Feline Infectious Peritonitis

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Feline infectious peritonitis (FIP) is a common disease and a frequent reason for referral; approximately 1 of every 200 new feline cases presented to American veterinary teaching hospitals represents a cat with FIP [1]. It is also a major factor in kitten mortality [2]. FIP is a fatal immune-mediated disease triggered by infection with a feline coronavirus (FCoV) [3]. FCoV belongs to the family Coronaviridae, a group of enveloped positive-stranded RNA viruses that are frequently found in cats [4]. Coronavirus-specific antibodies are present in up to 90% of cats in catteries and in up to 50% of those in single-cat households [5–8]. Only approximately 5% of FCoV-infected cats develop FIP in a cattery situation, however [5,9–11]. Because FIP is not only common but deadly and has no effective long-term management, a rapid and reliable diagnosis is critical for prognostic reasons. A reliable diagnostic test would lessen the suffering of affected patients while avoiding euthanasia of unaffected cats; however, unfortunately, such a test is not currently available. Difficulties in definitively diagnosing FIP arise from nonspecific clinical signs; lack of pathognomonic, hematologic, and biochemical abnormalities; and low sensitivity and specificity of tests routinely used in practice.

It was initially hypothesized that FCoV strains causing FIP are different from avirulent enteric FCoV strains [12]. Those former strains, however, are serologically and genetically indistinguishable [13–18] and represent virulent variants of the same virus rather than separate virus species [19]. It is now known that cats are infected with the primarily avirulent FCoV that replicates in enterocytes. In some instances, however, a mutation occurs in a certain region of the FCoV genome [20–22], leading to the ability of the virus to replicate within macrophages, which seems to be a key pathogenic event in the development of FIP [9,23]. Although intensive research has continuously led to new knowledge and understanding about FIP, it has

produced even more questions that still have to be answered. The objective of this article is to review recent knowledge and to increase understanding of the complex pathogenesis of FIP.

Etiology

The disease FIP was first described in 1963 as a syndrome in cats characterized by immune-mediated vasculitis and pyogranulomatous inflammatory reactions [24]. In 1978, a virus was identified as the etiologic agent, and in 1979, it was classified as a coronavirus labeled "feline infectious peritonitis virus" (FIPV) [25]. FIP has become an increasingly important disease for veterinarians and must now be considered to account for most infectious disease-related deaths in pet cats, thus taking over this title in recent years from feline leukemia virus (FeLV) infection, which is decreasing in prevalence and importance. A possible explanation for an increase in the prevalence of FIP is that management of domestic cats has changed [20]. With the introduction of litter boxes, more cats are kept permanently indoors, exposing them to large doses of FCoV in the feces that would previously have been buried outdoors. More and more cats are spending part of their life in crowded environments, such as at cat breeders or shelters, which increases their stress and exposure to FCoV while in such an environment [26].

Coronaviruses can cause harmless and mostly clinically inapparent enteral infections in cats, but they can also cause FIP. In earlier days, it was the common hypothesis that two different coronaviruses existed in cats, the "feline enteric coronavirus" (FECV) and the FIPV. Since then, it has become known that FIPV develops out of FECV spontaneously within the infected cat. Both viruses are identical with regard to their antigenetic properties and, with the exception of a single mutation, their genetic properties, but they are different with regard to their pathogenicity. This is why only the term *feline coronavirus* FCoV should be used to describe all coronaviruses in cats.

FCoV is an RNA virus and belongs to the genus *Coronavirus* of the family Coronaviridae. Coronaviruses are pleomorphic enveloped particles that average 100 nm in diameter (range: 60–120 nm) and contain single-stranded RNA. Characteristic petal-shaped projections called peplomers (range: 12–24 nm) protrude from the viral surface [29]. These peplomers are responsible for the crown-like ("corona") appearance of the virus when visualized under the electron microscope, which led to the term *coronavirus*. The peplomer proteins are used for virus attachment to cellular surface proteins, which act as receptors for the virus. They are shaped so that they can bind specifically to topical enterocytes. Replication of nonmutated FCoV is thus primarily restricted to enterocytes. The mutated FIP-causing FCoV has a broader cell spectrum, including macrophages.

FCoV belongs to the same taxonomic cluster of coronaviruses as transmissible gastroenteritis virus (TGEV), porcine respiratory coronavirus, canine coronavirus (CCV) [16,30–32], and some human coronaviruses [33]. In

many species of animals, coronaviruses have a relatively restricted organ tropism, mainly infecting respiratory or gastrointestinal cells [34]. In cats and mice, however, coronavirus infections can, under certain circumstances, involve several organs. Coronaviruses have a relatively low species specificity. CCV that can cause diarrhea in dogs is closely related to FCoV and can also infect cats. After contact with CCV-containing dog feces, cats develop antibodies that cross-react with FCoV. One CCV strain induced diarrhea in laboratory cats after experimental infection. In a cat infected with another CCV strain, histologic changes identical to changes typically seen in enteral FCoV infection were detected. In one study, CCV even caused FIP [35].

Depending on their antigenetic relation to CCV, FCoV strains can be classified into the subtypes serotype I and serotype II. Antibodies against CCV neutralize FCoV serotype II but not FCoV serotype I. FCoV serotype II strains are genetically more closely related to CCV than are FCoV serotype I strains, and FCoV serotype II strains seem to have arisen by recombination between FCoV serotype I strains and CCV [19,21,32]. Aside from the different degree of neutralization by antisera to CCV, serotypes I and II are different in their growth characteristics in cell culture and in their cytopathogenicity in vitro. FCoV serotype I strains are difficult to grow in cell culture and cause a slowly developing cytopathogenic effect. FCoV serotype II strains, however, grow more rapidly and produce a pronounced cytopathogenic effect [36]. Serotype I is the more prevalent serotype in field infections; between 70% and 95% of isolated FCoV strains in the field in the United States and Europe belong to serotype I. In Japan, however, serotype II predominates [19,37]. Most cats with FIP are infected with FCoV serotype I. Both serotypes can cause FIP, however, and both can cause clinically inapparent FCoV infections [38].

Epidemiology

FCoV and FIP are major problems in multiple-cat households and, to a much lesser extent, in free-roaming cats.

