leu substitution at position 1058 and (S1060A) the substitution of Ser-to-Ala at position 1060 [1].

4.3 Occurrence of Mutation

The current estimated error rate of RNA polymerases, which catalyse the transcription of RNA polymer DNA templates, is estimated to be 1/10000 nucleotides [10]. There is always a potential for FIPV to develop within an FCoV infection. The genome of the parental virus and the genome of the mutant virus are 99,5% homologous when compared [3]. Due to the change in the surface structure of the virus caused by the mutation, the virus can be phagocytised by the macrophages and bind to the ribosomes inside the macrophages. This process is one of the key events in the pathogenesis of FIPV. Certain breeds and younger age may be a predisposing factor for these mutations, as well as the immune status of the cat; cats infected with feline leukaemia virus (FeLV) or feline immunodeficiency virus (FIV) have a suppressed immune status, glucocorticoid treatment, stress, surgery, and the virulence and dosage of the virus may predispose cats to develop FIP due to an increased FCoV replication in the intestine [3].

The first gene linked with conversion of FECV to FIPV was the accessory gene ORF 3c, and later studies have confirmed similar findings. At least two-thirds of FIPVs have mutations in the ORF 3c gene that cause premature stop codons and frame shifts, as well as nucleotide deletions and insertions, resulting in truncated protein production. The third, unaffected by truncating mutations, has a higher number of nucleotide substitutions, which leading to an accumulation of non-synonymous amino acid substitutions in the 3' end of the gene [10]. Spontaneous mutations causing gene deletion also occurs in the ORF genes 7b and 7a. The accessory ORF gene's function is unknown. One of the most frequently observed mutations demonstrated in the study of Chang et al. were single-nucleotide mutations in the S gene encoding the fusion peptide, which may also be involved in the macrophage tropism [1]. During the early conversion of FECV to FIPV mutations at the S1/S2 cleavage site were shown to occur. This mutation allows a better replication of the virus in monocytes and macrophages [7].

4.4 Development and antibody enhancement

FCoV requires receptors to enter host cells. FIPV type 2 uses an enzyme called aminopeptidase-N to enter the host cell, and the FIPV type 1 receptor is not known, so it needs a co-receptor. Using the lectin dendritic cell-specific intracellular adhesion molecule-3-grapping non-integrin (DC-SIGN, CD 209) as a co-receptor, FIPV type 1 is able to enter the host cell [10]. These receptors and co-receptors allow FECV to bind to target enterocytes.

Fc-receptors, which are important for the complement binding and may play a role in FIPV entry into the target macrophages, are generally less specific.

The development of FIP depends on the immune status of the cat and is not caused by the virus itself. Involving of viral antigen, antiviral antibodies or virus and complement, FIP is an immune complex disease. FIP can be caused by various hematogenic immune complexes that cross from the blood into the endothelium, all causing granulomatous changes. Along with the first alternate, FIP could be caused by FECV-infected macrophages and monocytes leaving the bloodstream and entering various tissues have been identified as the target cells of FIPV. Granulomatous changes may develop due to an increase in neutrophils and macrophages on the side of the lesion as the virus attracts antibodies and complement. The mutated virus can be found around 14 days after the mutation happened in the region of abdominal organs such as the intestinal lymph nodes, spleen, liver, caecum, colon and the central nervous system (CNS) [3][13].

Cytokines such as IL-1ß, adhesion molecules (CD11b, CD18) and tumor necrosis factors are expressed by circulating monocytes which facilitate the interaction of monocytes with the activated endothelial cells in veins [13].

The cellular and humoral immune response decide the clinical course of the disease. The wet form of FIPV is associated with a strong B-cell response but has a weak cellular immunity. Unlike the wet form, the dry form of FIPV has a strong T-cell immunity. FIPV is controlled by a strong cellular immune response [13].

5 Clinical signs

Due to the accumulation of antigen-antibody complexes within the vascular epithelium, the immunological response of cats to the virus results in clinical signs and immune-mediated vasculitis. These clinical signs and symptoms of FIP can be divided into 3 forms which can easily change into each other. There is the wet effusive/exudative form, the dry non-effusive/exudative form, and the mixed form. The early clinical signs of FIP are non-specific and usually depend on the immune status of the cats and the virulence of the virus. They include pyrexia of unknown origin, usually below 40°C, anorexia, weight loss and gastrointestinal signs such as vomiting and diarrhoea [8]. Loss of appetite may be seen in some cats and an increase of appetite may be seen in others. If these clinical signs are seen in a cat, FIP should be considered as a differential diagnosis [3].

5.1 Effusive “wet” form

The effusive “wet” form of feline infectious peritonitis is considered to be a type 3 hypersensitivity reaction which may lead to vasculitis and granuloma formation [4]. Moreover the wet form tends to develop in the end stage of dry FIP likely due to an immune system suppression [13]. High protein effusions may lead to fibrinous peritonitis, pleuritis and rarely to fibrinous pericarditis. These occur in the abdominal cavity the pleural space as well as the pericardium. Ascites is often seen as a clinical sign in FIP (Figure 1 and 2). Organ involvement can lead to extensive damage and loss of function in gastrointestinal, respiratory, and genital organs. Liver involvement can lead to hepatitis, hyperbilirubinemia, and jaundice. Gastrointestinal involvement may cause vomiting and diarrhoea. Respiratory distress due to pleural effusion leads to dyspnoea (open-mouth breathing), tachypnoea and cyanotic mucous membranes. Scrotal swelling occurs due to extension of the peritonitis into the genital tract, leading to oedema within the scrotum in intact males [3].

Abdominal distension and pot belly may be observed by the owner (Figure 1). Palpation of the abdomen is not painful, and, in some cases, fluid may be palpated between the intestinal loops. Massive invasion of organ tissue can also lead to complete failure. This is most commonly seen in the liver and kidneys.

The course of the wet form of FIP is often quite acute and progresses within a few days or weeks, severely limiting the survival rate of the diseased cats.

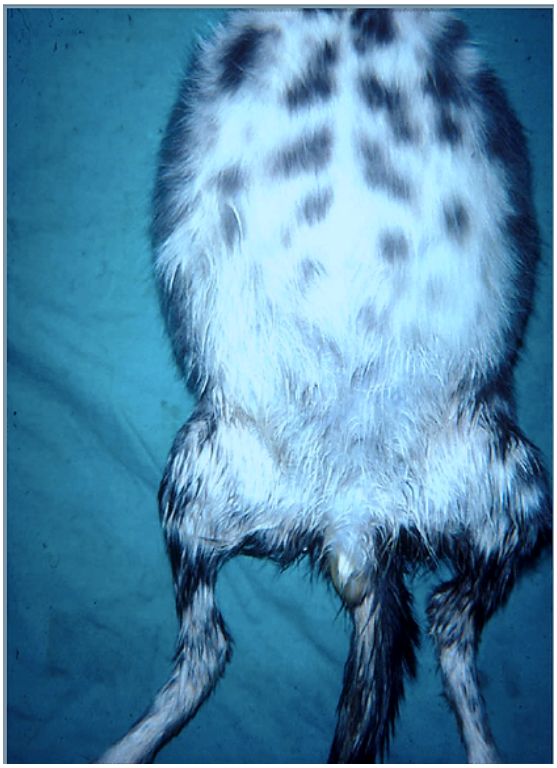

Figure 1 Distended abdomen (pot belly) of a cat with effusive FIP [9]

