

History of Feline infectious Peritonitis 1963-2022 – First description to Successful Treatment

Niels C. Pedersen

*Center for Companion Animal Health, School of Veterinary Medicine, University of California, 944 Garrod Drive, Davis, CA, 95616, USA
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Abstract

This article highlights knowledge of feline infectious peritonitis (FIP) as it evolved, starting at its recognition in 1963 to present time, and was prepared with veterinarians, cat rescuers and guardians, shelter staff, and cat lovers in mind. A brief mention is made of the causative feline coronavirus and its relationship to a ubiquitous and minimally pathogenic enteric coronavirus of felids, epizootiology, pathogenesis, pathology, clinical features, and diagnostics. Major emphasis is on risk factors affecting FIP prevalence, and the role of modern antiviral drugs in successful treatment.

Introduction

Feline infectious peritonitis (FIP) was described as a specific disease entity in 1963 by veterinarians at the Angell Memorial Animal Hospital in Boston (Holzworth 1963) (Fig. 1). Pathology records from this institution and The Ohio State University failed to identify earlier cases (Wolfe and Griesemer 1966), although identical cases were soon recognized worldwide. The initial pathologic descriptions were of a diffuse inflammation of the tissues lining the peritoneal cavity and abdominal organs with extensive inflammatory fluid effusion, from which the disease was ultimately named (Wolfe and Griesemer 1966, 1971) (Figs. 2,3). A second, and less common clinical form of FIP, manifested by less diffuse and more widespread granulomatous lesions involving organ parenchyma was first described in 1972 (Montali and Strandberg 1972) (Figs.3,4). The presence of inflammatory effusions in body cavity in the common form, and lack of effusions in the less common form, led to the names wet (effusive, non-parenchymatous) and dry (non-effusive, parenchymatous) FIP.



Figure 1. Photograph of the author and Dr. Jean Holzworth (1915-2007) taken in 1991. Dr. Holzworth was the finest feline veterinarian that the author has known and was responsible for the first report of FIP as a specific disease entity. She spent her entire career at the Angell Memorial Animal Hospital in Boston.



Figure 2. Gross necropsy appearance of the abdominal cavity of a cat with acute onset wet FIP. The abdomen is filled with several hundred ml of a yellow, viscous fluid, the omentum is reddened, edematous and contracted, and fibrin plaques are evident on the surfaces of the spleen and edges of liver (arrows). A strand of fibrin is seen on the spleen

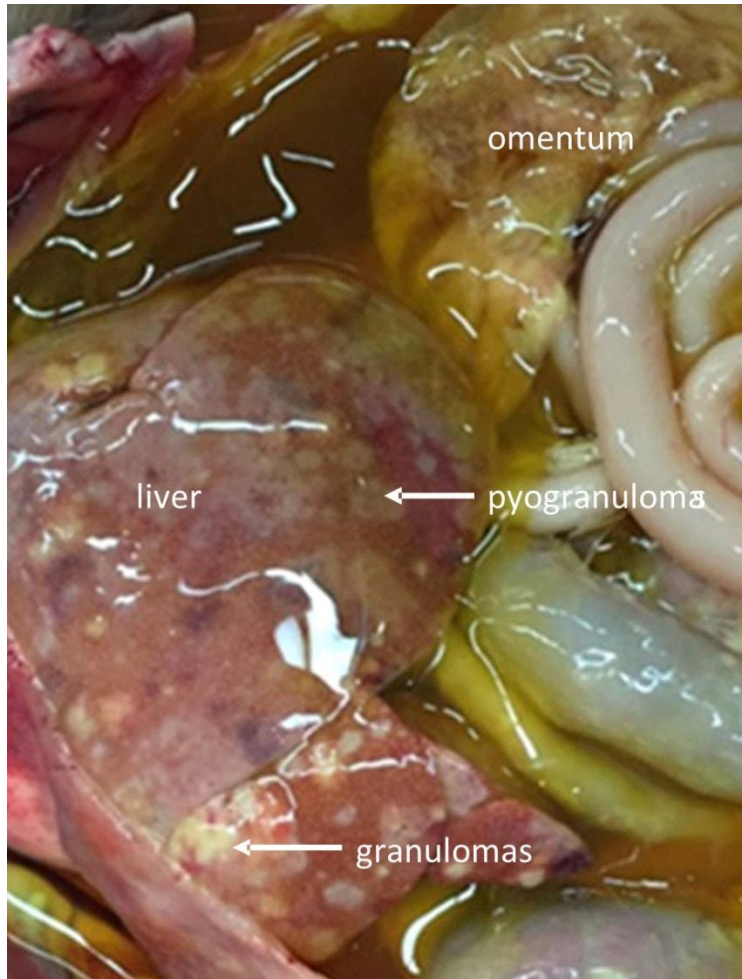


Figure 3. Appearance of the open abdomen at necropsy of a cat dying of a more chronic form of effusive FIP. The abdomen is filled with a viscous, yellow-tinged exudate and the omentum is thickened and contracted. The major lesions are in the liver, with numerous plaque-like structures (pyogranulomas) on the capsule. More defined lesions (granulomas), also serosal surface orientated, appear fleshier and are raised above the surface. These lesions also extend into the underlying liver parenchyma and are more typical of dry FIP. This is an example of a case of FIP that is transitioning between wet and dry (arrow).



A. **B.**
 Figure 4, A, B - Gross cross-section of a kidneys from two cats with the dry form of FIP. Lesions are surface orientated and extend down into the underlying parenchyma. B- The lesions of dry FIP in organs such as kidney, cecum, colon, and intestinal lymph nodes (Fig. 5) have been confused grossly with renal lymphoma.



Figure 5. Gross enlargement of ileo-cecal-colic lymph nodes in a cat with dry FIP.

The prevalence of FIP appeared to increase during the feline leukemia virus (FeLV) panzootic of the 1960s-80s, when many FIP cases were found to be FeLV associated (Cotter et al., 1973; Pedersen 1976a). The subsequent control of FeLV infection in owned cats with rapid testing and vaccination saw a plateau in FIP cases. However,

recent interest in foster/rescue, coupled with an effective treatment, has led to an increased awareness of the disease and its diagnosis.

Etiologic agent

Early attempts failed to identify a causative agent for FIP but confirmed its infectious nature (Wolfe and Griesemer 1966). A viral etiology was established in 1968 using ultrafiltrates of infectious material (Zook et al., 1968). The causative virus was subsequently identified as a coronavirus (Ward 1970) closely related to enteric coronaviruses of dogs and swine (Pedersen et al., 1978).

Confusion arose when a feline enteric coronavirus (FECV) was isolated from the feces of healthy cats and found indistinguishable to the feline infectious peritonitis virus (FIPV) (Pedersen et al., 1981). Unlike FIPVs, which readily recreated FIP in laboratory cats, experimental FECV infections were largely asymptomatic. The relationship of the two viruses was resolved when FIPVs were found to be mutants of FECVs that arise within the body of each cat with FIP (Vennema et al., 1995; Poland et al., 1996).

FECV is ubiquitous in cat populations around the world and is first shed in the feces starting at around 9-10 weeks of age coincident with the loss of maternal immunity (Pedersen et al., 2008;). Infection is by the fecal-oral route and targets the intestinal epithelium, and primary signs of enteritis are mild or inapparent (Pedersen et al., 2008; Vogel et al., 2010). Subsequent fecal shedding is from the colon, and usually ceases after several weeks or months (Herrewegh et al., 1997; Pedersen et al., 2008; Vogel et al., 2010). Immunity is short-lived, and recurrent infections are common (Pedersen et al., 2008; Pearson et al., 2016). Stronger immunity eventually develops over time and cats older than 3 years are less likely to be fecal shedders (Addie et al., 2003). FECV is continuously undergoing genetic drift into locally and regionally identifiable clades (Herrewegh et al., 1997; Pedersen et al., 2009).

FECV and FIPV are classified as biotypes of the subspecies feline coronavirus (FCoV). The genomes of FECV and FIPV biotypes are >98% related, yet with unique host cell tropisms and pathogenicity (Chang et al., 2012; Pedersen et al., 2009). FECVs infect mature intestinal epithelium, while FIPVs lose intestinal tropism and gain the ability to replicate in monocyte/macrophages. The published names FECV or FIPV will be used herein when referring to aspects of disease specific to each biotype, while the term FCoV will be used when referring to features common to both.

Three types of mutations have been implicated in the FECV-to-FIPV biotype change. The first type, which is unique to each cat with FIP (Poland et al., 1996), consists of an accumulation of missense and nonsense mutations in the c-terminus of the 3c accessory gene that frequently lead to a truncated 3c gene products (Pedersen et al., 2012; Vennema et al., 1995). The second type of mutations consist of two specific single nucleotide polymorphisms in the fusion peptide of the S gene, with one or the other forms shared by >95% of FIPVs and absent from FECVs (Chang et al., 2012). The third type of mutations, unique to each FIPV isolate and not found in FECVs, occur

in and around the furin cleavage motif between the receptor-binding (S1) and fusion (S2) domains of the spike (S) gene (Licitra et al., 2013). These mutations have variable effects on furin cleavage activity. Collectively, and in a yet to be determined manner, they are responsible for a shift in host cell tropism from enterocyte to macrophage, and a profound change in disease form.

FCoVs, and therefore FECVs and FIPVs, exist in two serotypes identified by antibodies to the virus neutralizing epitope on the S gene (Herrewegh et al., 1998; Terada et al., 2014). Serotype I FCoVs are recognized by cat sera and predominate in most countries. Serotype II FCoVs result from recombination with a portion of the S gene of canine coronavirus (Herrewegh et al., 1998; Terada et al., 2014), and identified by antibodies to canine coronavirus. Serotype II FIPVs are readily cultivated in tissue culture, while serotype I FIPVs are difficult to adapt to *in vitro* growth. Serotype I and II FECVs have not been grown in conventional cell cultures (Tekes et al., 2020).