Prevalence

FCoV is distributed worldwide in household and wild cats [27,28]. The virus is endemic especially in environments in which many cats are kept together in a small space (eg, catteries, shelters, pet stores). There is virtually no multiple-cat household without endemic FCoV. At least 50% of cats in the United States and Europe have antibodies against coronaviruses. In Switzerland, 80% of breeding cats and 50% of free-roaming cats tested positive for antibodies. In Great Britain, 82% of show cats, 53% of cats in breeding institutions, and 15% of cats in single-cat households had antibodies [8,27]. FCoV is relatively rare in free-roaming ownerless cats because stray cats are usually loners without close contact with each other. Most importantly, they do not use the same locations for dumping their

feces, which is the major route of transmission in multiple-cat households. In a study in Gainesville, Florida, 250 adult feral cats in a trap-neuter-return program were tested for antibodies to coronavirus; 88% of the sera were negative, confirming that most of these cats were not infected [39]. In another study, feral cats were tested at the time they were brought into local shelters (in which multiple cats were kept together) and at 1-to 2-week intervals thereafter. At the time of entering, only a small number of cats had antibodies (approximately 15%); the percentage, however, increased rapidly until virtually all cats in the shelters were infected with FCoV [40].

Although the prevalence of FCoV infection is high, only approximately 5% of cats in multiple-cat household situations develop FIP; the number is even lower in a single-cat environment [5,9,10]. The risk of developing FIP is higher for young and immune-compromised cats, because the replication of FCoV in these animals is less controlled, and the critical mutation is thus more likely to occur. More than half of the cats with FIP are younger than 12 months of age [41].

FCoV is also an important pathogen in nondomestic felids [42]. Kennedy et al [43] found evidence of FCoV infection in 195 of 342 investigated nondomestic felids in southern Africa, which included animals from wild populations and animals in captivity. There is also a high incidence of FIP in wild felids in captivity in the United States and Europe (eg, in zoos). Cheetahs are highly susceptible to development of FIP, and a genetic deficiency in their cellular immunity is thought to predispose them to the disease [44].

Transmission

Infection usually takes place oronasally.

Infection

Cats are usually infected with nonpathogenic FCoV through FCoV-containing feces shed by a cat with a harmless FCoV enteric infection or by a cat with FIP. Mutated FIP-causing FCoV has not been found in secretions or excretions of cats with FIP. Thus, transmission of the mutated FIP-causing FCoV is considered unlikely under natural circumstances. FIP-causing FCoV can, however, be transmitted iatrogenically or under experimental conditions if, for example, effusion from a cat with FIP containing infected macrophages is injected into a naive cat [45].

FCoV is a relatively fragile virus (inactivated at room temperature within 24 to 48 hours), but in dry conditions (eg, in carpet), it has been shown to survive for up to 7 weeks outside the cat [46]. Indirect fomite transmission is thus possible, and the virus can be transmitted through clothes, toys, and grooming tools. In organ homogenates, it is even resistant to repeated freezing at −70°C for many months. The virus is destroyed by most household disinfectants and detergents, however.

The most common mode of infection is through virus-containing feces. Thus, the major source of FCoV for uninfected cats is litter boxes shared

with infected cats [47]. If multiple cats are using the same litter box, they readily infect each other. Continuous reinfection through the contaminated litter box of a cat already infected also seems to play an important role in the endemic survival of the virus. Rarely, virus can be transmitted through saliva, by mutual grooming, by sharing the same food bowl, or through close contact. Sneezed droplet transmission is also possible. Whether or not FCoV transmission occurs to a significant degree at cat shows is still a point of discussion. In one survey, attending cat shows seemed to be a factor of minor significance affecting the incidence of FIP [48], but in another survey, more than 80% of cats at shows in the United Kingdom were found to have antibodies [8]. Transmission by lice or fleas is considered unlikely [33]. Transplacental transmission can occur, because FIP was found in a 4-day-old kitten and in stillborn and weak newborn kittens born to a queen that had FIP during the later stages of pregnancy [26]. This mode of transmission is uncommon under natural circumstances, however. Most kittens that are removed from contact with adult virus-shedding cats at 5 to 6 weeks of age do not become infected [7]. Most commonly, kittens are infected at the age of 6 to 8 weeks, at a time when their maternal antibodies wane, mostly through contact with feces from their mothers or other FCoV-excreting cats.

Virus shedding

FCoV is shed mainly in the feces. In early infection, it may be found in saliva when the virus replicates in tonsils and, possibly, in respiratory secretions and urine [49,50]. It is likely that when naive cats in a multiple-cat household first encounter FCoV all become infected (and develop antibodies) and most probably shed virus for a period of weeks or months. With extremely sensitive reverse transcriptase (RT)–polymerase chain reaction (PCR) techniques, it has been shown that many naturally infected healthy carrier cats shed FCoV for at least up to 10 months [50]. Most cats shed virus intermittently, but some become chronic FCoV shedders for years to lifelong, providing a continuous source for reinfection of other cats [51]. Cats that are antibody-negative are unlikely to shed [51,52], whereas approximately one third of FCoV antibody–positive cats shed virus [10]. It has been shown that cats with high antibody titers are more likely to shed FCoV and to shed more consistently and higher amounts of the virus [51]. Thus, the height of the titer is directly correlated with virus replication and the amount of virus in the intestines. Most cats with FIP also shed (nonmutated) FCoV [53]; however, the virus load in feces seems to decrease after a cat has developed FIP [51].

Pathogenesis

Nonmutated FCoV replicates in enterocytes, causing asymptomatic infection or diarrhea, whereas mutated FCoV replicates in macrophages, leading to FIP. It was once believed that avirulent FCoV remained confined

to the digestive tract, could not cross the gut mucosa, and was not spread beyond the intestinal epithelium and regional lymph nodes [12], whereas FIP-causing FCoV disseminated to other organs, most likely via bloodborne monocytes [54–56]. FCoV can be detected in the blood using RT-PCR, however, not only in cats with FIP but in healthy cats from households with endemic FCoV that never develop FIP [50,57–59], indicating that non-mutated FCoV may also cause viremia. It is likely that this viremia in cats that do not develop FIP may be only short term and low grade.

Pathogenesis of enteric feline coronavirus infection

After a cat becomes infected with FCoV by ingestion (or, rarely, by inhalation), the main site of viral replication is the intestinal epithelium. The specific receptor for FCoV (at least FCoV serotype I) is an enzyme, aminopeptidase-N, found in the intestinal brush border [60–62]. Replication of FCoV in the cytoplasm can cause destruction of intestinal epithelium cells. Cats may sometimes develop diarrhea, depending on the degree of virus replication. In many cats, infection persists over a long period without causing any clinical signs. These cats shed FCoV intermittently or continuously and act as a source of infection for other cats.