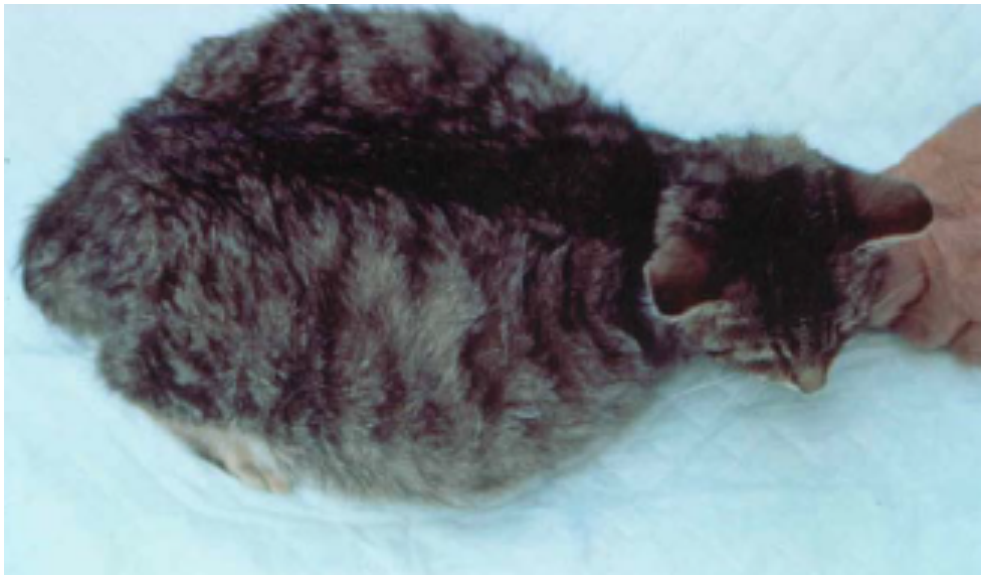

Figure 2 Cat with ascites caused by FIP [3]

5.2 Parenchymal “dry” form

The course of the non-effusive/exudative, granulomatous and parenchymatous dry form of FIP is considered chronic and progresses over weeks to months. Granulomatous changes can be observed in multiple organ systems including the eyes, central nervous system, gastrointestinal tract, and abdominal organs. It leads to pyogranulomatous inflammation in the affected organs. Affected kidneys have a nodular structure, nephromegaly and glomerulonephritis can be detected (Figure 3). Responsible for the glomerulonephritis are immunocomplexes. Granuloma formation in the gastrointestinal tract may lead to obstipation, obstruction, vomiting and diarrhoea. It is most commonly observed in the ileocaecal region, but can also be seen in the colon or small intestine [3]. Caeco-colic lymphadenopathy which is associated with signs of ulcerative colitis is a specific form of dry feline infectious peritonitis.

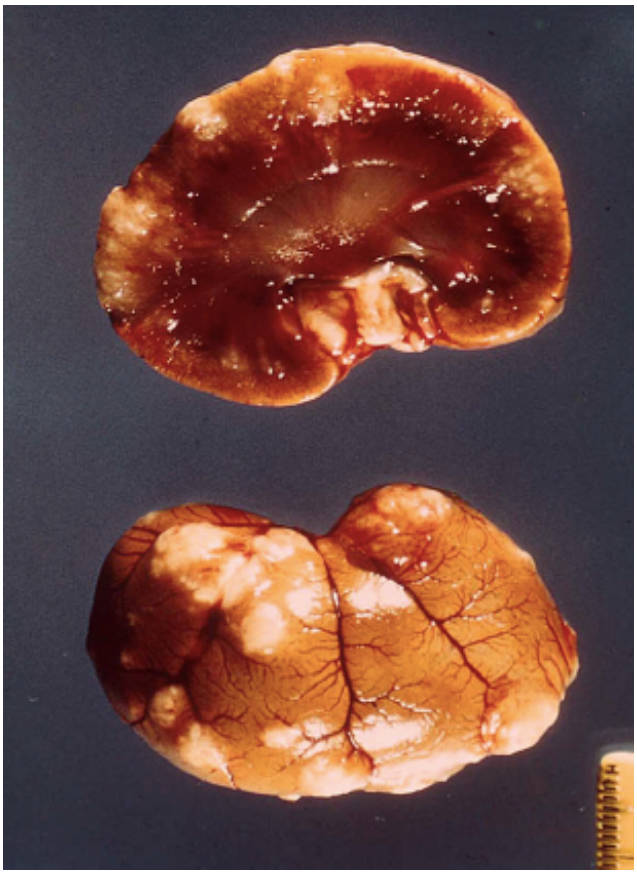

Figure 3 dry FIP - cross section of a kidney [9]

Skin signs such as cutaneous lesions can be overserved in cats diseased with FIP. Skin fragility syndrome of cats can be observed in middle to older aged cats and due to minor traumas it causes damage to the skin [15]. Poor hair coat, non-pruritic intradermal papules and priapism can be seen in cats diseased with FIP.

Ocular signs often occur in cats diseased with FIP. Retinal changes are one of the most common signs within FIP and can lead to fuzzy greyish lines in the blood vessels which arises from cuffing of the retinal vessels (Figure 4). Retinal detachment and haemorrhages are also signs of retinal changes due to FIP. Inflammation of the uvea, uveitis including the iris, ciliary body and choroidal vessels can be found (Figure 4). Bilateral uveitis is most common and, if mild, may cause colour changes. If the aqueous humour is tagged it may demonstrate an increase in protein and pleocytosis. Due to the increase in protein and cellular content in the aqueous humour aqueous flare and cloudiness in the anterior chamber can be seen (Figure 5). Keratic precipitates in the caudal cornea happens due to increased number of inflammatory cells in the anterior chamber [3]. Focal lesions in the iris can cause changes in the shape of the pupil.