FIPVs are found solely in activated monocytes and macrophages within diseased tissues and effusions and not shed externally. Therefore, cat-to-cat (horizontal) transmission of FIPVs is not the major mode of spread. Rather, FIP follows the pattern of the underlying enzootic FECV infection, with sporadic cases and occasional small clusters of disease (Foley et al., 1997). These clusters of cases can be mistaken for epizootics. A single report of epizootic FIP has been linked to a single serotype II virus that appeared to evolve within a shelter housing both dogs and cats (Wang et al., 2013). Horizontal transmission in this instance followed an epizootic rather than enzootic disease pattern, with infections spreading rapidly to cats of all ages and in close contact with an index case (Wang et al., 2013).

The low prevalence of FIP cases in a population suggests that FIPV mutants are generated infrequently. However, studies involving FECV infection in immunocompromised FIV and FeLV infected cats indicate that FIP mutants may be common but cause disease only under certain circumstances. Nineteen cats infected with feline immunodeficiency virus (FIV) for 6 years, and a control group of 20 FIV-naive siblings, were orally infected with FECV (Poland et al., 1996). Cats in both groups remained asymptomatic for two months, when two cats in the FIV-infected group developed FIP. In a second study, 26 young cats with enzootic FECV infection, and from a breeding colony with no history of FIP, were contact exposed to FeLV carriers (Pedersen et al., 1977). Two kittens in the group subsequently developed FIP 2-10 weeks after becoming FeLV viremic. A remaining question is how long FIPVs can survive in the body before being eliminated? One theory is that they persist in the body for some time and only become pathologic if immunity to them is impaired (Healey et al., 2022). This theory is supported by how immunity to FeLV develops. Most cats past kittenhood will resist FeLV viremia and develop a solid and lasting immunity, but this occurs over a period of weeks during which time the virus persists in a subclinical or latent state (Pedersen et al., 1982; Rojko et al., 1982). Methylprednisolone administered during this period, but not after, will abolish developing immunity and lead to a state of persistent viremia.

Epizootiology

Epizootiology is the study of incidence, distribution, and possible control of diseases of animals and the influence of environmental, host and agent factors. FIP is touted as one of the most important infectious causes of death in cats, although there are no accurate figures on prevalence. It has been estimated that 0.3-1.4% of deaths in cats presented to veterinary institutions are associated with FIP (Rohrbach et al., 2001; Pesteanu-Somogyi et al., 2006; Riemer et al., 2016), and as high as 3.6-7.8% in some shelters and catteries (Cave et al., 2002). FIP is also described as a disease of denser multi-cat environments. Three-fourths of FIP cases in a current ongoing treatment study came from the field via cat foster/rescues and shelters, 14% from catteries, and only 11% from homes.¹

Studies based on cases seen at academic institutions have shown the effect of age and sex on FIP prevalence (Rohrbach et al., 2001; Pesteanu-Somogyi et al., 2006; Pedersen 1976a; Worthing et al., 2012; Riemer et al., 2016). Three-fourths of cases in these cohorts occurred in cats under 3 years of age and few after 7 years. This was confirmed by a current and ongoing field study from the Czech Republic and Slovakia, which found that over 80% of FIP cases occurred in cats 3 years of age or younger and only 5% in cats older than 7 years (Fig. 6).¹ Earlier institutional studies varied as to the effect of sex, but indications were that males were somewhat more prone to FIP than females. This was confirmed by current data from the field showing a male to female ratio of 1.3:1.¹ It is unclear whether neutering affects FIP prevalence, with some reports suggesting that it may increase susceptibility (Riemer et al., 2016), while others do not show such a clear effect.¹

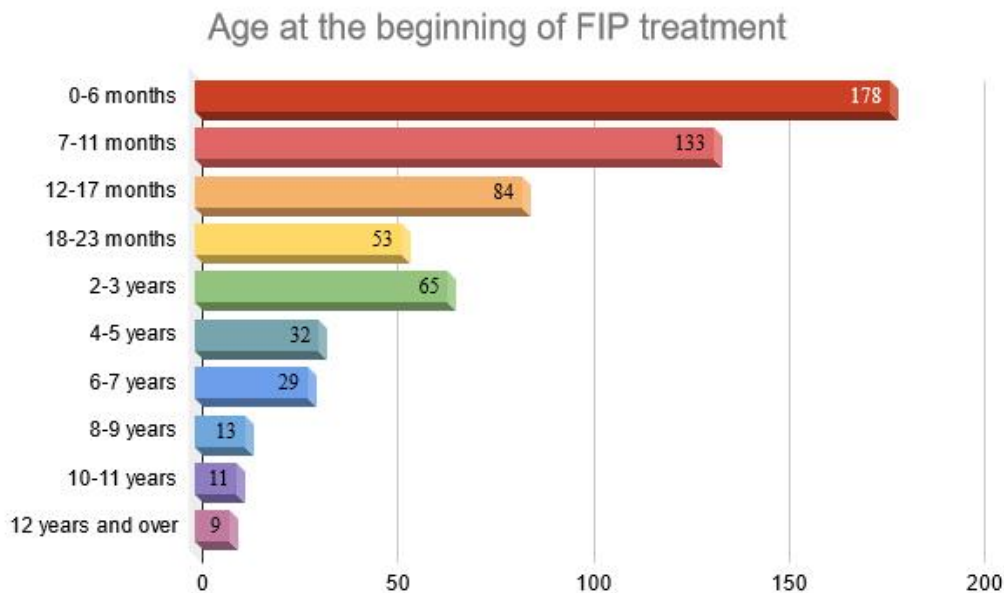


Figure 6. Ages of over 607 cats from the Czech Republic and Slovakia at the time of diagnosis and treatment for FIP.¹ Thirty percent of infections were seen in cats six-months of age or younger, 50% one-year and 85% three years of age or younger.

Additional environmental and virus-related risk factors have been implicated in increased prevalence of FIP, but their importance requires knowing disease incidence in their absence. A possible baseline may have been provided by a study of an enzootic FECV infection that was unknowingly present for many years in a well-managed specific pathogen free breeding colony (Hickman et al., 1995). This colony was maintained under strict quarantine free of other infections and the level of nutrition and husbandry were high. This colony produced hundreds of kittens each year before the first case of FIP was diagnosed. Such observations suggest that FIP may be a rare occurrence in the absence of risk factors.

The importance of re-homing as a risk factor for FIP is only now being appreciated. Pedigreed cat breeders, many of whom have suffered no cases of FIP within their catteries, have as their greatest fear notification that one of their kittens developed FIP shortly after going to a new home. A recent study found that over one-half of cats with FIP had experienced a change in environment, a stay in a shelter, or capture within the weeks preceding their illness.¹ Cats are known for hiding outward signs of stress, even when suffering serious internal effects. Procedures as simple as changing cages will suppress immunity and reactivate latent herpes virus shedding and disease signs in cats (Gaskell and Povey, 1977). Stressful situations, even those that seem minor, can cause decreased levels of lymphocytes and 'sickness behaviors' (Stella et al., 2013).

Variations in the genetic makeup of enzootic strains of FCoV may also be involved in FIP prevalence in a population. Serotype II FIPVs are thought to be more virulent than serotype I and more likely to be transmitted cat-to-cat (Lin et al., 2009; Wang et al., 2013). It is also possible that certain clades of FECV are more apt to mutate to FIPVs, and this should be studied. The author has also observed an inordinately high proportion of cats with neurological FIP in some regions such of the world, suggesting genetic determinants in certain strains of FCoVs may be more neurotropic.

Retrovirus-associated immunodeficiencies have been linked to FIP susceptibility. Up to one-half of FIP cases during height of the FeLV panzootic were persistently FeLV infected (Cotter et al., 1973; Pedersen 1976a; Hardy 1981). FeLV infection causes suppression of T-cell immunity, which can inhibit a protective immune response to FIP. The significance of FeLV infection for FIP incidence was greatly diminished starting in 1980s, when the removal of carriers and vaccination forced FeLV back into nature where exposures are less severe and immunity the usual outcome. Chronic feline immunodeficiency virus (FIV) infection has also been shown to be a risk factor for FIP in FECV infected cats under experimental conditions (Poland et al., 1996). FeLV infection was recognized in 2% and FIV in 1% of cats being treated for FIP in one recent field study.¹

The incidence of FIP purebred cats is reportedly higher than for random bred cats, with some breeds appearing more susceptible than others (Pesteanu-Somogyi et al., 2006; Worthing et al., 2012), suggesting a genetic component to susceptibility. Genetic

predisposition to FIP has been studied in several Persian catteries and was estimated to account for one-half of the disease risk (Foley et al., 1997). Some breeds, such as the Birman, are more apt to develop dry than wet FIP (Golovko et al., 2013). Attempts to identify specific genes associated with FIP susceptibility in Birman cats implicated several genes involved with immunity, but none achieved required significance (Golovko et al., 2013). The largest study of genetic susceptibility to FIP showed it to be extremely polymorphic and implicated inbreeding as the major risk factor (Pedersen et al., 2016). Specific polymorphisms in several genes have also been linked to high level FECV shedding among several pedigreed breeds of cats (Bubenikova et al., 2020).

Queens can develop FIP, usually the wet form, during pregnancy or in the perinatal period. This phenomenon resembles the suppression of immunity in pregnant women and predisposition to certain infections (Mor and Cardenas 2010). It is unclear whether subclinical FIP is activated by pregnancy or to increased susceptibility to a new infection. Infection of the queen early in pregnancy has led to fetal death and resorption, while later infections often result in abortion (Fig. 7). Kittens may also be born healthy but develop disease and die in the perinatal period. Some litters are born uninfected, due to the efficiency of the placental maternal/fetal blood barrier or the aid of antiviral treatment (Fig. 8).



Figure 7. Aborted kittens from a queen that developed wet FIP in the later stage of pregnancy. The abortion was the first indication of FIP, with classical signs of abdominal wet FIP rapidly following. The queen was successfully cured of FIP with the antiviral GS-441524.



Figure 8. This queen developed signs of wet abdominal FIP 3 weeks into pregnancy and was successfully cured with GS-441524. She subsequently delivered a litter of four kittens by C-section, one of which was dead and three that survived and grew up healthy. Treatment was given for the remaining 6 weeks of pregnancy and continued for 6 weeks during which kittens were successfully nursed. GS-441524 had no apparent side-effects to queen or kittens.