Pathogenesis of feline infectious peritonitis

FIP itself is not an infectious but a sporadic disease caused by a virus variant that has developed within a specific cat.

Occurrence of the mutation

FIP develops when there is a spontaneous mutation in a certain region of the FCoV genome (the genes 3C and 7B are being discussed as most important) [19]. Whenever FCoV infection exists, so does the potential for the development of FIP [11,63]. The critical mutation always occurs in those same genes, but the exact location varies. Comparison of the genome of the mutated virus with the parent virus revealed 99.5% homology [21,64,65]. The mutation leads to changes in the surface structures of the virus that allow the virus phagocytized by macrophages to bind to the ribosomes in these macrophages. Thus, this mutated virus, in contrast to its harmless relative, is all of a sudden able to replicate within macrophages; this is considered the key event in the pathogenesis of FIP.

Decreased suppression of the virus in the intestines by the immune system may allow for increased virus replication; this, in turn, predisposes the cat to FIP development through increased virus load, because increased virus replication makes the occurrence of a "virulent mutation" more likely [20,66]. Any factors that increase FCoV replication in the intestines increase the probability of the mutation to occur. These factors include physical characteristics (eg, young age and breed predisposition); immune status of

the cat, which may be compromised by infections (eg, feline immunodeficiency virus [FIV] or FeLV infection); stress; glucocorticoid treatment; surgery as well as dosage and virulence of the virus; and the reinfection rate in multiple-cat households [66]. It is likely that kittens developing FIP do so because they are subjected to a large virus dose at a time of life when their still undeveloped immune systems are also coping with other infections and the stresses of vaccination, relocation, and neutering [11,66]. The question as to why one cat develops FIP and many others do not is a subject of intensive research. A recent study failed to detect a correlation between genetic differences in the feline leukocyte antigen complex (class II polymorphisms) and susceptibility to FIP [67].

Development of the disease

FIP is an immune complex disease involving virus or viral antigen, antiviral antibodies, and complement. It is not the virus itself that causes major damage but the cat's own immune reaction that leads to the fatal consequences. Within approximately 14 days after the mutation has occurred, mutated viruses that have been distributed by macrophages in the whole body, are found in the cecum, colon, intestinal lymph nodes, spleen, liver, and central nervous system (CNS). There are two possible explanations for the events occurring after viral dissemination from the intestines. The first proposed mechanism is that FCoV-infected macrophages leave the bloodstream and enable virus to enter the tissues. The virus attracts antibodies, complement is fixed, and more macrophages and neutrophils are attracted to the lesion [20]; as a consequence, typical granulomatous changes develop. The alternative explanation is that FIP occurs as a result of circulating immune complexes exiting from the circulation into blood vessel walls, fixing complement [68] and leading to the development of the granulomatous changes. It is assumed that these antigen antibody complexes are recognized by macrophages but are not, as they should be, presented to killer cells and thus are not destroyed. The consequences of the formation of immune complexes in cats depend on their size, antibody concentration, and antigen content. Immune complex deposition most likely occurs at sites of high blood pressure and turbulence, and such conditions occur at blood vessel bifurcations. FIP lesions are common in the peritoneum, kidney, and uvea, all of which are sites of high blood pressure and turbulence [26].

Not only virus but chemotactic substances, including complement and inflammatory mediators, are released from infected and dying macrophages. Complement fixation leads to the release of vasoactive amines, which causes endothelial cell retraction and thus increased vascular permeability. Retraction of capillary endothelial cells allows exudation of plasma proteins, hence the development of characteristic protein-rich exudates [36]. Inflammatory mediators activate proteolytic enzymes that cause tissue damage. The immune-mediated vasculitis leads to activation of the coagulatory system and to disseminated intravascular coagulation (DIC).

An imbalance in certain cytokines (eg, increase in tumor necrosis factor-α [TNFα], decrease in interferon-γ) can be found early in experimentally induced FIP [69–71]. Acute-phase proteins are altered in cats with FIP [72]. It has been suggested that increase of the acute-phase protein α_1-acid glycoprotein and changes in its glycosylation play a role in the pathogenesis of FIP [73]. The tissue distribution of the α_1-acid glycoprotein–related protein is, however, not dependent on the presence of FCoV, suggesting that this protein is not directly involved in the pathogenesis of FIP [74].

Antibody-dependent enhancement

In many infectious diseases, preexisting antibodies protect against subsequent challenge. In experimentally induced FIP, however, an enhanced form of disease may occur in cats that already have preexisting antibodies [75–79]. The proposed mechanism of this so-called "antibody-dependent enhancement" (ADE) is that antibodies facilitate the uptake of FCoV into macrophages [18,80–83]. Because of ADE, a higher proportion of antibody-positive cats died compared with antibody-negative controls, and the antibody-positive cats developed disease earlier (12 days compared with 28 days or more for controls) [78]. These findings have complicated the search for an effective and safe vaccine, because ADE occurred after vaccination in many vaccine experiments. ADE does not seem to play a major role in the field, however. Antibody-positive pet cats that were naturally reinfected by FCoV showed no evidence of ADE [26].

Clinical findings

The clinical signs totally depend on whether the "virulent mutation" occurs or not.

Feline coronavirus infection

After initial FCoV infection, there may be a short episode of upper respiratory tract signs, although these signs are usually not severe enough to warrant veterinary attention [26]. FCoV infection can cause a transient and clinically mild diarrhea or vomiting [20] as a result of replication of FCoV in enterocytes. Kittens infected with FCoV generally more commonly develop diarrhea, sometimes have a history of stunted growth, and occasionally have upper respiratory tract signs [7]. Rarely, the virus can be responsible for severe acute or chronic vomiting or diarrhea with weight loss, which may be unresponsive to treatment and continue for months. Most FCoV-infected cats, however, are asymptomatic.

Feline infectious peritonitis

Clinical signs of FIP can be variable, because many organs, including the liver, kidneys, pancreas, and eyes, as well as the CNS can be involved. The

clinical signs and pathologic findings that occur in FIP are a direct consequence of the vasculitis and organ failure resulting from damage to the blood vessels that supply them. In all cats with nonspecific clinical signs, such as chronic weight loss or fever of unknown origin resistant to antibiotic treatment or recurrent in nature, FIP should be on the list of differential diagnoses.