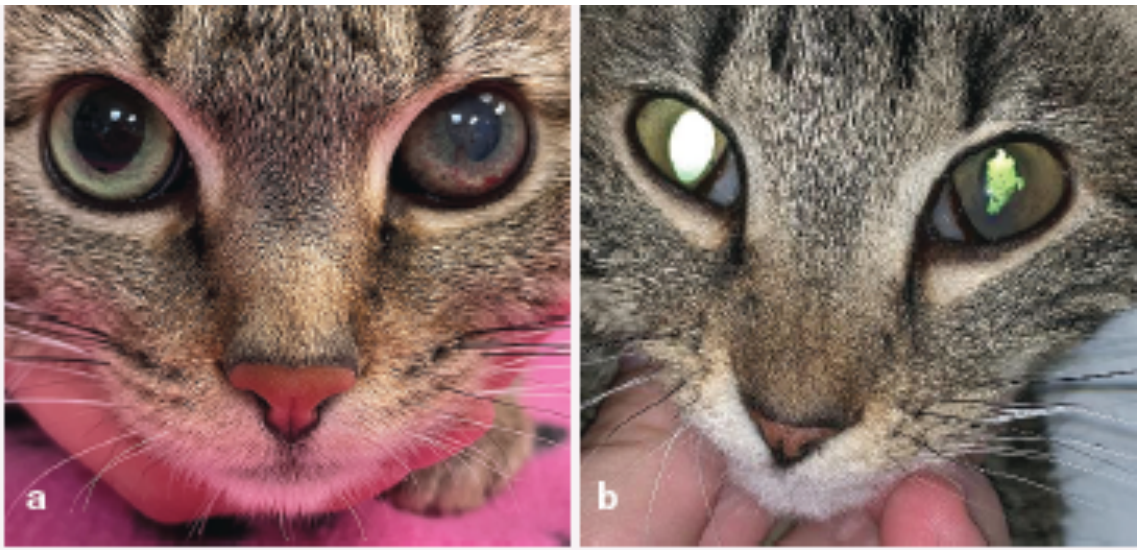

Figure 4 Difference in the clinical presentation of anterior uveitis which is caused by FIP [14]

Figure 5 Cat with anterior uveitis and corneal oedema [14]

Some patients exhibit neurological changes, including incoordination – ataxia, seizures, central vestibular signs such as nystagmus, head tilt, circling and an obtuse appearance, and behavioural changes such as aggressiveness, hiding, and rage [14].

The peripheral nerves defects affect the spinal column causing lameness, progressive ataxia, tetraparesis, hemiparesis or paraparesis. Defects of the cranial nerves can induce visual deficits and loss of the menace nerve. Hydrocephalus is detected in 75% of 24 cats examined. Neurological signs are in up to 13% of cats with FIP [3][4].

6 Pathology

The main features of FIP are fibrinous granulomatous serositis, protein-rich serous effusion and pyogranulomatous lesions arising from central aggregates of macrophages (Figure 6). Multiple organ systems are involved in FIP. Due to the small size of the lesions, histological examination is required for the final identification.

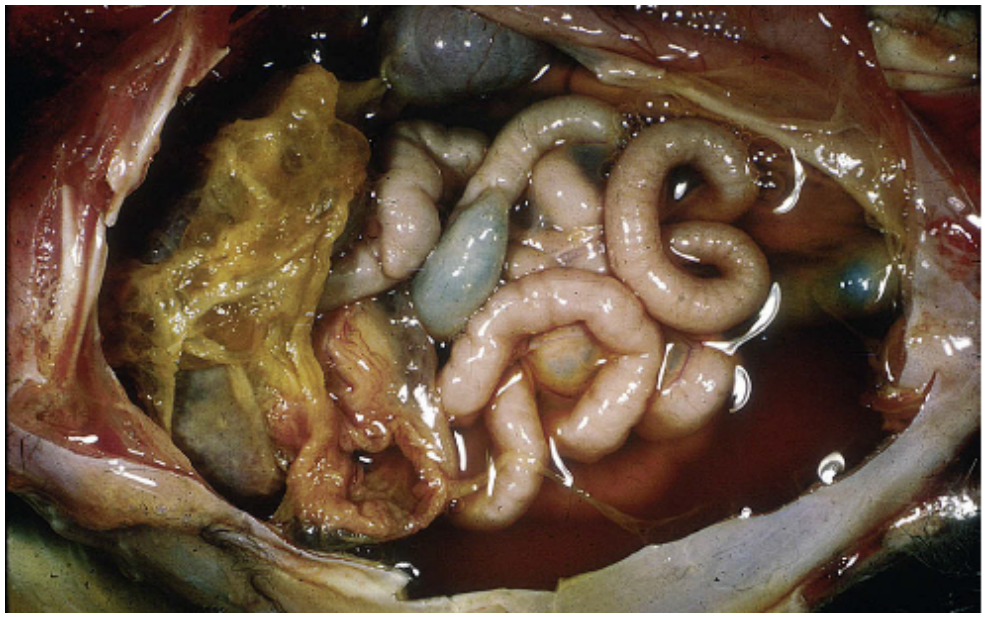

Figure 6 Effusive FIP: abdominal viscera of a cat, fibrinous plaques on serosal surface of the intestines and spleen. classic pyogranulomas of effusive FIP [9]

On post-mortem examination the mixed form is more common. Effusion is seen together with parenchymal and serosal lesions. Furthermore, 4 types of lesions can be identified. Granulomas may be seen with or without necrosis, perivascular B-cell and plasma cell infiltrates, diffuse changes on the serosal surface and phlebitis which may be granulomatous – necrotizing. All of these may be seen alone or together [5]. Peritoneal involvement occurs in 75% of infected cats, abdominal effusion in 69% and sometimes pleural effusion. One of the most commonly affected organs is the kidney, followed by the eyes and the CNS (Figure 7). Ocular lesions occur in 29% of infected cats and are bilateral in 68% [5]. The tunica vaginalis can also be affected by the virus. In FIP, vasculitis is usually confined to small to medium sized veins in the leptomeninges, renal cortex, eye and rarely in the liver and lungs. Pyogranulomas result from a central aggregation of macrophages and are surrounded by inflammatory exudate containing neutrophils and macrophages with a dispersion of T-lymphocytes and plasma cells [9]. In wet FIP, macrophages contain a high concentration of antigen. Pyogranulomas follow the cranial mesenteric artery and invade the omentum and

the serosal surface of the abdominal viscera. The underlying organ parenchyma or muscle is infiltrated by focal lesions of phlebitis, inflammatory cell infiltrates, oriented to the surface. Oedema, hyperemia, fibrin deposition, protein exudate and necrosis are more common in the wet form of FIP than in the dry form. In the dry form of FIP, the vessels are surrounded by foci of macrophages. Plasma cells and lymphocytes surround these foci. Extraperitoneal abdominal and pleural lesions penetrate the parenchyma along the vessels (Figure 7). Granulomas may be confused with cancer as they may vary in size and diameter. The lesions are most seen in the abdomen, as in wet FIP, but in dry FIP the CNS and the eyes are more commonly involved. Within the central nervous system, the meninges, leptomeninges, ependyma, brain, spinal cord, and spinal nerves are most involved in the posterior ventral aspect of the brain. Ocular lesions include anterior uveal infiltration by lymphocytic and plasmocytic cells, which may be nodular or diffuse, resulting in iris discolouration and oedema. Keratic or mutton fat percipitates may be seen on the caudal side of the cornea (Figure 8)[9].