A possible surge in FIP cases has been observed in cats over 10 years of age in studies reported 50 years ago (Pedersen 1976a). Somewhat over 3% of FIP cases in a recent study occurred in cats 10 years of age and older and 1.5% in cats 12 years or older (Fig. 6).¹ The occurrence of FIP in aged often involves two different scenarios. The first scenario also involves exposure to FECV fecal shedders, but in a unique manner. It is common for aged cats to be paired as kittens and live together in relative isolation not exposed to FECV for many years. One cat of the pair dies, leaving it alone, and a much younger companion obtained from a rescue organization, shelter, or cattery and with a high likelihood that it is shedding FECV is brought into the home. Aged cats are also susceptible to the same FIP risk factors of younger cats, but also to additional factors associated with old age. The first of these is the effect of aging on the immune system, the most consistent being an impairment of cell-mediated immune function (Day 2010). Additional risk factors associated with aged cats are include the debilitating and potentially immunosuppressive effects of diseases such as cancer, and chronic diseases of kidney, liver, oral cavity, and bowel. Some diseases of aged cats can be confused for FIP or complicate the treatment of FIP if present at the same time.

Additional risk factors needing further study include loss of maternal systemic immunity by separation at birth, early weaning and loss of lactogenic immunity, malnutrition, common infectious diseases of kittenhood, early neutering, vaccinations, congenital heart disease, and even a shelter fire (Drechsler et al., 2011; Healey et al., 2022; Pedersen 2009, Pedersen et al. 2019).¹ However, the most important positive risk factor remains the presence of FECV within a population (Addie et al., 1995). The prevalence of FIP in several Persian catteries was also related in one study to the proportion of cats that shed FECV at a given time and the fraction of those cats that are chronic shedders

(Foley et al., 1997). The importance of FECV exposure supports the need to find ways to either prevent infection or decrease its severity. One of the first steps is to better understand FECV immunity (Pearson et al., 2019).

Pathogenesis

The first interface between FECV and the immune system is the lymphoid tissues of the intestine (Malbon et al., 2019, 2020). Although subsequent events leading to FIP are not entirely understood, it is possible to speculate from what is already known about FECV and FIPV infections, other macrophage-tropic infections, and viral immunity in general. FECV particles and proteins will be brought to regional lymphoid tissues during intestinal infection and processed by phagocytic cells, first to peptides, and ultimately to amino acids. Certain of these peptides will be recognized as foreign when arrayed on the cell surface, triggering innate (natural or non-specific) and adaptive (acquired or specific) immune responses (Pearson et al., 2016). FECVs are also undergoing mutation to FIPVs at the same time and the same type cells. Some of these mutations will allow the virus to replicate within these or closely related cells of a specific monocyte/macrophage lineage.

The host cell for FIPVs appears to be a specific class of activated monocytes found around venules in surfaces of intestinal and thoracic organs, mesenteries, omentum, uveal tract, meninges, choroid and ependyma of brain and spinal cord, and free in effusions. These cells are of the activated (M1) class (Watanabe et al., 2018) and resemble a subpopulation of small peritoneal macrophages described in mice (Cassado et al., 2015). This cell type is generated from circulating bone-marrow-derived monocytes that are rapidly mobilized from blood in response to infectious or inflammatory stimuli. An identical appearing population of activated monocytes has been described around blood vessels in FIP diseased retinas (Ziolkowska et al., 2017). These cells stained for Calprotectin, indicating their blood origin. Although FIPV infection occurs initially in smaller activated monocytes, virus replication is most intense in large, vacuolated, terminally differentiated macrophages (Watanabe et al., 2018). Virus released from these cells will rapidly infect activated monocytes produced in bone marrow and drawn to the site from the bloodstream.

The cellular receptor used by FECVs to infect intestinal epithelial cells has yet to be determined. The cellular receptor used by FIPVs to infect activated monocytes is likewise unknown. RNAs for conventional coronavirus receptors such as aminopeptidase N (APN), angiotensin converting enzyme 2 (ACE2), and CD209L (L-SIGN) were not upregulated in infected peritoneal cells from cats with experimental FIP, and CD209 (DC-SIGN) was significantly under-expressed (Watanabe et al., 2018). An alternative route of activated monocyte infection may involve immune complexing of the virus and cell entry by phagocytosis (Dewerchin et al., 2008, 2014; Van Hamme et al., 2008). Activated monocytes in lesions stain strongly positive for FIPV antigen, IgG, and complement (Pedersen 2009) and the mRNA for FcγRIIIA (CD16A/ADCC receptor) is significantly upregulated in infected cells (Watanabe et al., 2018), supporting infection by immune complexing and alternative receptors related to phagocytosis.

Macrophage pathogens are intracellular, and elimination of infected cells is by lymphocyte-mediated killing. The first line of defense is non-specific natural killer lymphocytes, and if this fails, an adaptive immune response by FIPV specific T-killer lymphocytes will ensue. Failure to contain and eliminate infected activated monocytes and macrophages will allow them to spread locally in the abdomen, presumably from lymph nodes regional to the lower intestine and site of FECV replication. Dissemination, locally and to distant sites through the bloodstream, is by infected monocytic cells (Kipar et al., 2005).

FIP occurs in two basic forms, wet (effusive, non-parenchymatous) (Figs. 2, 3) or dry (non-effusive, parenchymatous) (Figs. 4, 5), with wet FIP accounting for 80% of cases.¹ The term 'wet' applies to the characteristic fluid effusion in the abdomen or chest (Wolfe and Griesemer 1966, 1971). Lesions of wet FIP are dominated by inflammation resembling immediate- or Arthus-type hypersensitivity (Pedersen and Boyle, 1980), while lesions of dry FIP resemble delayed-type hypersensitivity reactions (Montali and Strandberg 1972; Pedersen 2009). Therefore, wet, and dry forms of FIP reflect the competing influences of antibody-mediated and cell-mediated immunity and associated cytokine pathways (Malbon et al., 2020, Pedersen 2009). Immunity to FIPV infected cells, which is the norm, is presumed to involve strong cell mediated responses (Kamal et al. 2019). Dry FIP is presumed to occur when cell mediated immunity is partially effective in containing the infection, and wet FIP when cellular immunity is ineffective and humoral immune responses dominate.

FIP is viewed as unique among macrophage infections for being viral, but the dry form shares many clinical and pathogenic features with diseases of cats caused by systemic mycobacterial (Gunn-Moore et al., 2012) and fungal infections (Lloret et al., 2013). Similarities in pathogenesis also exist between wet FIP and antibody-enhanced viral infections such as Dengue fever and Dengue hemorrhagic shock syndrome (Pedersen and Boyle 1980; Rothman et al., 1999, Weiss and Scott 1981).

It is assumed that host responses solely determine the outcome of FIPV infection and resultant disease forms. However, macrophage-tropic pathogens have evolved their own unique defense mechanisms against the host (Leseigneur et al., 2020). One mechanism is to delay programmed cell death (apoptosis). Delayed apoptosis allows for sustained microbial replication and eventual release of larger numbers of infectious agents, as also described in FIPV infected macrophages (Watanabe et al., 2018). FIPV may also control the recognition and destruction of infected activated monocytes by specific or non-specific T-cells. The cell surface target for T-cell killing of infected cells is presumably FIPV proteins (antigens) expressed on major histocompatibility-class I (MHC-I) receptors. However, no surface expression of viral antigens by MHC-I receptors was detected on FIPV-positive cells harvested from FIP tissues or effusions (Cornelissen et al., 2007). DC-Sign has been suggested as a receptor for FIPV (Regan and Whitaker, 2008), but RNA for DC-Sign is significantly under-expressed by infected peritoneal cells, while Fc (MHC-II) receptor RNAs are significantly over-expressed and MHC-I RNA down-regulated (Watanabe et al., 2018). This suggests that the normal

route of infection of host cells may be altered by FIPVs to favor infection by phagocytosis rather than by binding to specific viral receptors on the cell surface, cell membrane fusion, and internalization.

Pathology

Detailed descriptions of gross and microscopic lesions in the wet form of FIP were first reported by Wolfe and Griesemer (1966, 1971). Disease is characterized by vasculitis involving venules in tissues lining the abdominal or thoracic cavity, surfaces of organs, and supporting tissues such as mesenteries, omentum, and mediastinum. The inflammatory process leads to abdominal or thoracic effusions up to a liter or more (Figs. 2, 3). The basic lesion is the pyogranuloma, consisting of a focal accumulation of activated monocytic cells in various stages of differentiation, interspersed with non-degenerate neutrophils and sparse numbers of lymphocytes. Pyogranulomas are surface orientated and appear grossly and microscopically as individual and coalescing plaques (Fig. 2).

FIPV antigen is seen by immunohistochemistry (IHC) only in activated monocytes within lesions and in effusions (Litster et al., 2013). Large vacuolated terminally differentiated macrophages are particularly rich in virus (Watanabe et al., 2018), a feature reminiscent of the lepromatous form of leprosy (deSousa et al., 2017). Lymph nodes regional to sites of inflammation are hyperplastic and enlarged.

The relationship of dry to wet FIP was first described in 1972 in a report of cases of unknown etiology with similar pathology (Montali and Strandberg 1972). As reported by the authors, 'This pathologic syndrome was characterized by granulomatous inflammation in a variety of organs, but principally affected the kidneys, visceral lymph nodes, lungs, liver, eyes, and leptomeninges.' Tissue extracts of these lesions produced wet FIP in laboratory cats, confirming that wet and dry FIP were caused by the same agent.

The gross and microscopic pathology of dry FIP resembles that of other macrophage-tropic infections such as feline systemic blastomycosis, histoplasmosis, coccidioidomycosis (Lloret et al., 2013), tuberculosis and leprosy (Gunn-Moore et al., 2012). Lesions of dry FIP involve mainly abdominal organs (Figs. 5, 6) and are uncommon in the thoracic cavity (Montali and Strandberg 1972; Pedersen 2009). Lesions are less widespread and focal than in wet FIP, with a tendency to extend from serosal surfaces into underlying organ parenchyma (Figs. 5, 6). The targets of the host immune response are small aggregates of infected monocytic cells associated with venules, like pyogranulomas in wet FIP, but surrounded by dense accumulations of lymphocytes and plasma cells and variable fibrosis. The florid hyperemia, edema and microhemorrhage associated with wet FIP are largely absent, hence the lack of significant body cavity effusions. The host response to foci of infection gives lesions a gross tumor-like appearance (Figs. 5, 6). Infected activated monocytes within the central focus of infection are less dense and contain lower levels of virus than in the wet form (Pedersen 2009;), a feature of the tuberculoid form of leprosy (de Sousa et al.,

2017). Lesions in some sites, such as the wall of the colon may elicit a dense surrounding zone of fibrosis, reminiscent of the classic granulomas of tuberculosis. Transitional forms also exist between wet to dry forms in a small proportion of cases and most recognizable at necropsy (Fig. 3).