In the case of natural infection, the exact duration of time between mutation and development of clinical signs is unknown and almost certainly depends on the immune system of the individual cat. Most likely, the disease becomes apparent a few weeks to 2 years after the mutation has occurred. The time between infection with ''harmless'' FCoV and the development of FIP is even more unpredictable and depends on the event of spontaneous mutation. It has been shown that cats are at greatest risk of developing FIP in the first 6 to 18 months after infection with FCoV and that the risk falls to approximately 4% at 36 months after infection [11].

Three different forms of FIP have been identified: (1) an effusive, exudative, wet form; (2) a noneffusive, nonexudative, dry, granulomatous, parenchymatous form; and (3) a mixed form. The first form is characterized by a fibrinous peritonitis, pleuritis, or pericarditis with effusions in the abdomen, thorax, and/or pericardium, respectively. The second form without obvious effusions is characterized by granulomatous changes in different organs, including the eyes, as well as the CNS. In the meantime, it has been shown that differentiation between these forms is not useful (and is only of value for the diagnostic approach), because there is always effusion to a greater or lesser degree in combination with more or less granulomatous organ changes present in each cat with FIP. In addition, the forms can transform into each other. FIP can thus simply be more or less exudative or productive in a certain cat at a given time point.

Effusions

Many cats with FIP develop effusions. Cats with effusions have ascites (Fig. 1), thoracic effusions, and/or pericardial effusion. In a survey of 390 cats with FIP with effusions, 62% had ascites, 17% had thoracic effusions, and 21% had effusions in both body cavities [41]. Nevertheless, it is important to consider that of all cats with effusions, less than 50% actually have FIP. In a study including 197 cats with effusions caused by various reasons, approximately 30% of cats with thoracic effusions and 30% of cats with both abdominal and thoracic effusions had FIP. Of the cats with ascites, approximately 60% had FIP [84].

In cats with ascites, an abdominal swelling is commonly noticed by the owner and sometimes may be confused with pregnancy. Fluctuation and a fluid wave may be present; in less severe cases, fluid can be palpated between the intestinal loops. Abdominal masses may sometimes be palpated, reflecting omental and visceral adhesion or enlarged mesenteric

Fig. 1. Cat with ascites caused by FIP.

lymph nodes. Thoracic effusions usually manifest in dyspnea and tachypnea, and sometimes in open-mouth breathing and cyanotic mucous membranes. Auscultation reveals muffled heart sounds [84]. Pericardial effusions may be present in addition to or without other effusions. In these cats, heart sounds are muffled and typical changes can be seen on EKG and echocardiography. In one survey, FIP accounted for 14% of cats with pericardial effusion, second to congestive heart failure (28%) [85].

Some cats with effusions may be bright and alert, whereas others are depressed. Some of these cats eat with a normal or even increased appetite, whereas others are anorectic. Some cats have a fever, and some show weight loss. Signs of organ failure can be present in addition to the effusion (eg, icterus). Effusions can be visualized by diagnostic imaging (eg, radiographs, ultrasound). Their presence is verified by tapping the fluid.

Changes in abdominal and thoracic organs

In cats without effusion, signs are often vague and include fever, weight loss, lethargy, and decreased appetite. Cats may be icteric. If the lungs are involved, cats may be dyspneic and thoracic radiographs may reveal patchy densities in the lungs [86]. Abdominal palpation may reveal enlarged mesenteric lymph nodes and irregular kidneys or nodular irregularities in other viscera. Presenting clinical signs can be unusual. In some cats, abdominal tumors are suspected, but FIP is finally diagnosed at necropsy [87]. Other cats are presented with only gastrointestinal obstruction [88]. In one case report, a cat suffered from necrotizing orchitis because of FIP but had no other signs [89]. Although believed to be so in the 1970s, reproductive disorders, neonatal deaths, and fading of kittens are not usually associated with FIP [26].

Sometimes, the main or only organ affected by granulomatous changes is the intestine. Lesions are commonly found only in the ileocecocolic junction but may also be present in other areas (eg, colon or small intestine). Cats may have a variety of clinical signs as a result of these lesions, most

commonly chronic diarrhea but sometimes vomiting. Obstipation can also occur [26,90,91]. Palpation of the abdomen often reveals a thickened intestinal area. Hematology sometimes shows increased numbers of Heinz bodies, which is a result of decreased absorption of vitamin B_{12}.

Ocular changes

Cats with FIP frequently have ocular lesions. The most common but not obvious ocular lesions are retinal changes. Therefore, a retinal examination should be performed in all cats in which FIP is suspected. FIP can cause cuffing of the retinal vasculature, which appears as fuzzy grayish lines on either side of the blood vessels. Occasionally, granulomatous changes are seen on the retina [26]. Retinal hemorrhage or detachment may also occur. The changes, however, are not pathognomonic. Similar changes can be seen in other systemic infectious diseases, including toxoplasmosis, systemic fungus infections and FIV and FeLV infection.

Another common manifestation is uveitis (Fig. 2) [92]. Uveitis is an inflammation of the uveal coat of the eye, which consists of the iris, ciliary body, and choroidal vessels. The uveal coat can be seeded by immunologically competent cells that migrate into the eye. The eye can thus undergo all types of immunologically mediated inflammation [93]. Mild uveitis can manifest as color change of the iris. Usually, part of or all the iris becomes brown, although blue eyes occasionally appear to be green. Uveitis may also manifest as aqueous flare, with cloudiness of the anterior chamber, which can sometimes be detected only in a darkened room using focal illumination. Large numbers of inflammatory cells in the anterior chamber settle out on the back of the cornea and cause keratic precipitates, which may be hidden by the nictitating membrane. In some cats, there is hemorrhage into the anterior chamber. If aqueous humor is tapped, it may reveal elevated protein and pleocytosis [26].

Fig. 2. Cat with uveitis caused by FIP.

Neurologic signs

FIP is a common reason for neurologic disorders in cats. In a retrospective study of 286 cats with neurologic signs, more than half of the cats (47) in the largest disease category (inflammatory diseases) had FIP [94]. Of all cats with FIP, approximately 13% have neurologic signs [95]. These are variable and reflect the area of CNS involvement. Usually, the lesions are multifocal [96]. The most common clinical sign is ataxia, followed by nystagmus and seizures [97]. In addition, incoordination, intention tremors, hyperesthesia, behavioral changes, and cranial nerve defects can be seen [98,99]. If cranial nerves are involved, neurologic signs like visual deficits and loss of menace reflex may be present, depending on which cranial nerve is damaged. When the FIP lesion is located on a peripheral nerve or the spinal column, lameness, progressive ataxia, tetraparesis, hemiparesis, or paraparesis may be observed [26]. In a study of 24 cats with FIP with neurologic involvement, 75% were found to have hydrocephalus on postmortem examination. Finding hydrocephalus on a CT scan is suggestive of neurologic FIP, because other diseases, such as cryptococcosis, toxoplasmosis, and lymphoma, have not been reported to cause these findings [97].