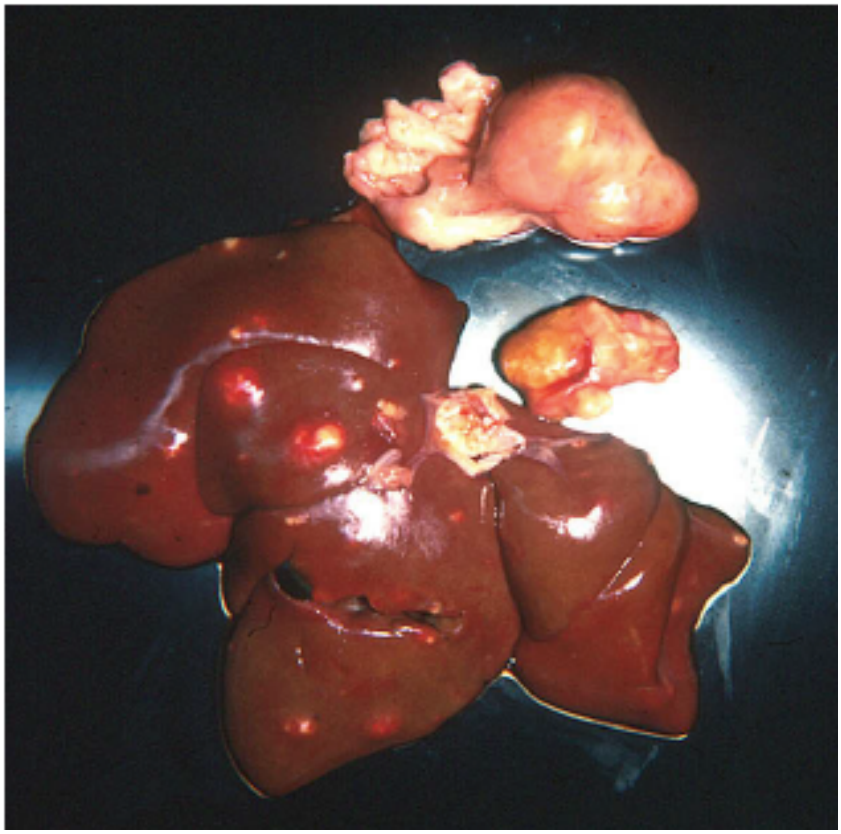

Figure 7 Cat with dry FIP, showing its hepatic and mesenteric lymph nodes and liver [9]

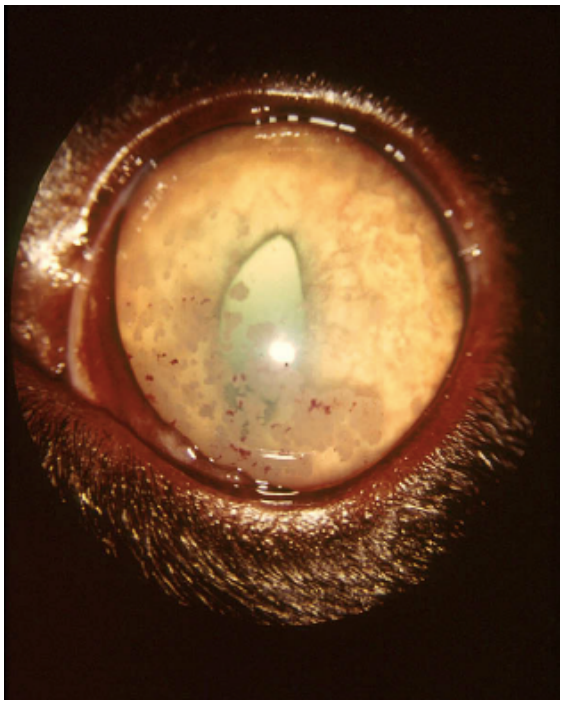

Figure 8 Keratic precipitates on the cornea of a cat with non-effusive FIP [9]

The mixed form of FIPV, includes lymphoid lesions. Enlargement of the spleen may be caused due to infiltration of the red pulp by histiocytic and plasmacytic cells or because of hyperplasia of lymphoid components within the white pulp. Fibrin deposition may lead to necrotic splenitis. Abdominal and thoracic lymph node enlargement may be observed [9]. Within the lymphoid tissue there is a depletion of the T and B cells which includes massive to complete thymic atrophy or involution. The incubation of neutral FIP infection is not understood.

7 Diagnosis

The diagnosis of FIP is a combination of the patient history, clinical signs, and diagnostic testing of the cat. It can be straightforward if the typical signs and effusion are present, otherwise it can be challenging. The clinical signs of FIP can be systemic or organ specific. Within the history a few risk factors of the development of FIP can be identified such as the breed, age, sex and neuter status, housing conditions, stress, and retroviruses [14]. A common way to diagnose FIP is through exclusion of various differential diagnoses, which include but are not limited to septic peritonitis and pleuritis, neoplasia such as lymphomas (common symptoms are involvement of multiple lymph nodes and organs), toxoplasmosis, pancreatitis (abdominal effusion), lymphocytic cholangitis (increase in liver enzymes, jaundice and hyperbilirubinemia, also associated with IBD), congestive heart failure

(pericardial effusion, heart murmur and gallop rhythm), mycobacteriosis (fever, lymphadenopathy, respiratory signs, masses in the abdomen and uveitis), and trauma can be a differential diagnosis as well [14].

7.1 Physical examination

Cats diseased with FIP most commonly show non-specific clinical signs such as, lethargy, anorexia, weight loss or failure to gain weight in case of young cats/kittens, fever usually below 40°C, jaundice, lymphadenopathy, and pale mucous membranes. In addition, cats infected with FIP may show abdominal distension, ascites, signs of respiratory distress such as dyspnoea and tachypnoea, cardiac tamponade and heart failure due to pericardial effusion, scrotal enlargement, neurological signs such as seizures, dementia, aggression, central vestibular signs, ocular changes and dermatological changes may be present [14].

7.2 Laboratory changes

A secure diagnosis is only possible through laboratory work, a short example of which is listed below.

The diagnostic tests for FIP are described by statistical terms like sensitivity which describes the ability to recognize cats diseased with FIP, specificity describes the ability to recognize cats not diseased with FIP, predictive value shows the probability of cats with a positive test result (PPV) or the probability of cats with a negative test result (NPV), LR (likelihood ratio) and diagnostic accuracy (true positives added to true negatives divided by the total number of test results). Sensitivity, specificity and likelihood ratio are not influenced by the prevalence but the predictive value is [14].

For the routine diagnostic of FIP the usage of multiple tests is necessary. In FIP diagnosis, blood tests such as AGP (alpha-1-acid glycoprotein), CBC, and serum biochemistry play a crucial role. An AGP level exceeding 1.5 g/l indicates a likelihood of FIP, while levels surpassing 3.0 g/l strongly suggest an FIP infection. The CBC does not provide specific FIP findings, but it often shows non-regenerative anemia, lymphopenia, microcytosis, thrombocytopenia, and band neutrophilia, which support the diagnosis.