Ocular and neurological FIP are categorized as forms of dry FIP (Montali and Strandberg 1972). However, pathology in the uveal tract and retina of the eye, and ependyma and meninges of the brain and spinal cord, is intermediate in appearance between wet and dry FIP (Fankhauser and Fatzer 1977; Peiffer and Wilcock 1991). This can be explained by the effectiveness of blood-eye and blood-brain barriers in shielding these areas from systemic immune responses.

Clinical features of FIP

The five most common presenting signs in cats with FIP, regardless of clinical form and in order of frequency, are lethargy, inappetence, enlarged abdominal lymph nodes, weight loss, fever, and deteriorating coat.¹ These signs may occur rapidly, over a week or so, or exist for many weeks and even months before a diagnosis is made. The disease course tends to be more rapid in cats with wet FIP than dry FIP and retarded growth is common in young cats, especially those with more chronic disease. Twenty percent of cats with fever as a major presenting sign will ultimately be diagnosed with FIP (Spencer et al., 2017).

Wet FIP is the presenting form in about 80% of cases, more common in younger cats, and tends to be more severe and rapidly progressive than the dry form. Abdominal effusion (ascites) is four times more common than pleural effusion, with abdominal distension (Fig. 9) and dyspnea being frequent presenting signs for the respective forms. Pyrexia and jaundice are more common presenting signs in cats with wet than dry FIP (Tasker, 2018).



Figure 9. (left) An adult long-haired cat with chronic abdominal wet FIP. The cat was in reasonable health other than mild weight loss, lethargy, decline in coat quality, and intermittent low-grade fever. Abdominal distension was not appreciated for some time and the abdominal fluid had a relatively low protein and white cell count. (right) A young cat that presented with a rapid onset of high fever, inappetence, distension of the abdomen and abdominal fluid containing high levels of protein and white cells.

Most cats with dry FIP have disease signs limited to the abdomen and/or chest at presentation. The most common clinical features of dry FIP are palpable or ultrasound identifiable masses in kidney (Fig. 4), cecum, colon, liver, and associated lymph nodes (Fig. 5). Lesions of dry FIP tend to spare the thoracic cavity, and rarely seen in skin, nasal passages, pericardium, and testicles as part of a wider systemic disease.

Neurological and ocular disease are sole or secondary features of 10% of total FIP cases and 10 times more likely to be associated with dry than wet FIP (Pedersen 2009). Neurological, and ocular forms of FIP have been classified as forms of dry FIP, but it may be preferable to classify them as distinct forms of FIP resulting from the modifying effects of the blood/eye and blood/brain barriers behind which they occur. These barriers have a strong influence on the nature of disease in eyes and central nervous system (CNS) and response to anti-viral drug therapies.

Clinical signs of neurological FIP relate to both brain and spinal cord and include posterior weakness and ataxia, generalized incoordination, seizures, mental dullness, anisocoria, and varying degrees of fecal and/or urinary incontinence (Foley et al., 1998; Dickinson et al., 2020) (Fig. 10). Extreme intracranial pressure can lead to sudden herniation of the cerebellum and brainstem into the spinal canal and spinal shock syndrome. Prodromal signs include compulsive licking of walls or floors, eating litter,

involuntary muscle twitching, and reluctance or inability to jump to high places. Ocular involvement can precede or accompany neurological disease. Neurological FIP is a common occurrence in antiviral drug therapy, either appearing during treatment of non-CNS forms of FIP or as a manifestation of disease relapse after treatment has ended (Pedersen et al., 2018, 2019; Dickinson et al., 2020).



Figure 10. A young cat with dry FIP and neurological involvement. The cat is lethargic, thin, and with a poor coat. Hair in the perineal area is wet and stained from urinary incontinence.

Ocular involvement is usually grossly apparent and confirmed on ophthalmoscopic examination of anterior and posterior chambers. Ocular FIP targets the iris, ciliary body, retina, and optic disc to varying degrees (Peiffer and Wilcock 1991; Ziłkowska et al., 2017; Andrew, 2000). The earliest sign is often unilateral discoloration of the iris (Fig. 11). The anterior chamber may appear cloudy and exhibit high protein levels and aqueous flare with refracted light. There is an outpouring of inflammatory products into the anterior chamber in the form of activated macrophages, red cells, fibrin tags, and small blood clots. This material often adheres to the back side of the cornea as keratic precipitates (Fig. 12). The disease may also involve the retina in tapetal and non-tapetal areas and lead to retinal detachments. Intraocular pressures are usually low, except in cases complicated by involvement of the ciliary body and glaucoma (Figs. 12, 13).



Figure 11. Discoloration of the iris in the right eye of this cat was the earliest sign of FIP-associated uveitis. There is a slight haziness to the anterior chamber and deposits of red cell rich fibrin on the inside of the cornea. The pupils are also uneven (anisocoria).



Figure 12. A young cat with ocular FIP manifested in the right eye as anterior uveitis with secondary glaucoma causing enlargement of the globe. The iris has changed color due to inflammation, blood vessels at the base of the iris are engorged, and there is a cloudiness to the aqueous humor and inflammatory products on the back side of the cornea. Intraocular pressure is usually low in uncomplicated uveitis but increased in cats with glaucoma.



Figure 13. This young cat presented with anterior uveitis but treatment for FIP with GS-441524 was delayed, which allowed glaucoma to develop in both eyes. Treatment eliminated the underlying uveitis and greatly improved outward health, but secondary glaucoma and blindness persisted.

Diagnosis of FIP

The signalment, environmental history, clinical signs, and findings on physical examination are often indicative of FIP (Tasker, 2018). A thorough physical examination should include body weight and temperature, status of coat and flesh, manual palpation of the abdomen and abdominal organs, gross evaluation of cardiac and pulmonary function, and cursory examination of the eyes and neurological system. A strong suspicion of effusion in the abdomen or chest may warrant a confirmatory aspiration and even in-house fluid analysis as part of the initial examination.

Abnormalities in a complete blood count (CBC) and a basic serum biochemistry panel are important for FIP diagnosis (Tasker, 2018; Felten and Hartmann, 2019) and monitoring antiviral drug therapy (Pedersen et al., 2018, 2019; Jones et al., 2021; Krentz et al., 2021) (Fig. 14). The total leukocyte count is most likely to be high in cats with wet FIP, but low counts can occur with severe inflammation. High leukocyte counts are often associated with neutrophilia, lymphopenia and eosinopenia. A mild to moderately severe non-regenerative anemia is also frequently observed in both wet and dry FIP. Total proteins are usually elevated due to increased levels of globulin, while albumin values tend to be low (Fig. 14). This results in an A:G ratio that is often below 0.5-0.6 and considered one of the most consistent indicators of FIP. However, a low A:G ratio can occur in situations where both albumin and globulin are in their reference interval or in other diseases. Therefore, the A:G ratio should not be the sole indicator of FIP and should always be evaluated in context with other indicators of FIP (Tasker, 2018; Felten and Hartmann, 2019). Serum protein values obtained from most serum chemistry panels are usually sufficient. Serum protein electrophoresis can provide

additional information, especially when protein values from serum chemistry are questionable (Stranieri et al., 2017).

CBC STANDARD

Test	Result	Reference Range	Low	Normal	High
WBC	8.7	4.2 - 15.6 K/uL			
RBC	2.92	6.0 - 10.0 M/uL	LOW		
HGB	4.1	9.5 - 15 g/dL	LOW		
HCT	11.3	29 - 45 %	LOW		
MCV	39	41 - 58 fL	LOW		
MCH	14.0	11.0 - 17.5 pg			
MCHC	36.3	29 - 36 g/dL	HIGH		
% RETICULOCYTE	0.2	%			
RETICULOCYTE	6	3 - 50 K/uL			
NEUTROPHIL SEG	76.3	35 - 75 %	HIGH		
NEUTROPHIL BANDS	2.0	0 - 3 %			
LYMPHOCYTES	8.7	20 - 55 %	LOW		
MONOCYTES	12.1	1 - 4 %	HIGH		
EOSINOPHIL	0.9	2 - 12 %	LOW		
BASOPHIL	0.0	0 - 1 %			
AUTO PLATELET ANISOCYTOSIS	95	170 - 600 K/uL	LOW		
ABSOLUTE NEUTROPHIL SEG	6638	2500 - 12500 /uL			
ABSOLUTE NEUTROPHIL BAND	174	0 - 300 /uL			
ABSOLUTE LYMPHOCYTE	757	1500 - 7000 /uL	LOW		
ABSOLUTE MONOCYTE	1053	0 - 850 /uL	HIGH		
ABSOLUTE EOSINOPHIL	78	0 - 1500 /uL			
ABSOLUTE BASOPHIL	0	0 - 100 /uL			