Diagnosis

Diagnosing enteral FCoV can be performed by RT-PCR in feces [51,100] or by electron microscopy of fecal samples. Intestinal biopsies are of limited value, because the histopathologic features of villus tip ulceration, stunting, and fusion are nonspecific [26]. FCoV infection as the cause of diarrhea can only be confirmed if immunohistochemical or immunofluorescent staining of intestinal biopsies is positive.

Definitively diagnosing FIP antemortem can be extremely challenging in many clinical cases. FIP is often misdiagnosed [29]. Many times, its general clinical signs (eg, chronic fever, weight loss, anorexia, malaise) are nonspecific. A fast and reliable diagnosis would be critical for prognostic reasons and to avoid suffering of the patient. Difficulties in definitively diagnosing FIP, however, arise from unspecific clinical signs; lack of pathognomonic, hematologic, and biochemical abnormalities; and low sensitivity and specificity of tests routinely used in practice. The diagnostic value of frequently used parameters is only known in experimental settings, and some tests have not been widely used in clinical patients. A weighted score system for FIP diagnosis that takes several parameters into account, including background of the cat, history, presence of clinical signs, laboratory changes, and height of antibody titers, has been suggested [95]. This, however, only leads to a certain score or percentage of likelihood of FIP, and thus does not help to confirm the diagnosis definitively. There are, however, certain tests available in the meantime (eg, staining of antigen in macrophages in effusion or tissue) that, at least in the case of a positive result, confirm the diagnosis of FIP 100% [101].

Laboratory changes

There are a number of laboratory changes that are common in cats with FIP; they are not pathognomonic, however, and FIP cannot be diagnosed based on these findings.

Complete blood cell counts and coagulation parameters

Blood cell counts are often changed in cats with FIP [102,103]; however, changes are not pathognomonic. White blood cells can be decreased or increased. Although it is often stated that lymphopenia and neutrophilia are typical for FIP, this change can be interpreted as a typical "stress leukogram" that occurs in many severe systemic diseases in cats [101]. In up to 65% of cats with FIP, anemia is present, usually with only a mild decrease in hematocrit. The anemia can be regenerative; in these cases, it is caused mainly by a secondary autoimmune hemolytic anemia (AIHA) in which autoantibodies to erythrocytes can be found and Coomb's test results are positive. In cats with severe intestinal changes, Heinz bodies can be found in large numbers in erythrocytes [26], and this can also lead to hemolysis. Alternatively, anemia can be nonregenerative and is then mainly caused by anemia associated with chronic inflammation [41]. Approximately 50% of cats with FIP have nonspecific reactive changes of the bone marrow at necropsy [104]. Thrombocytopenia can commonly be found in cats with FIP as a result of DIC. In experimental infection, thrombocytopenia was detected as early as 4 days after infection [105]. Other parameters indicating DIC, including fibrinogen degradation products (FDPs) and D-dimers, are also commonly increased.

Serum chemistry

The most consistent laboratory finding in cats with FIP is an increase in total serum protein concentration [41,101,106]. This is found in approximately 50% of cats with effusion and 70% of cats without effusion [107]. This increase in total protein is caused by increased globulins, mainly γ-globulins, also leading to a decrease in the albumin-to-globulin ratio [101,108,109]. In experimental infections, an early increase of α_2-globulins was reported [49], whereas γ-globulins and antibody titers increase just before the appearance of clinical signs [5,49,69,77]. The characteristically high levels of γ-globulins [110,111] and the increased antibody titers [5,112] invite the conclusion that hypergammaglobulinemia is caused by a specific anti-FCoV immune response. Antibody titers and hypergammaglobulinemia show a linear correlation, but the wide variation in anti-FCoV titers at a given concentration of γ-globulins indicates that additional (autoimmune) reactions occur during the pathogenesis of FIP [113,114]. It has been discussed that stimulation of B cells by interleukin-6, which is produced as part of the disease process, additionally contributes to the increase in γ-globulins [115]. Total protein in cats with FIP can reach high concentrations

of up to 12 g/dL (120 g/L) and more. This, however, only reflects the chronic antigenic stimulation that generally can be caused by any chronic infection the cat is not able to clear through its immune response. Even if the serum total protein concentration is 120 g/L or greater, the likelihood of FIP is only 90%. Cats with these high serum protein concentrations that do not have FIP may suffer from severe chronic stomatitis, chronic upper respiratory disease, dirofilariasis, or multiple myeloma [101].

In a recent study of cats with FIP, comparison of total serum protein concentration, γ-globulins, and the albumin-to-globulin ratio revealed that the albumin-to-globulin ratio has a statistically significantly better diagnostic value than the other two parameters [101]. Thus, not only the increase in globulins but the decrease in albumin concentrations seems to be characteristic of FIP. A decrease in serum albumin occurs through decreased production because of liver failure or through protein loss. Protein loss can be attributed to glomerulopathy caused by immune complex deposition, loss of protein caused by exudative enteropathy in case of granulomatous changes in the intestines, or loss of protein-rich fluid in vasculitis. It can also be explained by decreased production in the liver (without compromised liver function), because not only albumin but globulins contribute (although not as importantly) to the plasma oncotic pressure. Thus, an increase in globulins may cause a negative feedback on albumin production in the liver. An optimum cutoff value (maximum efficiency) of 0.8 was determined for the albumin-to-globulin ratio. If the serum albumin-to-globulin ratio is less than 0.8, the probability that the cat has FIP is high (92% positive predictive value); if the albumin-to-globulin ratio is higher than 0.8, the cat likely does not have FIP (61% negative predictive value) [101].

Electrophoresis is often performed, and the rational behind it is to quantify γ-globulins and to distinguish a polyclonal from a monoclonal hypergammaglobulinemia so as to differentiate FIP (and other chronic infections) from tumors like multiple myelomas or other plasma cell tumors. Quantification of γ-globulins is not more useful than measurement of total proteins [101], however. In addition, polyclonal and monoclonal hypergammaglobulinemia can occur in cats with FIP, and the same is true in multiple myeloma. Thus, the value of electrophoresis is limited.