Serum biochemistry results may reveal hyperglobulinemia, hypoalbuminemia, hyperbilirubinemia, and a low albumin to globulin ratio [14][2]. However, it is essential to remember that these laboratory findings alone cannot definitively diagnose FIP, as similar changes can occur in various systemic diseases [2]. Changes in the complete blood cell count

and coagulation parameters can also be observed, including increased or decreased leukocyte counts, lymphopenia, neutrophilia as shown by a stress leukogram, and anemia, which can be regenerative or non-regenerative. Non-regenerative anaemia is usually caused by chronic inflammation, and regenerative anaemia is usually caused by a secondary autoimmune haemolytic anaemia, leading to a positive Coombs test. Hemolysis occurs due to a large number of Heinz bodies found in cats with extensive intestinal changes. As a result of DIC (disseminated intravascular coagulopathy), thrombocytopenia occurs in cats with FIP. Additionally, serum protein concentration often increases in FIP, with hypergammaglobulinemia being a common finding due to a specific anti-FCoV immune response. It is worth noting that while hypergammaglobulinemia and antibody titres correlate, the latter can vary with gamma globulin concentration [3].

7.3 Test on effusion fluid

The most frequently used test, due to its simple, quick, and inexpensive nature is the Rivalta's test [2]. The test is used to differentiate between fluids with high protein content and presence of inflammatory mediators (like FIP effusion) and those who do not contain proteins. If the fluid contains a high enough protein content, the droplet that is given into an acetic solution will precipitate making the test positive. If the droplet disappears completely and the solution is clear the Rivalta's test is considered to be negative and its unlike that the cat is infected with FIP.

An easy way to rule out various differential diagnosis like septic effusion or neoplasia is through the effusion fluids cell count and cytology. FIP usually presents with low to moderate cellularity as well as pyogranulomatous inflammation.

Another way to rule out septic effusion is bacterial culture which is usually negative in FIP and positive in septic effusion. While the albumin to globulin ratio as well as the AGP has been discussed previously it can also be used in effusion testing [14].

A routine diagnostic test for FIP is through the cerebrospinal fluids (CSF) cell count, cytology, and protein concentration. CSF testing is helpful in ruling out differential diagnoses in cats with FIP that present with neurological signs. Cell count and cytology show moderate to high pleocytosis, mononuclear, neutrophilic, mixed, or pyogranulomatous inflammation. The protein concentration in the CSF is moderately to markedly elevated [14].

Testing of the cell count and cytology in the aqueous humour shows a neutrophilic, pyogranulomatous, or mixed inflammation in cats with FIP and it is helpful to rule out

differential diagnosis in cats that present with neurological signs which are non-specific for FIP infection.

Effusion analysis in FIP may show a yellow and sticky consistency, and in some cats, it may be more pink tinged or watery with a non-sticky consistency. Effusion in FIP is usually high in protein and low in white blood cell count. Effusions can be classified as modified transudate or exudate based on protein content and white blood cell. Usual laboratory findings in tested effusion shows that average effusion in FIP patients presents with a protein content of less than 35g/l, a cell count of < (5×10^9), high AGP levels > 1550ug/ml and an Albumin to Globulin ratio of < 0,4 [14].

7.4 Securing diagnosis

As mentioned before FIP can present in many different forms as it is able to invade multiple different tissues therefore leading to different clinical signs. There are multiple ways to fasten a FIP diagnosis. The first step usually being diagnostic imaging. An abdominal focused assessment with sonography for trauma, triage and tracking (AFAST) is usually performed in emergency settings to determine if there is any free fluid in the patient's abdominal cavity. If FIP is suspected an AFAST can be modified and used as a point-of-care ultrasound (POCUS). This is beneficial due to the minimal invasive nature of ultrasonography leading to relatively good tolerance in feline patients. Due to FIP's progressive nature, patients with a suspected FIP infection should be screened with ASFAST/POCUS regularly [14].

Patients with suspected FIP infection and a positive AFAST (showing anechoic fluids) should get a fluid sample and analysis taken immediately. When clinical signs as well as patients' history make a FIP diagnosis most likely, but AFAST shows no sign of free fluid a full abdominal ultrasound is indicated. If a patient presented is suspected of having pleural effusions thoracic radiographs can be used to determine the stage of effusion. Depending on patients' general state and vital parameters standing dorsoventral views should be used to avoid inducing respiratory arrest. In patients that show no signs of respiratory distress a TFAST (thoracic focused assessment with sonography for trauma, triage, and tracking) should be preferred over radiography since ultrasonography can detect small amounts of fluid with a higher accuracy [14].

FIP's typical lesions have a specific histopathology. Therefore, they can be used to solidify FIP diagnosis, unfortunately sampling is very invasive leading to it often only being used post mortem. Sensitivity can be improved by sampling multiple tissues including intestines, omentum, spleen, kidney, liver, and mesenteric lymph nodes. Typical histopathology of lesions may be vasculitis and perivascular necrosis. This in combination with immunohistochemistry is considered the gold standard of diagnosis, however patients may be too sick and fragile to survive surgical sample collection. Due to these concerns minimal invasive techniques are seen as preferrable, examples being true cut biopsy (TCB) of kidney and liver or ultrasound guided fine needle aspiration (FNA) [14].

Methods of identifying a FCoV infection can be divided into direct and indirect detection. Direct methods focus on detecting viral genome by real time RT-PCR or viral antigens. Blood, effusion, cerebrospinal fluid, aqueous humour, tissue can be used for direct detection with varying sensitivity and specificity. All including testing methods for example real time RT-PCR, S gene RT-PCR, sequencing for S gene mutations and antibody detection including 7b ELISA do not provide basis for secure diagnosis because of issues in either low specificity or tendency to give false positive result. Therefore, it is advised to use the aforementioned gold standard of immunohistochemistry in tissue to gain security in diagnosis [14].

8 Treatment highlighting GS – 441524

8.1 Therapy prior to the GS material

Prior to GS-441524, clinicians had few effective treatment options, but recent advances in research have helped make treating FIP patients less challenging. In absence of a curative treatment the approach has been to use symptomatic treatment to prolong life while reducing pain and symptom-related complications, combined with antivirals and human or feline interferon. Symptomatic treatment is always patient-specific and usually starts with high-dose corticosteroids to suppress the immune response, which are slowly tapered as symptoms subside. Combined with daily effusion removal to reduce dyspnoea dexamethasone injection into the abdominal and thoracic cavities would be performed until there was no effusion detectable [14][11]. Supportive fluid therapy and antibiotic treatment should be used for as long as patients are tolerating treatment.

1-ß-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide (RTCA) a triazole nucleoside with proven antiviral activity, by interfering in protein formation instead of polymerase

inhibition, has been shown to be noneffective in treatment of cats. Furthermore, kittens treated with RTCA show more severe clinical signs and a reduced survival time. The side effects of RTCA include haemolysis, a toxic effect on bone marrow (especially the megakaryocytes leading to thrombocytopenia and haemorrhages) which is dosage dependent, and liver toxicity has been reported in few cases.

Human interferon alpha (IFN-α) has a direct antiviral and immunomodulatory effect against DNA and RNA viruses including FCoV, unfortunately application can be complicated. Long-term systemic treatment leads to the development of antibodies against human protein after 3 to 7 weeks, thus inhibiting the drug activity. However, oral administration can be given over a longer period. While gastric acid inactivates IFN-α, therefore not leading to high enough serum titres for systemic treatment, immunomodulating activity can still be exerted on oropharyngeal lymphoid tissue [12][3].