Test	Result	Reference Range	Low	Normal	High
ALK. PHOSPHATASE	5	0 - 62 U/L			
ALT (SGPT)	45	28 - 100 U/L			
AST (SGOT)	74	5 - 55 U/L	HIGH		
CK	512	64 - 440 U/L	HIGH		
GGT	2	0 - 6 U/L			
ALBUMIN	2.0	2.3 - 3.9 g/dL	LOW		
TOTAL PROTEIN	9.4	5.9 - 8.5 g/dL	HIGH		
GLOBULIN	7.4	3.0 - 5.6 g/dL	HIGH		
TOTAL BILIRUBIN	1.2	0.0 - 0.4 mg/dL	HIGH		
DIRECT BILIRUBIN	0.5	0.0 - 0.2 mg/dL	HIGH		
BUN	21	15 - 34 mg/dL			
CREATININE	0.8	0.8 - 2.3 mg/dL			
CHOLESTEROL	177	82 - 218 mg/dL			
GLUCOSE	112	70 - 150 mg/dL			
CALCIUM	8.4	8.2 - 11.8 mg/dL			
PHOSPHORUS	5.4	3.0 - 7.0 mg/dL			
TCO ₂ (BICARBONATE)	13	13 - 25 mEq/L			
CHLORIDE	120	111 - 125 mEq/L			
POTASSIUM	3.7	3.9 - 5.3 mEq/L	LOW		
SODIUM	148	147 - 156 mEq/L			
A/G RATIO	0.3	0.4 - 0.8	LOW		
INDIRECT BILIRUBIN	0.7	0 - 0.3 mg/dL	HIGH		
NA/K RATIO	40				

Figure 14. Complete blood count (CBC) (a) and serum chemistry (b) panels from a young cat with acute wet abdominal FIP. Although the leukocyte count was not elevated, there was a relative but not absolute neutrophilia, relative and absolute lymphopenia, relative and absolute eosinopenia and non-responsive anemia as indicated by low red blood cells, hematocrit, and hemoglobin with normal reticulocyte count. The relevant values in the serum chemistry panel were the elevated total protein, low albumin, high globulin, low Albumin/Globulin (A:G) ratio, and an elevated total and direct bilirubin. Liver enzymes were normal except for mild elevation of AST, and BUN and Creatinine are normal, indicating absence of significant liver or renal disease. Globulin values are not always provided but a reasonable estimate can be calculated by subtracting albumin levels from the total protein.

Over-reliance on abnormalities in CBC and serum biochemistry panels can lead to diagnostic uncertainty when absent, even with the realization that no test value is consistently abnormal in all FIP cases (Tasker, 2018).¹ The greatest variation is between the presenting clinical form, with leukocytosis and lymphopenia being more common in cats with wet than dry FIP (Riemer et al., 2016). Hyperbilirubinemia is common in cats with FIP, but mainly in those with wet FIP (Tasker, 2018). The author has also found that many cats with primary neurological FIP have minor or no blood abnormalities. Blood test values for FIP also vary between studies (Tasker, 2018).

Complete analysis of the effusion is important for diagnosing wet FIP and for ruling out other potential causes of fluid accumulation (Dempsey and Ewing, 2011). This includes color (clear or yellow), viscosity (thin or viscous), presence of precipitates, ability to form partial clot on standing, protein content, leukocyte count and differential. The character of the fluid can vary based on duration of the disease and its severity. Effusions in cats with more severe disease signs usually have protein values near serum levels, are more viscous, contain higher numbers of leukocytes, more yellow-tinged, and more apt to form partial clots on standing. Chronic effusions tend to be less inflammatory in nature, with lower levels of protein and leukocytes, less viscous, and clearer. These values can be determined in-house in most clinics. Clotting property is determined by comparing fluid collected in serum and anticoagulant tubes after standing. Color and viscosity can be grossly determined, and protein levels estimated with a handheld total solids' refractometer. Cells are pelleted from fluid and analyzed on a quick-stained slide by light microscopy and leukocyte numbers and differential estimated. Cells include non-septic appearing neutrophils, small and medium size mononuclear cells, and large vacuolated macrophages (Fig. 15). It is important to note that effusions may occur with a wide range of diseases, such as heart failure, cancer, hypoproteinemia, and bacterial infections. Effusions from these other disorders usually have distinct identifying characteristics.

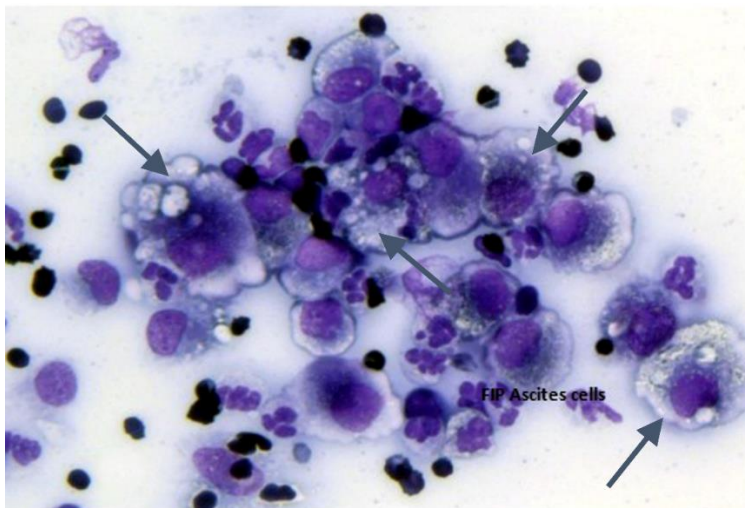


Figure 15. Stained smear of peritoneal cells centrifuged from abdominal fluid of a cat with wet FIP and examined on a quick stained slide by light microscopy. The predominant cells are large heavily vacuolated macrophages, smaller differentiating activated monocytes, and neutrophils. The largest concentration of viral particles is within intracytoplasmic vacuoles of macrophages (arrows).

A positive Rivalta test on abdominal or thoracic fluid is frequently used to diagnose FIP as the cause of an effusion and a negative test tends to exclude it (Fischer et al., 2010) (Fig.16). However, the test may be positive in inflammatory effusions of other cause and negative in some cats with FIP. Therefore, the Rivalta test is most helpful when coupled with other clinical findings of FIP and should not be a replacement for a thorough fluid analysis (Felten and Hartmann, 2019).



Figure 16. A positive Rivalta test result. A small sample of abdominal or thoracic fluid is dropped gently into a small glass filled with dilute acetic acid (8 ml distilled water and 1 drop of concentrated acetic acid). Inflammatory proteins will almost immediately congeal and sink to the bottom (positive). Less inflammatory fluids will form diffuse clots (questionable) or diffuse freely in the solution (negative).

Serum total and direct bilirubin levels are frequently elevated, especially in cats with wet FIP (Fig. 14) and may be associated with jaundice and bilirubinuria. Hyperbilirubinemia in FIP is not due to liver disease (Tasker, 2018), but more likely to vasculitis, micro-hemorrhaging, hemolysis, and destruction of damaged red blood cells by macrophages locally and in the liver. The released hemoglobin is ultimately metabolized to bilirubin, which is then conjugated in hepatocytes and excreted in urine. Glucuronidation is essential for bilirubin secretion and genetic disorders affecting glucuronidation in humans will impede its excretion (Kalakonda et al., 2021). Cats, as a species, are deficient in the enzymes required for glucuronidation, which makes it more difficult for them to excrete substances such as bilirubin (Court and Greenblatt 2000).

Although FIP can involve kidneys and liver, it is not severe enough to cause significant loss of renal or hepatic function. However, serum tests for blood urea nitrogen (BUN) and creatinine as a measure of kidney disease and alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma glutamyl transferase (GGT) for liver disease may be mildly elevated in cats with FIP, especially in cats with more acute and severe

disease (Fig. 14). Therefore, mildly abnormal test values should not be over-interpreted in the absence of other clinical features of liver or kidney disease, while significant increases should point to the possibility of concurrent, and possibly predisposing, diseases of those organs.

Serum can also be tested for additional markers of systemic inflammation, such as elevated levels of alpha-1-acid glycoprotein (AGP) (Paltrinieri et al., 2007) and feline serum amyloid A (fSAA) (Yuki et al., 2020). They may also prove useful in monitoring response to antiviral drug treatment (Krentz et al., 2021).

Radiography can be helpful in identifying thoracic and abdominal effusions. Abdominal ultrasound can detect smaller amounts of effusion or identify enlarged mesenteric and ileo-cecal-colic lymph nodes, colonic wall thickening, and lesions in organs such as the kidney, liver, and spleen (Lewis and O'Brien 2010). It can also be useful in scanning the chest for lesions, and assist with needle aspiration or biopsy.

The value placed on FCoV antibody titers has diminished since first reported almost 50 years ago (Pedersen 1976b). The reference antibody test employs indirect fluorescent antibody (IFA) staining. IFA titers $\geq 1:3200$ in cats with FIP are higher than for most FECV exposed cats (1:25-1:400). Newer tests often use ELISA procedures for rapid in-house or laboratory testing, but they are more qualitative than quantitative. IFA antibody titers decrease during successful antiviral drug treatment in many cats but remain high in others (Dickinson et al., 2020; Krentz et al., 2021). Sequential titers may show a progressive rise in titers as FIP develops (Pedersen et al., 1977), but prior serum samples are seldom available for comparison. Like most tests, FCoV antibody levels should not be used as the sole criterion for diagnosing or excluding FIP (Felten and Hartmann, 2019) or for evaluating treatment success (Krentz et al., 2021).

The reverse transcriptase polymerase chain reaction (RT-PCR) is the primary means to identify FCoV RNA in inflammatory effusions, fluids, or diseased tissues (Felten and Hartmann, 2019). RNA of the 7b accessory gene is present at the highest level in both FECV or FIPV infected tissues, fluids, or excretions, which makes it the most sensitive target for detecting low levels of virus (Gut et al., 1999). RT-PCR for the FIPV S gene mutations is often used in samples testing positive for 7b RNA to make it specific for FIPV (Felten et al., 2017). Other studies suggest that RT-PCR tests for FIPV specific S gene mutations have similar specificity for FIP but at a significant loss of sensitivity (Barker et al., 2017). A decrease in sensitivity relates to an increase in false negatives. False negative RT-PCR tests also occur in samples that contain insufficient infected macrophages or in cats with very low virus levels. False negatives are particularly common when testing whole blood.

Immunohistochemistry (IHC) detects feline coronavirus nucleocapsid protein in formalin fixed tissues with high sensitivity and specificity but has not been as popular as RT-PCR (Litster et al., 2013; Ziłkowska et al., 2019). Samples for IHC must contain intact infected macrophages (Fig.17), which requires careful separation of cells from effusions and placement on slides, or diseased tissues fixed in formalin and embedded in paraffin

that show lesions compatible with FIP. Coronavirus antigen in a macrophage within a typical FIP lesion or fluid, is observed only with FIP, giving IHC a high level of specificity.