Other laboratory parameters (eg, liver enzymes, bilirubin, urea, creatinine) can be variably increased depending on the degree and localization of organ damage [116,117], but they are not helpful in making an etiologic diagnosis. Hyperbilirubinemia and icterus are often observed and are frequently a reflection of hepatic necrosis, despite the fact that alkaline phosphatase (ALP) and alanine aminotransferase (ALT) activities are often not increased as dramatically as they are with other liver diseases, such as cholangiohepatitis and hepatic lipidosis [26]. Hyperbilirubinemia is caused rarely by hemolysis as a result of secondary AIHA; however, the hemolysis has to be severe to cause icterus. Bilirubin is sometimes increased in cats with FIP without evidence of hemolysis, liver disease, or cholestasis. It has been

speculated that the bilirubin metabolism and excretion into the biliary system are compromised in cats with FIP, similar to the findings in sepsis.

Measurement of α_1-acid glycoprotein may be helpful in the diagnosis of FIP [118]. This acute-phase protein is increased in several infectious diseases of cats, and thus is not specific for FIP. Nevertheless, α_1-acid glycoprotein levels in plasma (or effusion) are usually greater than 1500 µg/mL in cats with FIP, which may help to distinguish FIP from other clinically similar conditions [26].

Tests on effusion fluid

If there is effusion, the most important diagnostic step is to sample the fluid, because tests of effusion have a much higher diagnostic value than tests performed using blood. Thus, fluid should be collected before blood is taken to avoid a waste of money with expensive blood tests. Only approximately half of the cats with effusions suffer from FIP [84]. Thus, although effusions of a clear yellow color and sticky consistency are often called "typical," the presence of this type of fluid in body cavities alone is not diagnostic (Fig. 3). The effusion in FIP may be clear, straw-colored, or viscous and may froth on shaking because of the high protein content. The effusion may clot when stored refrigerated [26]. If the sample is bloody, pus filled, or foul smelling or is chylus, FIP is less likely [95], although effusions in FIP can be different and sometimes red, pink, or almost colorless in appearance. Some cases of cats with FIP with pure chylus effusion have even been reported [119].

The effusion in FIP is usually classified as a modified transudate or exudate typically combining characteristics of both transudates and exudates. The protein content is usually high (>35 g/L), reflecting the composition of the serum, whereas the cellular content is low and approaches that of a pure transudate (<1000 nucleated cells per milliliter). The protein content of effusion is high because of the high concentration of γ-globulins. Other diseases causing similar effusions include lymphoma, heart failure, cholangiohepatitis, and bacterial peritonitis or pleuritis.

Fig. 3. "Typical" effusion in cat with FIP.

Measurement of enzyme activity in effusion also is an indication that FIP might be the underlying disease. Lactate dehydrogenase (LDH) is typically high (>300 IU/L) in effusions caused by FIP because it is released from inflammatory cells. Activity of α-amylase also is often high, likely as a result of common pancreatic involvement. The enzyme adenosine deaminase (AD) has been used to distinguish different causes of effusions, and its activity was significantly high in cats with FIP [120].

Cytologic evaluation of effusion in cats with FIP typically shows a pyogranulomatous character, predominantly with macrophages and neutrophils (Fig. 4). Cytologic findings may appear similar in cats with bacterial serositis or, sometimes, with lymphoma; these effusions often can be differentiated, however, by the presence of malignant cells or bacteria, respectively. Bacterial cultures should be performed in unclear cases.

A simple test, the so-called "Rivalta's test," (Fig. 5) has been used to differentiate transudates from exudates. This test was originally developed by an Italian researcher named Rivalta around 1900 and was used to differentiate transudates and exudates in human patients [121]. Other methods have replaced this test in human medicine because of its limited diagnostic value in people. It has not been shown to be diagnostically helpful in dogs with effusion [122]. Nevertheless, this test seems to be useful in cats to differentiate between effusions caused by FIP and effusions caused by other diseases [101]. It is not only the high protein content but the high concentrations of fibrin and inflammatory mediators that induce a positive reaction. To perform this test, three quarters of a reagent tube is filled with distilled water, to which one drop of acetic acid (98%) is added and is mixed thoroughly. On the surface of this solution, one drop of the effusion fluid is carefully layered. If the drop disappears and the solution remains clear, the Rivalta's test result is defined as negative. If the drop retains its shape, stays attached to the surface, or slowly floats down to the bottom of the tube (drop-like or jellyfish-like), the Rivalta's test result is defined as positive. In
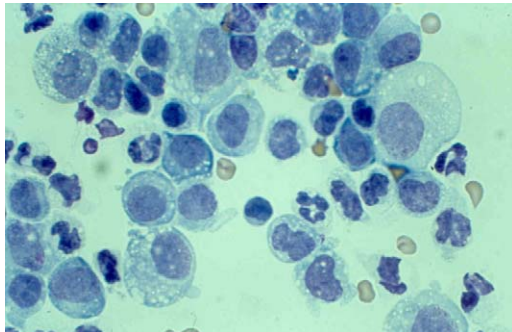

Fig. 4. Typical cytology of the effusion in a cat with FIP.

Fig. 5. Positive Rivalta's test in a cat with FIP.

a recent study, the Rivalta's test had a positive predictive value of 86% and a negative predictive value of 97% [101]. There are some false-positive results in cats with bacterial peritonitis. Those effusions, however, are usually easy to differentiate (through macroscopic examination, cytology, and bacterial culture). Some cats with lymphoma also have a positive Rivalta's test result, but many of these cases can be differentiated cytologically [101]. Overall, the Rivalta's test is an easy and inexpensive method that does not require special laboratory equipment and can be easily performed in private practice. It provides good predictive values, and thus is a helpful diagnostic test.

Tests on cerebrospinal fluid

Analysis of cerebrospinal fluid (CSF) from cats with neurologic signs caused by FIP lesions may reveal elevated protein (50–350 mg/dL, with a normal value of less than 25 mg/dL) and pleocytosis (100–10,000 nucleated cells per milliliter) containing mainly neutrophils, lymphocytes, and macrophages [97,123,124], which is a relatively nonspecific finding, however. Many cats with FIP and neurologic signs have normal CSF taps.