Feline interferon-omega is a recombinant form of interferon which is species-specific and is only available in some European countries and Japan. It is administered at 1000000 U/kg subcutaneously every second day switching to twice weekly once remission is achieved. While one study shows promising results, the state of research is still very limited [3][12].

As there is currently no cure, measures should be taken to improve quality of life and increase survival time in cats. These measures can be categorized as supportive treatment and include nutritional support (via tube feeding techniques), parenteral fluid therapy, antibiotics (to control bacterial infections), aspirin (to inhibit platelet aggregation which is caused by vasculitis), topical corticosteroids and atropine (to treat anterior uveitis), blood transfusion (to treat severe non-regenerative anaemia) and stress reduction [12].

8.2 Therapy with GS-441524

One of the most effective antiviral drugs used against emerging RNA viruses are GS-441524 and GS-5734, who have been discovered through the extensive research on human coronaviruses during the COVID-19 pandemic. Based on promising results in human patients with severe cases of COVID-19, remdesivir and its active form GS-441524 have attracted the interest of veterinary researchers within the hope that they may be applicable to feline patients. However, remdesivir is currently only licensed for treatment in humans, leading to activists and patients performing unlicensed medicine by using unlicensed and uncontrolled substances [6]. At the time, only the injectable compound remdesivir was available, which lead to treatment regiments where patients had to undergo injections for up

to 12 weeks or longer. This, combined with the feline predisposition for FISS (feline injection site sarcoma) emphasized the need for an orally applicable medicine. Since research has advanced, an orally administrable drug GS-441524 has been made available, improving possible treatment plans while still being unlicensed. Remdesivir is an adenosine nucleoside monophosphate, while GS-441524 is a nucleoside analogue. Being a small molecule with a weight of <900 daltons and a size of 1 nm, this improves target cell penetration. The nucleoside analogue directly interferes with the RNA replication process, acting as an alternative substrate for viral RNA synthesis and leading to RNA chain termination during viral RNA transcription by inhibiting RNA-dependent RNA polymerase [11].

GS-441524 can be administered subcutaneously or orally. When administered subcutaneously, the dosage is 2 mg/kg every 24 hours for 12 weeks, in the event of a relapse, 4 mg/kg can be administered every 24 hours. Within 2 weeks of treatment initiation, rapid clinical improvement may be seen. Of the original 31 cats, 25 (80,7%) were classified as long-term survivors after successful treatment [11].

Research on the two promising antiviral drugs against FIP has shown that GS-441524 and GS-5734 have a comparable CC50 (<100 micrometer) and EC50 (1.0 micrometer) and with these results the study focused on the less chemically complex of the two, GS-441524.

As the treatment period for drugs containing GS-441524 is 84 days, it is preferred to be administered as an oral medication, as subcutaneous injections can be painful due to the drugs low pH. In addition, studies show that the subcutaneous injection of the drug may be associated with Feline injection site sarcoma (FISS).

Xraphconn® produced the chemical GS-441524 in an oral form. The study conducted by Krentz et al. showed that the FIP cats that participated in the study improved significantly after being treated with this multi-component drug produced by Xraphconn®. In fact, this drug was shown to significantly reduce viral load within the first few days of treatment. Xraphconn® was given at a concentration of 2,5 mg or 10 mg tablet. For patient to get included into the study they had to be diagnosed either via Immunohistochemistry, FCoV antigens within macrophages, detection of mutated strains in effusion, blood, FNA or by RT-PCR. They must be tested negative for FIV and FELV and have at least 2 kg bodyweight. Moreover, no other underlying severe diseases. All cats undergo a history check, physical examination, abdominal ultrasound on day (0,4,7,14,28,56,83) of the study, in case of a thoracic effusion they have to undergo an echocardiography and a check of effusion viral

load on day 0,7,14,28,58,83; in case of neurological signs a neurological examination was performed to enter the study, and a check of haematology was performed. In case of exclusion of cats from the study, they showed severe moribund or comatose condition, oral medication was not possible in these cats, or the owners were not educated enough to treat the cats with oral medication. At the end of the trail from 20 cats two got excluded due to their moribund health condition and 18 cats entered the study (Figure 9). The cats got divided into patients with ocular and neurological signs (2) which are treated with a higher dosage (10 mg/kg) and patients without ocular and neurological signs (16) treated with a lower dosage (5 mg/kg). The cats that participated in the study have an average age of 7,7 months and 61,1% were European shorthair (ESH) mostly males from which 5 of them were neutered and 6 female cats from which 3 were neutered. The treatment of cats with FIP are 84 days with the oral Xraphconn®, administration should happen at the same time every day on an empty stomach, once the drug was administered the cats are allowed to eat within half an hour later. All cats were hospitalized for the first 8 days of the study and went through an intensive surveillance, medical care and intensive care for 24 hours a day, moreover they had to undergo all diagnostic tests needed for this study. On the 8th day the cats got discharged and the owners received an education on how to administer the tablets and how to monitor the cats closely. During the study the cats should stay indoors [6].