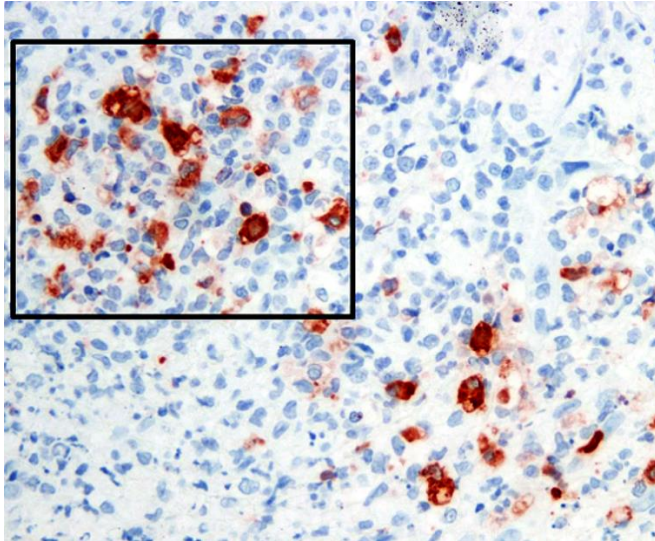


Figure 17. Histologic section from the thickened colon of a cat with the colonic form of FIP. The thickened wall contained foci of macrophages (square area) that stained positive (brownish red) by immunoperoxidase for the nucleocapsid protein of FIPV.

A thorough ophthalmologic examination is essential for diagnosing characteristic lesions of FIP (Pfeiffer and Wilcock 1991; Andrew, 2000). A sample of aqueous humor from the anterior chamber of an inflamed eye can also be useful for cytology, PCR, and IHC.

Neurological FIP is frequently diagnosed by magnetic resonance imaging (MRI) with contrast enhancement and is often coupled with cerebrospinal fluid (CSF) analysis (Crawford et al., 2017; Tasker, 2018; Dickinson et al., 2020). However, these are expensive procedures that are not always available and carry some risk to the cat. MRI lesions include obstructive hydrocephalus, syringomyelia, and foramen magnum herniation, with contrast enhancement of the meninges of the brain and spinal cord and ependyma of the third ventricle, mesencephalic aqueduct, and brainstem. CSF shows increased protein and cell count (neutrophils, lymphocytes, monocyte/macrophages), and when these are present, it can be a reliable source for PCR or IHC testing.

The neurological and/or ocular forms of FIP is often confused with feline systemic toxoplasmosis and many cats with FIP are treated empirically for toxoplasmosis before the diagnosis of FIP is made. Fortunately, the availability of an effective treatment for FIP has reduced this practice. Systemic toxoplasmosis is much less prevalent than FIP and less than 1% of cats with FIP in one field study were serologically positive.¹ Therefore, testing or treatment for toxoplasmosis should be considered only after the diagnosis of FIP has been adequately pursued.

Antiviral treatment as a diagnostic tool

Situations commonly arrive where clinical findings point to FIP, but doubt remains. A choice at that point is to do more diagnostic tests that may not lead to a more definitive diagnosis. An alternative diagnostic approach is to treat with an appropriate antiviral drug for 1-2 weeks at a correct dosage for the suspected form of FIP.² Treatment will often cause clinical improvement in as little as 24-48h and this will rapidly progress over the next 2 weeks and the full treatment given (Fig. 18). No response to test treatment and/or a deterioration in health would indicate a need to further investigate the cause(s) of ill-health.



Figure 18. Cat with FIP at the start of treatment with GS-441524 (a) and after 1 week (b). The response is rapid with fever disappearing in 24-48h and significant improvement in outward health within 1-2 weeks. This type of response is often used to confirm a diagnosis of FIP.

Treatment of FIP

There was no cure for FIP before 2017 and treatments were directed mainly at lessening disease signs (Izes et al., 2020). Such supportive care was focused on maintaining good nutrition, controlling inflammation (corticosteroids), altering immune responses (interferons, cyclophosphamide, chlorambucil), and inhibiting key cytokine responses (pentoxifylline and other TNF-alpha inhibitors). Dietary supplements claiming to help specific organ functions were also commonly used, such as one claiming to improve immunity and prolong survival in cats with dry, but not wet, FIP (Legendre et al., 2017). The effect of good supportive care on survival was impossible to determine, because most cats have been euthanized upon diagnosis or within several days or weeks. The survival rate even with the mildest forms of dry FIP and most persistent

treatment in one study was only 13% at 200 days and 6% at 300 days (Legendre et al., 2017).

Many commercially available drugs and compounds will inhibit FIPV infection or replication *in vitro*, some being repurposed drugs known to inhibit specific proteins of HIV or hepatitis C virus, while others work by inhibiting normal cellular processes usurped by the virus for its own life cycle (Hsieh et al., 2010; Izes et al., 2020; Delaplace et al., 2021). These various drugs and substances include cyclosporine and related immunophilins, several nucleosides and protease inhibitors, viopirin inhibitors, pyridine N-oxide derivatives, chloroquine, and related compounds, ivermectin, several plant lectins, ubiquitin inhibitors, itraconazole, and several antibiotics. However, the concentrations needed to inhibit virus replication *in vitro* are often near toxic levels to cells. It has also been difficult to translate favorable *in vitro* findings to animals and studies on diseased cats seldom follow. Ribavirin will inhibit FIPV replication *in vitro* but was not effective as a treatment of experimental FIP (Weiss et al., 1993). Chloroquine was tested for efficacy in FIPV infected laboratory cats, but clinical scores in treated cats were only slightly better than untreated cats and there was evidence of hepatotoxicity (Takano et al., 2013). A 3-month-old kitten with thoracic wet FIP was treated with itraconazole and prednisolone developed neurological FIP and was euthanized after 38 days of treatment (Kameshima et al., 2020). Mefloquine has also inhibited FIPV replication at low concentrations in cultured feline cells without cytotoxic effects and preliminary pharmacokinetic studies in cats appeared favorable (Yu et al., 2020), but evidence of its safety and efficacy in clinical trials of cats with FIP has yet to be published.

A breakthrough in the treatment of FIP came about in 2016-2019 with reports of antiviral drugs that targeted specific FIPV proteins essential for replication. The first of these drugs was GC376, an inhibitor of the main protease (M^{pro}) of FIPV (Kim et al., 2016; Pedersen et al., 2018). Protease inhibitors prevent the formation of individual viral proteins by inhibiting their cleavage from polyprotein precursors. GC376 was able to cure all experimentally infected cats and 7 of 21 cats with naturally occurring wet and dry FIP but it was less efficacious for cats with ocular or neurological signs (Pedersen et al., 2018). The second of these drugs was GS-441514, the active moiety of the prodrug remdesivir (Gilead Sciences; Murphy et al., 2018; Pedersen et al., 2019). GS-441524 is an adenine nucleotide analog that blocks replication of FIPV by inserting a nonsense adenine in the developing viral RNA. GS-441524 was also able to cure all experimentally infected cats (Murphy et al., 2018) and 25/31 cats with naturally occurring wet and dry FIP (Pedersen et al., 2019). It also appeared to be effective in several cats with ocular and neurological FIP at a higher dosage (Pedersen et al., 2019) and is currently the drug of choice for cats with neurological FIP (Dickinson et al., 2020). GS-441524 has treated thousands of cats with FIP from around the world over the last three years with an overall cure rate just over 90% (Jones et al., 2021).¹

Even though the ability of GC376 and GS-441524 to cure cats has been known for several years, neither drug is legally available at this time in most countries. The rights for GC376 were purchased by Anivive, but is yet to be marketed.³ Potential conflicts

with remdesivir's development for treatment of COVID-19 led Gilead Sciences to withhold animal rights for GS-441524, which prompted the creation of an unapproved source for GS-441524 out of China (Jones et al., 2021).^{1,2,4} Remdesivir is rapidly converted to GS-441524 in the body and has been allowed for FIP treatment in some countries.² GS-441524 can also be given orally at a higher dosage and now commonly used in the field (Krentz et al., 2021).¹

The efficacy of drugs like GC376 and GS-441524 for FIP of cats, whose use predated the COVID-19 pandemic, has been recognized by researchers studying related inhibitors of SARS-CoV 2 (Yan et al., 2020; Vuong et al., 2021). Remdesivir, an injectable drug marketed under the name veklury (Gilead), has been used worldwide to lower mortality to COVID-19 (Beigel et al., 2020). GC373, the active form of the prodrug GC376, has undergone simple modifications to enhance efficacy and oral bioavailability (Vuong et al., 2021). A GC373-related drug, nirmatrelvir, was successfully tested against early COVID-19 infections and has been approved for early COVID-19 and marketed under the name paxlovid (Pfizer). Paxlovid consists of two drugs, nirmatrelvir and the HIV protease inhibitor ritonavir. Ritonovir is not a significant inhibitor of SARS-CoV 2, but reportedly extends the half-life of M^{PRO} inhibitors when used in combination (Vuong et al., 2020). Nirmatrelvir and paxlovid have not been tested in cats with FIP at this time, but based on experience with the closely related GC376, it may be an important oral treatment for some forms of FIP in the future.

Two additional nucleoside analogs. EIDD-1931 and EIDD-2801, have been researched for treatment of several RNA virus infections in people and animals (Painter et al., 2021). EIDD-1931 is the experimental designation for beta-D-N4-hydroxycytidine, a compound widely studied since the 1970s. Beta-D-N4-hydroxycytidine is metabolized into a ribonucleoside analog, which is incorporated into RNA in place of cytidine and results in fatal mutations in the viral RNA chain. The compound is inhibitory to a broad range of human and animal RNA viruses including all known coronaviruses. EIDD-1931 was modified to increase oral absorption and named EIDD-2801 (molnupiravir) (Painter et al., 2021). Molnupiravir is de-esterified in the body to its active ingredient, beta-D-N4-hydroxycytidine. Therefore, EIDD-1931 and molnupiravir are analogous to GS-441524 and remdesivir, respectively. Molnupiravir is marketed for in-home treatment of primary COVID-19 under the names lagevrio (Merck, USA) or molnulup (Lupin, India).