Measurement of antibodies

Antibody titers measured in serum are an extensively used diagnostic tool [6,125]. In view of the facts that a large percentage of the healthy cat population is FCoV antibody–positive, that high and rising titers are frequently found in asymptomatic cats, and that most of those cats never

develop FIP [126], antibody titers must be interpreted extremely cautiously [7,10,127,128]. From the time when the first "FIP test" was described more than two decades ago [9] to the present, the inadequacies and pitfalls of the test have been the topic of continuous discussion and controversy. Meanwhile, the so-called "FIP test" is referred to as the "feline coronavirus antibody test," emphasizing that the latter more correctly describes the antibodies that are detected and react with a large group of closely related coronaviruses. At times, clinicians have mistakenly taken a positive titer to equate with a diagnosis of FIP, and it has been assumed that more cats have died of FCoV antibody tests than of FIP [77]. FCoV tests are often performed for inappropriate reasons. There are five major indications to test for FCoV antibodies: (1) for the diagnosis of FCoV-induced enteritis or to narrow the diagnosis of FIP, (2) for a healthy cat that has had contact with a suspected or known excretor of FCoV, (3) for a cat-breeding facility with the aim of obtaining an FCoV-free environment, (4) to screen a cattery for the presence of FCoV, and (5) to screen a cat for introduction into a FCoV-free cattery [26].

Antibodies in blood

Although frequently criticized, antibody testing has a certain role in the diagnosis and, more importantly, in the management of FCoV infection when it is performed by appropriate methodologies and results are properly interpreted. Antibody testing can only be useful if the laboratory is reliable and consistent. Methodologies and antibody titer results may vary significantly. A single serum sample divided and sent to five different laboratories in the United States yielded five different results [26]. The antigen used in a test, for example, can play an important role in test sensitivity and specificity (eg, if the antigen used for the test is derived from nonfeline viruses, which is practiced by many commercial laboratories). Thus, it is essential that antibody results that are interpreted and compared by the clinician are always obtained with the same method performed by the same laboratory, and it is essential to use antibody tests validated by the scientific community. Evaluating titers of antibodies gives an idea of the amount of antibodies present. In contrast, tests (eg, in-house tests) that only indicate the presence of antibodies without quantification are not useful. They also produce a high number of false-positive and false-negative results [129]. The choice of the laboratory to be used is critical, and only those that perform quantitative titer evaluations should be used. The laboratory should have established two levels: one is its least significant level of reactivity (or lowest positive titer), and the other is its highest antibody titer value. In searching for a reliable laboratory, repeat samples from the same animal should be sent without warning to the same laboratory and to an FCoV-referenced laboratory for comparison to enable useful interpretation. Serum or plasma samples store well at $-20°C$ without loss of antibody concentration [26].

The presence of antibodies does not indicate FIP, and the absence of antibodies does not exclude FIP. Many authors agree that low or medium titers do not have any diagnostic value [101,130,131]. Approximately 10% of the cats with clinically manifest FIP have negative results. It has been shown that in cats with fulminant FIP, titers decrease terminally [77]. Cats with effusions sometimes have low titers or even no antibodies. This is because large amounts of virus in the cat's body bind to antibodies and render them unavailable to bind antigen in the antibody test or because the antibodies are lost in effusion when protein is translocated in vasculitis. Extremely high titers are of a certain diagnostic value. If the highest measurable titer is present in a cat (thus, it is important to know what the highest titer in a specific laboratory is), it increases the likelihood of FIP. In a recent study, the probability of FIP was 94% in cats with the highest titer when investigating a cat population in which FIP was suspected [101]. The diagnostic value of a high titer is also dependent on the background of the cat. The highest titer in a cat coming out of a multiple-cat household situation is not extremely predictive, because in those households, FCoV is endemic and many cats have high titers, whereas the highest titer in a cat from a single-cat environment is unusual and a stronger indicator of FIP.

Although antibody testing in sick cats that are suspected to have FIP is of limited value, there are a number of other situations in which antibody testing is a useful tool. A healthy cat that has no antibodies is considered likely to be free of FCoV, and thus is not infectious to others, does not shed FCoV, and does not develop FIP [10]. It has been shown that the height of the antibody titer directly correlates with the amount of virus that is shed with feces; cats with high antibody titers are more likely to shed FCoV and to shed more consistently with higher amounts of the virus [51]. Thus, height of the titer is directly correlated with the virus replication rate and the amount of virus in the intestines. Antibody measurement is important for the common situation in practice in which a cat is presented because it has been in contact with a cat with FIP or a suspected or known virus excretor. The owner wants to know the prognosis for an exposed cat or wishes to obtain another cat and needs to know whether the exposed cat is shedding FCoV. Also, cat breeders may request testing, with the goal of creating an FCoV-free cattery. Screening a cattery for the presence of FCoV and screening a cat before introduction into an FCoV-free cattery are also important indications.

Antibodies in effusion

Some studies have evaluated the diagnostic value of antibody detection in fluids other than serum, such as in effusions [132]. The presence of antibodies in effusion is correlated with the presence of antibodies in blood [133]. In a study by Kennedy et al [132], antibody titers in effusions were not helpful, because all cats in their study had medium antibody titers irrespective of whether they had FIP or not. In a study by Hartmann et al [101], however, the presence of anti-FCoV antibodies in effusion had a high

positive predictive value (90%) and a high negative predictive value (79%), although height of titers was not correlated with the presence of FIP. The measurement of antibodies in effusions is at least more useful than the measurement of antibodies in blood.

Antibodies in cerebrospinal fluid

Foley et al [134] determined the diagnostic value of antibody detection in CSF and found a good correlation to the presence of FIP when compared with histopathologic findings, whereas in a study by Boettcher et al [135], there was no significant difference in antibody titers in CSF from cats with neurologic signs caused by FIP compared with cats with other neurologic diseases confirmed by histopathologic findings.

Polymerase chain reaction

Compared with serology, RT-PCR provides the obvious advantage of directly detecting the ongoing infection rather than documenting a previous immune system encounter with a coronavirus.