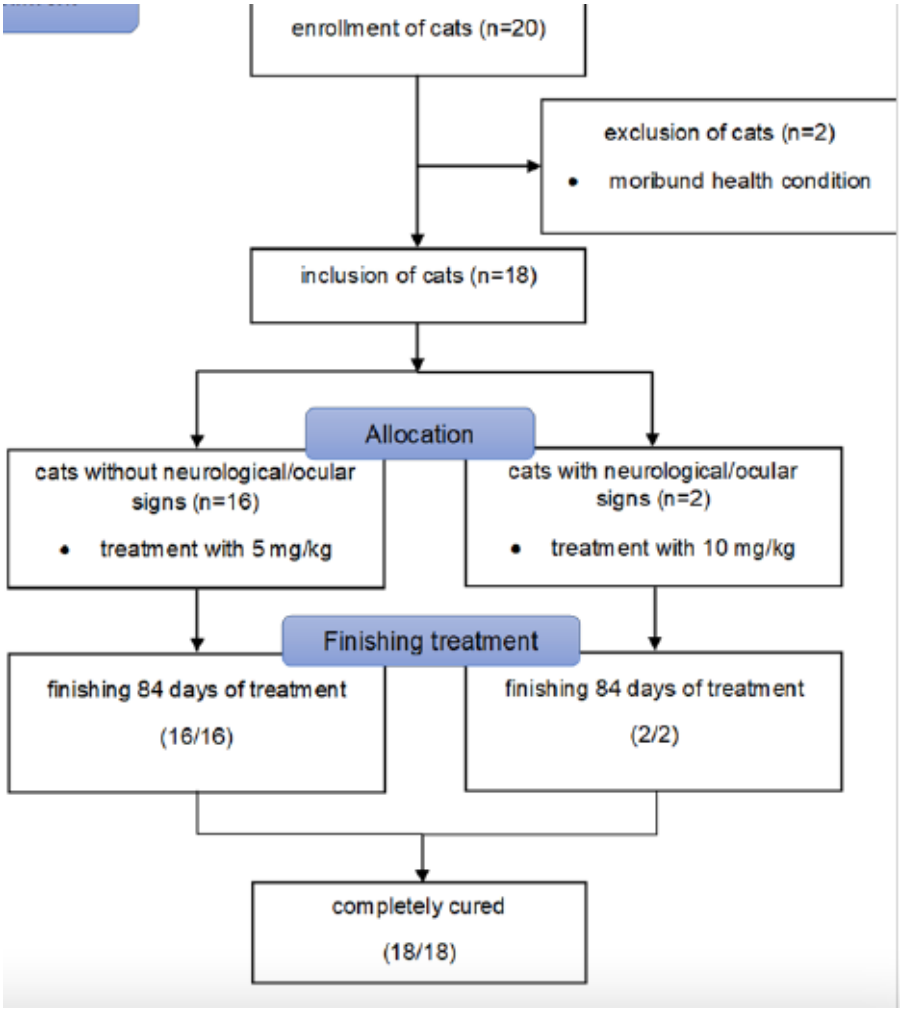

Figure 9 flow diagram showing enrollment, inclusion, allociation process, low- and high dose treatment [6]

The results of the study showed that all the cats were clinically recovered after 84 days of treatment, and there was no relapse at the time of publication. One cat, which had renal azotaemia at the beginning of the study recovered from all FIP signs but developed unilateral renal mineralization which was first detected in day 21 of the treatment. All cats showed an improvement of clinical and laboratory signs and gained bodyweight rapidly. Furthermore, they had a normal body temperatures, and the amount of effusion decreased quickly [6].

8.3 Side Effects

Injection

Immediate pain response due to the acidic nature of the compound is one of the main side effects of GS-441524 and includes vocalisation, growling, changes in body posture. The

pain response improves with routine in both owner and cat. Out of 26 cats, 16 cats show signs of pain at the injection, most commonly within the first 4 weeks. Ulceration can also be seen in a small number of cats, but this improves within 2 weeks, and is treated by clipping the surrounding hair and cleaning of the wound with hydrogen peroxide and two parts of water twice a day is considered treatment for these ulcerations. 3 out of 26 cats have scarring at the injection site [11]. Krentz et al. 2021 suggest that the side effects may be related to feline injection site sarcoma (FISS); in the case of chronic infection, FISS is thought to arise from fibroblasts and myofibroblasts [6].

Necropsy findings of cats treated with GS-441524 are that all cats showed an abdominal effusive disease. Two of the cats examined showed had pyogranulomatous vasculitis involving the abdominal viscera, CNS, and the eyes. One cat had secondary bacterial sepsis and one cat (CT 72) had abdominal pyogranulomatous vasculitis together with peripheral oedema and mineralisation of the adrenal cortex. Another cat had a fibrinosuppurative peritonitis and severe pyogranulomatous peritonitis. CT 75 showed signs of a chronic FIP infection such as severe growth retardation, low protein effusion and low cell count abdominal effusion, galloping rhythm and a bilateral atrial enlargement. This can be seen on an echocardiogram but is not usually indicative of a primary cardiac disease. The galloping rhythm may indicate an impaired cardiac function [11].

Oral

The use of a multi-component oral medication does not appear to be associated with any serious adverse effects. Mild Heinz body anaemia was observed in one cat out of 18 and lymphocytosis in 14 cats out of 18, the lymphocytosis occurred mainly mild to moderate and rarely severe. Three of the 18 cats had moderate and two severe lymphocytosis prior to treatment with Xraphoconn®. In addition, a mild to moderate increase in the liver enzymes (ALT, ALP) was diagnosed in 11 of the 18 cats [6].

9 Results

Coming back to the initial question of this review, regarding the treatment of feline infectious peritonitis the featured studies show improvement regarding applicability as well as incidence and severity of side effects.

With one study reporting a 100% occurring surviving rate (18 out of 18 cats) with mild side effects in patients. The mentioned study featured 20 patients out of which two had to be disqualified due to underlining health conditions. The sample group was further divided into two different groups. Cats showing neurological and ocular signs were treated with 10 mg/kg and cats without neurological or ocular signs were treated with 10 mg/kg. The cats were treated for 84 days and only showed mild adverse effects.

Administration routes have been shown to lead to different side effects. Injection reportedly led to pain at the injection side due to its acidic compounds, ulcerations were mentioned. Injections also increase the risk of patients suffering from FISS. Oral administration was described as the option with less reverse side effects.
Overall, these studies give a promising outlook on future treatment options of this disease.

10 Conclusion

This thesis has used a review of literature to work through the issue of feline infectious peritonitis. A major problem with FIP research is that there is currently a lack of data. The studies presented in this thesis have small sample sizes and should therefore be treated with caution. While there is a current increase in studies with bigger sample sizes, these studies still have not been concluded nor published. The issue of lack of research is also represented in lack of understanding the disease. Because it is not yet known how and where the feline enteric coronavirus mutates, it is almost impossible to find a way to prevent the disease.
There are several tests available to diagnose FIP, while this multitude of test allows for a certain flexibility in samples none of the test used right now offers direct results that lead to a certain FIP diagnosis. Therefore, the practitioner still has to rely on multiple tests and interpretations of the results. The wide differential diagnosis of FIP makes it difficult to diagnose the disease based on clinical and laboratory findings alone.
Prior to the development of GS-441524, treatment was mainly focused on symptomatic and supportive care. While this improved quality of life for a short period of time, it did not cure patients, leading to unsatisfactory results for owners and veterinarians alike. With the development of GS-441524 and its rapid results, a thriving black market developed to treat cats with imported drugs without the supervision of medical staff. With clinical trials being the only viable option for legal treatment, many owners are dependent on black market drugs. As black-market drugs are usually not subject to quality control, there is no guarantee that patients will receive a product that is similar in both dosage and chemical composition

every time. As a result, the potentially lifesaving treatment is still at risk. In the absence of professional veterinary supervision, owners are left to inject or administer oral medication without proper education.
The studies used in this thesis show promising results for the treatment of feline infectious peritonitis.