Both EIDD-1931 and EIDD-2801 have been shown to be effective in inhibiting FIPV in tissue culture (Cook et al., 2021) and EIDD-2801 is currently being used to treat some FIP cases in the field.^{5,7} The effective concentration-50% (EC₅₀) for EIDD-1931 against FIPV is 0.09 μ M, EIDD-2801 0.4 μ M and GS-441524 0.66 μ M (Cook et al., 2021). The percent cytotoxicity at 100 μ M is 2.8, 3.8 and 0.0 for these compounds, respectively. Therefore, EIDD-1931 and -2801 are slightly more virus inhibitory but more cytotoxic than GS-441524. Resistance to GS-441524 is seen in some cases of FIP (Pedersen et al., 2019) and to remdesivir in COVID-19 patients (Painter et al., 2021), but these isolates remain susceptible to molnupiravir (Sheahan et al., 2020). This may prove helpful in the countering GS-441524 resistance in cats and people, and in the development of multi-drug treatments to prevent resistance from occurring.

What will full approval of drugs like molnupiravir and paxlovid for people mean for cats? Full approval for people should allow veterinarians in most countries to legally procure human approved drugs for direct use in animals, providing guidelines for extra label use in nonfood-producing animals are followed.⁶ This requires reformulating a drug made for people and purchased at the human price. Hopefully, antiviral drugs similar or identical to those approved for people will be licensed exclusively for animals and sold at a much lower cost, but this is likely to be years away.

Status of FIP treatment in the field

The current drug of choice for treatment of FIP is the adenine nucleotide analog GS-441524, first reported in the scientific literature under experimental conditions (Murphy et al., 2018) and later against naturally occurring disease (Pedersen et al., 2019). Although initial experimental and field studies of GS-441524 were done as a collaboration between researchers at Gilead Sciences and UC Davis, the relationship of Remdesivir to GS-441524 and the start of the COVID-19 pandemic in 2019 led Gilead Sciences to ultimately withhold granting animal rights for GS-441524 on the basis that it may interfere with development of Remdesivir for human use.⁴ Objections to this decision were expressed directly to the company and in a number of online forums.⁴ Subsequent pressure from cat owners, cat rescue groups, and cat aficionados, coupled with opportunistic Chinese drug makers, rapidly created an alternative unapproved source of GS-441524, a market for it, and a treatment network.⁴ This network has largely bypassed veterinarians, most of whom have chosen to wait for the drug to be legalized (Jones et al. 2021). The result of this relationship was an almost seamless transition of GS-441524 treatment of FIP from the laboratory to a rapidly expanding worldwide network of groups, loosely under the banner of FIP Warriors (Jones et al., 2021).^{4,7}

The sale and use of GS-441524 in the field for the treatment of FIP began almost immediately with the first publication of the first field trial results (Pedersen et al., 2019) (Fig. 19).

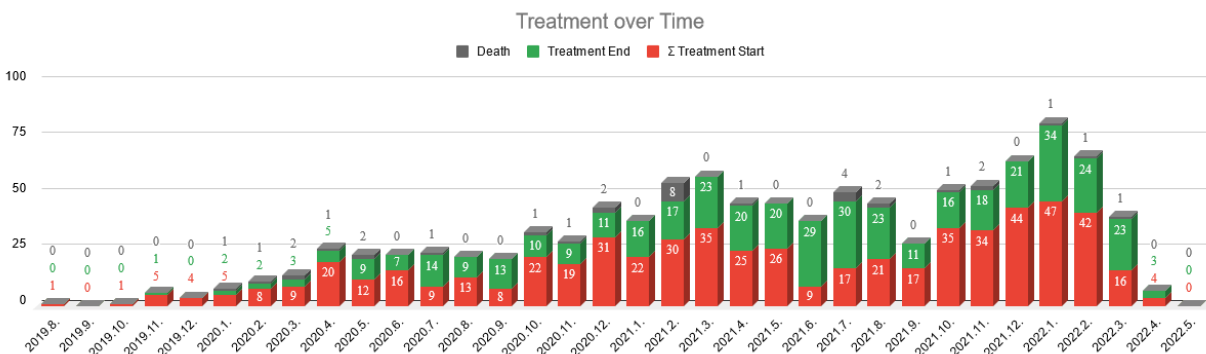


Figure 19. Graph of monthly treatment status of cats from the Czech Republic and Slovakia beginning in August 2019. This graph is from the FIP Warrior CZ/SK website.¹ This data mirrors the experiences of other FIP Warrior groups around the world. Thousands of cats have now been successfully treated for FIP around the world since 2019 when the first GS-441524 field trial was published (Pedersen et al. 2019). Winter peaks in

disease reflect late Spring and summer surge of kitten births and the high incidence of FIP usually starting at 3-6 months of age (Fig. 6). This graph is from the FIP Warrior CZ/SK website.¹

The fact that GS-441524 is not legally approved for animal use has prevented many veterinarians from accepting or participating in the treatment. Only 25% of cats in the CZ/SK treatment group received veterinary support in administering the treatment (Fig. 20), although more veterinarians may have been involved in diagnosing the disease. Interestingly, this was higher than the 8.7% of treated cats in the USA that received veterinary care (Jones et al., 2021). However, participants in the CZ/SK study, and in similar groups around the world, are not without medical expertise, as many are involved with foster/rescue and had considerable direct and indirect veterinary experience with feline diseases and treatments and spay/neuter programs.

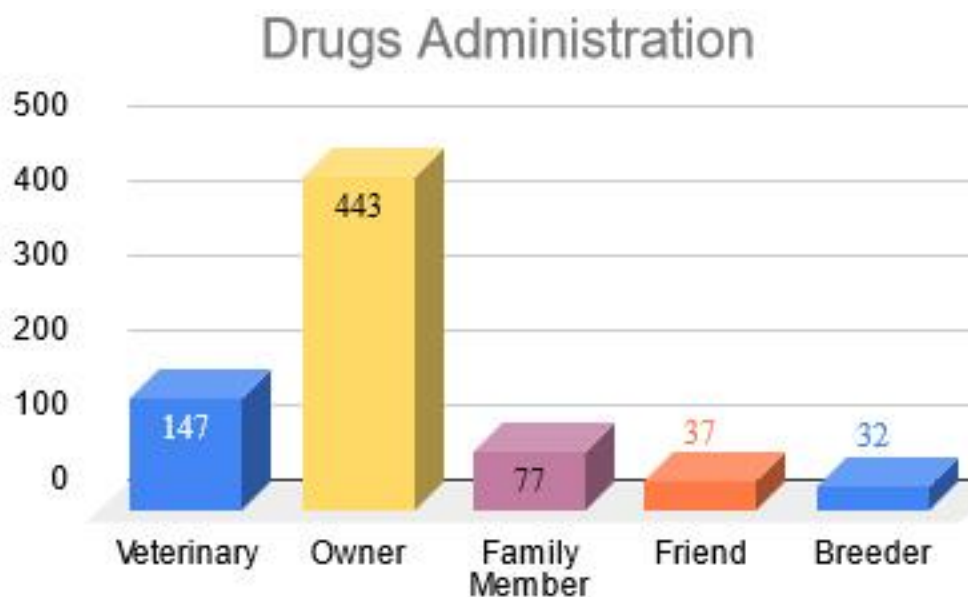


Figure 20. Major participants in administering GS-441524 treatment. This graph is from the FIP Warrior CZ/SK website.¹

It was known from initial laboratory studies and research by early Chinese sellers that GS-441524 could be absorbed by the oral route, but with less efficiency.⁹ Early GS-441524 sellers researched this further and determined that effective blood levels could be achieved by increasing the amount given orally compared to injection.⁸ Supplements were often added to oral GS-441524 capsules or tablets with claims that they enhanced absorption or had additive therapeutic benefits (Krentz et al., 2011). Most major sellers of injectable GS-441524 now offer oral versions and oral treatment has become increasingly popular either as a sole treatment or in combination with injectable GS-441524 (Figure 21). The success rate for oral GS-441524 is not significantly different from injectable GS-441524 (Figure 22).

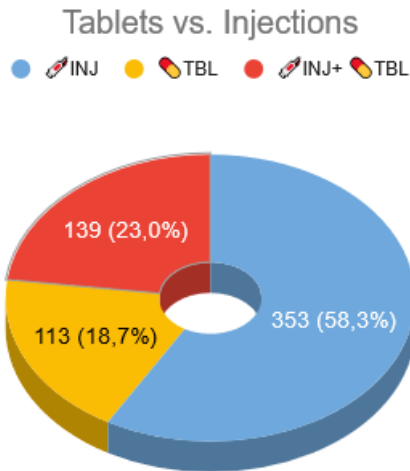


Figure 21. Comparative use of oral (tablets or capsules) vs injectable (subcutaneous) forms of GS-441524 for FIP treatment of cats from the Czech Republic and Slovakia. This graph is from the FIP Warrior CZ/SK website.¹

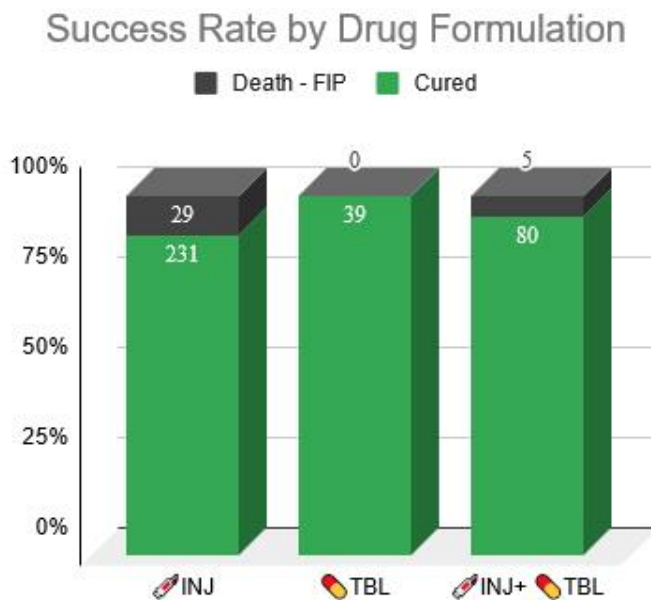


Figure 22. There is no significant difference in treatment success with oral GS-441524 vs. subcutaneously administered GS, but the actual amount (mg) of drug given orally in each dose is up to twice the amount contained in the same dose of injectable GS. This graph is from the FIP Warrior CZ/SK website.¹

The recommended dosage of GS-441524 for cats with wet or dry FIP and no ocular or neurological signs based on published field trial data was 4 mg/kg, subcutaneously (SC), every day (q24h), i.e., 4 mg/kg, SC, q24h for 84 days (Pedersen et al., 2019). This recommended starting dosage has tended to increase overtime to 6 mg/kg SC q24h

(Fig. 23). Eight mg/kg SC q24h is the current recommended starting dosage for cats with ocular signs and 10-12 mg/kg SC q24h for cats with neurological signs.