A significant development in veterinary medicine is the introduction of GS-441524 as a candidate treatment for Feline infectious peritonitis. FIP has long been a challenge for veterinarians as it is a devastating and complex disease. The emergence of GS-441524 brings new hope to cats suffering from this disease, as treatment options are very limited. Early research has highlighted the promising results therapeutic potential of GS-441524 in the treatment of FIP. In particular, this treatment has been associated with improvements in survival rates and clinical outcomes, giving both owners and veterinarians cause for optimism. The potential of GS-441524 as a ground-breaking therapy for FIP is underlined by the high number of survivors following successful GS treatment. It is encouraging that the majority of treated cats show a significant and sustained improvement in their condition. These results are leading the way to a possible paradigm shift in the treatment of FIP. The potential for a more effective treatment for FIP offers a ray of hope in the face of a previously poor prognosis and has the potential to improve the lives of many feline patients and their caretakers.
Diagnosis of FIP is a complex task, especially in the absence of typical clinical symptoms and effusion. The disease presents a wide range of clinical signs, making an accurate diagnosis a formidable challenge. The consideration of risk factors such as age, breed, housing conditions, and the presence of retroviruses is a critical component of the diagnostic process. These factors provide important insights into the evaluation of potential FIP cases. However, in the absence of these risk factors, the diagnostic journey requires the exclusion of other potential differential diagnoses. In addition, it is crucial to differentiate FIP from diseases that have similar clinical manifestations. Conditions such as septic peritonitis, pleuritis, toxoplasmosis, neoplasms such as lymphoma, and others can mimic FIP, amplifying the complexity of the diagnostic process. An incorrect diagnosis can have serious consequences, potentially leading to inappropriate treatment. Therefore, to ensure an accurate and early diagnosis, a comprehensive understanding of the multifaceted nature of FIP is indispensable.

A variety of diagnostic tests and tools, each with their own strengths and limitations, is employed in the pursuit of a FIP diagnosis. These diagnostic tools are indispensable for acquiring essential information about the presence of FIP and for confirming or ruling out the disease from the list of potential diagnoses. Notably, these tests provide various statistical parameters, including sensitivities and specificities, to assist veterinarians in their diagnostic endeavours. Among these diagnostic methods, laboratory tests play a key role. Blood tests such as AGP, CBC, and serum biochemistry provide valuable information to aid in the diagnosis of FIP. Although they may not provide FIP-specific findings, they may reveal characteristic abnormalities such as lymphopenia, hyperglobulinemia, non-regenerative anemia, and other anomalies. Importantly, it's vital to recognize that these laboratory changes are not pathognomonic; in other words, they are not exclusive to FIP and can be manifest in many systemic diseases. A comprehensive understanding of these diagnostic techniques is essential to enable veterinarians to make informed decisions when diagnosing FIP. Furthermore, continued refinement and improvement of these diagnostic techniques are essential to improve the accuracy of FIP identification and, consequently, the quality of patient care.

The integration of minimally invasive diagnostic techniques represents a significant advance in the diagnosis of FIP. These approaches, such as point-of-care ultrasound (POCUS) and fine needle aspiration (FNA), offer significant advantages over traditional methods. Their main benefit is to reduce patient discomfort and invasiveness, while expediting the diagnostic process. In particular, POCUS provides a non-invasive means of detecting even the smallest fluid accumulations with a remarkable level of accuracy. Notably, POCUS is relatively well tolerated by cats, making it a compelling choice in a variety of clinical scenarios. On the other hand, FNA offers the opportunity to obtain diagnostic samples with minimal invasiveness. By analysing cellular material from affected areas, this versatile technique provides valuable diagnostic information. Beyond alleviating patient discomfort, these techniques accelerate the diagnostic process by expediting the collection and analysis of relevant samples. The integration of minimally invasive diagnostic techniques into the realm of FIP diagnosis serves to enhance patient experiences, minimize stress, and most importantly, enable veterinarians to make more accurate diagnoses.

The use of off-label compounds, such as GS-441524, in the treatment of FIP introduces a multitude of ethical and legal considerations into the realm of veterinary medicine. It is important to approach this landscape with caution, although the promise of novel treatments is exciting and offers potentially ground-breaking advances. Off-label drugs bring to the fore

ethical issues relating to the care of patients and the ethical obligations of veterinarians. Veterinarians must balance their commitment to improving patient care with their ethical duty to provide safe and effective care. The use of off-label compounds requires careful consideration of the potential risks and benefits, as well as obtaining the consent of cat owners who rely on the competence of the veterinarians.

Moreover, barriers to the broader utilization of innovative treatments in veterinary medicine include legal challenges and constraints on the use of unlicensed medications. The lack of FDA approval underscores the need for further research, clinical trials, and regulatory evaluation to ensure the safety and efficacy of new treatments. The key issue in the treatment of FIP remains the balance between innovation and responsible veterinary care. Veterinary medicine is a field characterized by constant progress, and this advancement must be guided by ethical principles and rigorous regulation to ensure the well-being of feline patients.

In conclusion, the complex interplay of legal, ethical, and clinical considerations surrounding the use of off-label substances in the treatment of FIP requires careful guidance to ensure patient welfare and the preservation of veterinary integrity.

11 Summary

This retrospective study focused on the diagnostic tools and treatment management of feline infectious peritonitis. FIP belongs to the feline coronaviruses and is a complex and fatal disease worldwide. Feline coronavirus can be divided into two biotypes: feline enteric coronavirus and feline infectious peritonitis, which results from a mutation of the less severe FECV[3]. A shift in tropism from enterocytes to macrophages allows the virus to be transported to its target organs by macrophages [10]. The virus is transmitted indirectly, directly and rarely horizontally [3]. Feline patients can be infected by the faecal-oral route, as FCoV is mainly shed in the faeces. In general, there are three forms of clinical signs and symptoms. These include the effusive, non-effusive and mixed form. Early clinical signs of FIP are usually non-specific and depend on the immune status of the cat. FIP can cause changes in various organs and can lead to fibrinous granulomatous serositis, protein-rich serous effusion and pyogranulomatous lesions [3][14]. The diagnostic approach to FIP is a combination of patient's history, clinical signs and diagnostic tests including Rivalta's test, RT-PCR, FNA TCB, and many others. Even with all these tests, the diagnosis of FIP is considered to be challenging [14].

In terms of treatment methods, prior to GS-441524, the only option was to treat the disease symptomatically because there was no curative treatment available. Recent research has led to the development of oral and injectable antiviral drugs for the treatment of FIP. Unfortunately, they are not yet licensed for the legal use in most countries.

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I hereby confirm that I am familiar with the content of the thesis entitled

Feline infectious peritonitis - A literature review

written by Lisa Haas

(student name) which I deem suitable for submission and defence.

Date: Budapest, 14 day 11 month 2023 year

Dr. Anna Szilasi

Supervisor name and signature

Department of Pathology

Department

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Name of student: Lina Haas

Neptun code of the student: QH7J8V

Name and title of the supervisor: Dr. Szilasi Anna

Department: Pathology

Thesis title: Feline infectious peritonitis: Literature review

Consultation – 1st semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2022	11	16	Discussion on FIP	
2.	2023	01	11	Choosin available literature	
3.	2023	02	08	Introduction	
4.	2023	03	22	Choosin clinical case docs	
5.	2023	05	10	New insights to treatment	

Grade achieved at the end of the first semester: ..... jeles (5) .....

Consultation – 2nd semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2023	06	21	Overview of literature part 1	
2.	2023	08	23	-"- part 2	

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3.	2023	09	13	Correction part 1	
4.	2023	10	11	— " — 2	
5.	2023	10	25	Final review, abstract	

Grade achieved at the end of the second semester: .....jeles (5).....

The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence,

.....
signature of the supervisor

Signature of the student: .....

Signature of the secretary of the department: .....

Date of handing the thesis in..... .....