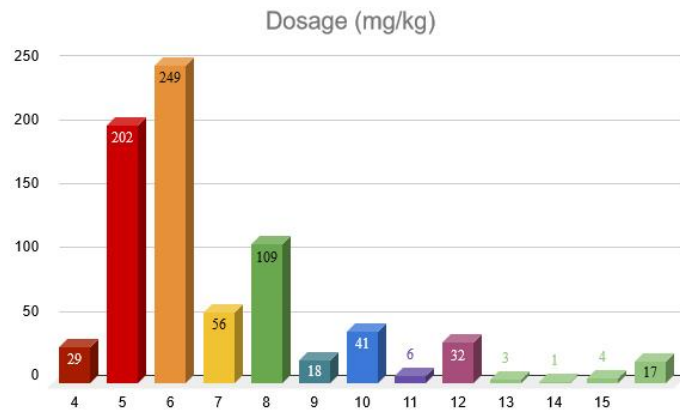


Figure 23. Daily dosage of GS-441524 that was used to treat FIP in cats from the Czech Republic and Slovakia. The common starting dosage was 6 mg/daily with higher dosages being required in some cats based on response to treatment, form of the disease, and occurrence of relapses after what appeared to be a successful treatment. Oral preparations of GS-441524 are usually labelled to correspond to the dosage used for injectable drug but contain up to twice the labelled amount. This graph is from the FIP Warrior CZ/SK website.¹

The optimum treatment duration as determined by the initial field trial was 84 days (Pedersen et al., 2019). Cures have been achieved in some cases of acute wet FIP in younger cats in 6-8 weeks, but some cats take longer than the 84 days. As noted in figure 24, 72% of cats were treated for 81-90 days, 19% longer, and only 9% treated for shorter times. Unfortunately, there is not a simple and accurate test to predict when a cure is obtained, and the decision to stop treatment is based on a full return to health and normal blood test values. Cats treated for a much greater time than 100 days were usually those requiring a GS dosage greater than 12 mg/kg daily by injection or equivalent oral dose, cats suffering disease relapses within the 12-week post-treatment observation period, cats with neurological disease, or cats that became resistant to GS-441524.

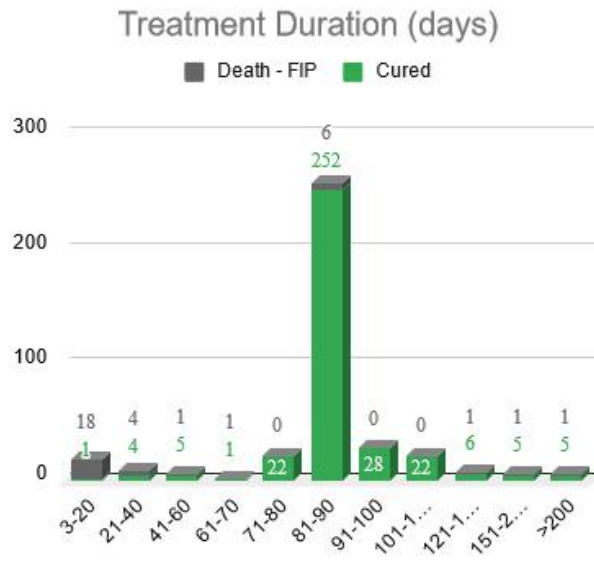


Figure 24. Duration of GS-141524 treatment in 351 cats successfully treated for all forms of FIP. This graph is from the FIP Warrior CZ/SK website.¹

The treatment success rate for all forms of FIP in cats from the Czech Republic and Slovakia was 88.1% with initial treatment, but when the 3.1% of cats that relapsed after first treatment and cured with additional treatment were included, the overall success rate was just over 91% (Fig. 24). This rate of cure coincides with that of other FIP Warrior groups (Jones et al., 2021). Treatment success is no different between cats with wet or dry FIP and no ocular or neurological involvement (Fig. 25). However, the cure rate in cats with ocular and neurological involvement was lower at 80% and 76%, respectively compared to 92% for all other forms of FIP (Fig. 25).

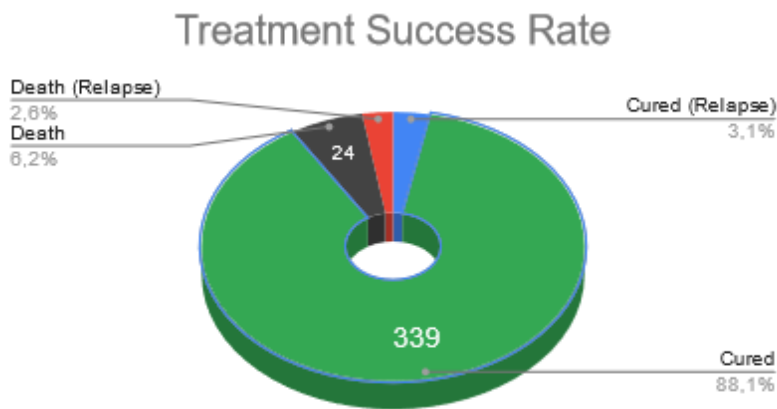


Figure 24. Initial treatment was successful in 88.1% of cats and 6.2% died or were euthanized either from lack of response to treatment, financial reasons, or treatment side-effects. An additional 5.7% of cats relapsed after initial treatment, and about equal numbers were either cured after additional treatment or died. This graph is from the FIP Warrior CZ/SK website.¹

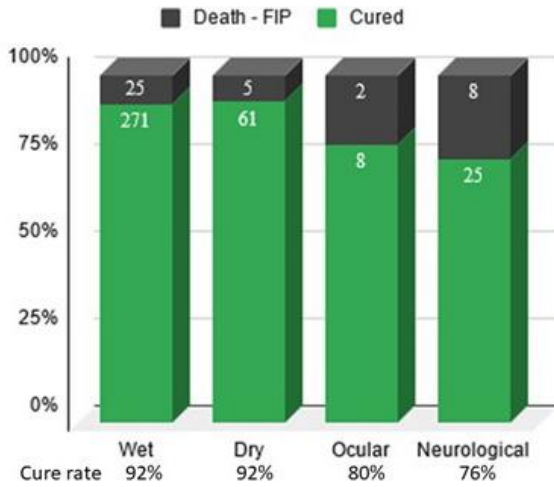


Figure 25. Cure rate for cats presenting with wet or dry FIP and no ocular or neurological signs, and for cats presenting with ocular or neurological disease as a major feature of their illness. This graph is from the FIP Warrior CZ/SK website.¹

Cats that have been successfully treated for FIP have been followed for periods of 4-5 years if cases published in the first field trials reported are included. There have been no relapses or recurrences of FIP in this first field trial group to date. One year survival figures are available from the much larger CZ/SK study population, which show 90.5% of cats still healthy one year after completing treatment (Fig.26). Only 1.3% of these cats have died of causes other than FIP, and 8.2% of the cohort are currently of unknown health status. The low proportion of cats that died of unknown causes during the year following treatment, and their positive response to treatment, suggests that FIP was being correctly diagnosed.

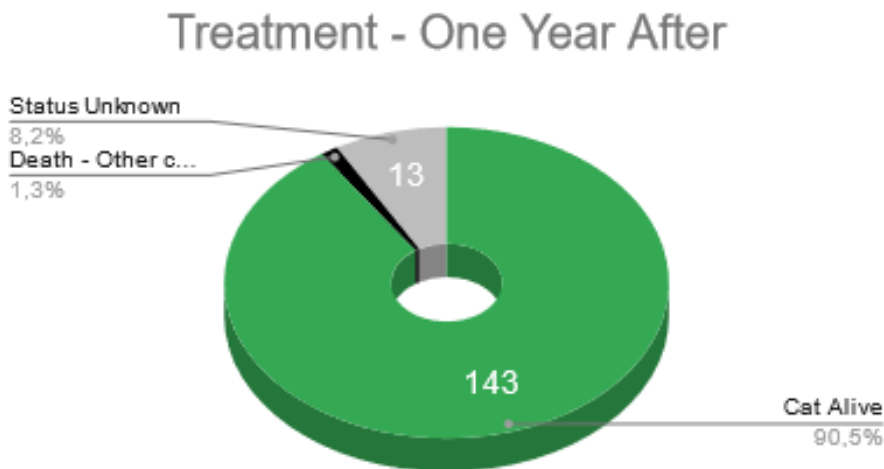


Figure 26. Health status of cats one year after successfully completing GS-441524 treatment. This graph is from the FIP Warrior CZ/SK website.¹

EIDD-2801 (Molnupiravir) is just now seeing use in the field for both initial treatment and for cats with GS-441524 resistance.^{5,7,9} EIDD-1931, the active form of EIDD-2081, needs to be researched as it is out of patent and could be readily approved for animal use if found safe and effective.⁵ Nirmatrelvir, an oral form of GC373, and closely related to GC376, also need to be studied for FIP treatment with or without ritonavir augmentation.

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I am indebted to Ladislav Mihok and his associates at “FIP Warriors Czech Republic/Slovakia” for allowing me to share figures from their website. This website contains the most significant, thorough, and organized collection of data on antiviral drug treatment of FIP in the field today. The website also contains helpful information and advice on initiating, managing, and monitoring the actual treatment. The collection of cats and their data is ongoing and regularly updated and at the time this article was written involved over 600 cats with FIP.

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Footnotes

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