Polymerase chain reaction in blood

RT-PCR can be performed to reverse-transcribe coronavirus RNA to cDNA and then to make large quantities of DNA visually detectable. Although FIP-causing viruses are genetic mutants of harmless enteric FCoV, numerous sites exist in the 3C and 7B genes that can be mutated or deleted and confer on the virus the capability to infect and replicate within macrophages. Sometimes, the change can be a single RNA base. As a result, PCR primers to discriminate between FIP-causing viruses and harmless enteric FCoV cannot be designed, and it is not possible to distinguish between a mutated and nonmutated virus by PCR [136]. There are a number of reasons why RT-PCR results are not always easy to interpret. There are several plausible explanations for false-negative PCR results. The assay requires reverse transcription of viral RNA to DNA before amplification of DNA, and degradation of RNA could be a potential problem, because RNases are virtually ubiquitous. There may be sufficient strain and nucleotide sequence variation such that the target sequence chosen for the assay may not detect all strains of FIPV [19]. There are also a number of explanations for false-positive results. First, the assay does not distinguish between "virulent" and "avirulent" FCoV strains, nor does it differentiate FCoV from CCV or TGEV. Although the role of these viruses in the field is unknown, cats can be experimentally infected with CCV and TGEV [35,137,138]; these infections could result in a positive PCR result. Second, recent studies support the hypothesis that viremia occurs not only in cats with FIP but in healthy carriers. FCoV RNA could be detected in the blood of cats with FIP as well as in the blood of healthy cats that did not develop FIP for a period of up to 70 months [50,57,58,136,139]. In a study by Gunn-

Moore et al [59], it was shown that in households in which FCoV is endemic, up to 80% of the cats can be viremic, irrespective of their health status, and that the presence of viremia does not seem to predispose the cats to the development of FIP. Therefore, the results of PCR tests must be interpreted in conjunction with other clinical findings and cannot be used as the sole criterion for diagnosing FIP.

Polymerase chain reaction in effusion

RT-PCR in effusion has been discussed as an interesting diagnostic tool. Data on the usefulness of this approach are limited, however. So far, only one study including information about RT-PCR on ascites fluid of a limited number of cats has been reported. In this study, six of six cats with confirmed FIP had positive RT-PCR results, and one of one cat with ascites caused by another disease had a negative RT-PCR result [101]. These numbers are, however, not sufficient to judge that approach sufficiently.

Polymerase chain reaction in cerebrospinal fluid

CSF has not been recommended for RT-PCR because it may contain low numbers of virus also in cats that do not have FIP if the blood-brain barrier is compromised. Accurate studies are needed, however.

Polymerase chain reaction in feces

RT-PCR has been used to detect FCoV in fecal samples and is sensitive and useful for documenting that a cat is shedding FCoV in feces [100]. Because cats vary in how much FCoV is shed in feces, repeated PCR should be performed daily over 4 to 5 days to detect accurately whether a given cat is shedding FCoV. Samples for RT-PCR must be carefully handled, kept frozen, and protected from RNA-degrading enzymes (which are ubiquitous in most environments). PCR should be performed as quickly as possible after collection, even if samples are frozen; delays in testing may result in false-negative results. Positive RT-PCR results in fecal samples document FCoV infection. The strength of the PCR signal in feces correlates with the amount of virus present in the intestines [51].

Antibody antigen complex detection

Because FIP is an immune-mediated disease and antibody antigen complexes play an important role, it has been suggested to look for circulating complexes in serum and effusions [113,140]. Antibody antigen complex detection can be performed using a competitive ELISA. Usefulness, however, is limited; the positive predictive value of the test was not high (67%) in one study, because there were many false-positive results [101].

Antigen detection

Other methods to detect the virus include searching for the presence of FCoV antigen (Fig. 6).
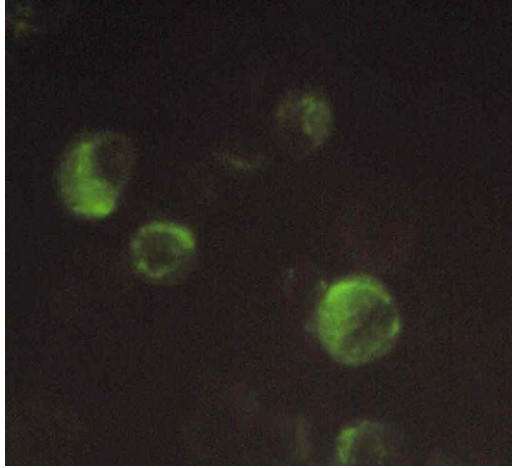
Fig. 6. Immunofluorescent staining of macrophages.

Immunofluorescence staining of feline coronavirus antigen in effusion

In a study by Parodi et al [141], an immunofluorescence assay detecting intracellular FCoV antigen in cells within effusion was used; however, the number of cats enrolled in that study was limited. Hirschberger et al [84] detected FCoV antigen in 34 of 34 samples from cats with FIP-induced effusions. In a recent study involving a large number of cats, immunofluorescence staining of intracellular FCoV antigen in macrophages of effusion had a positive predictive value of 100%. There were no false-positive results. This means that if this staining test is positive, it predicts 100% that the cat has FIP. Unfortunately, the negative predictive value was not high (57%). Cases that stained negative (although the cats did have FIP) can be explained by the fact that the number of macrophages on the effusion smear is sometimes insufficient. Another explanation is a potential masking of the antigen by competitive binding of FCoV antibodies in effusion that displace binding of fluorescence antibodies [101].

Antigen in tissue

Immunohistochemistry can also be used to detect the expression of FCoV antigen in tissue [142]. Tammer et al [143] used immunohistochemistry to detect intracellular FCoV antigen in paraffin-embedded tissues of euthanized cats and found FCoV antigen only in macrophages of cats that had FIP and not in control cats. Hök [144] was able to demonstrate FCoV antigen in the membrana nictitans of cats with FIP. It was shown that positive staining of macrophages in effusion predicts FIP 100% [101]; the same seems to be true for immunohistochemical staining of tissue macrophages. Immunostaining cannot differentiate between the "harmless" nonmutated FCoV and the mutated FIP-causing FCoV. Obviously, only FIP-causing virus is able to

replicate in sufficiently large amounts in macrophages, which results in positive staining. Therefore, in addition to histopathology (if pathognomonic lesions are present), detection of intracellular FCoV antigen by immunofluorescence or immunohistochemistry is the only way to diagnose FIP definitively. This tool should be used whenever possible.

Histology

Diagnosis of FIP can be established in many cases with just histopathologic testing of biopsy or necropsy samples. Hematoxylin and eosin–stained samples typically contain localized perivascular mixed inflammation with macrophages, neutrophils, lymphocytes, and plasma cells. Pyogranulomas may be large and consolidated, sometimes with focal tissue necrosis, or numerous and small. Lymphoid tissues in cats with FIP often show lymphoid depletion caused by apoptosis [26,145,146]. If histologic testing is not diagnostic, staining of antigen in macrophages [146] or detection of nucleic acids in tissue [147] can be used to confirm FIP (Fig. 7).

Therapy

Virtually every cat with confirmed FIP dies. Fast and reliable diagnosis of FIP and differentiating it from harmless enteric FCoV infection are crucial for prognostic reasons.
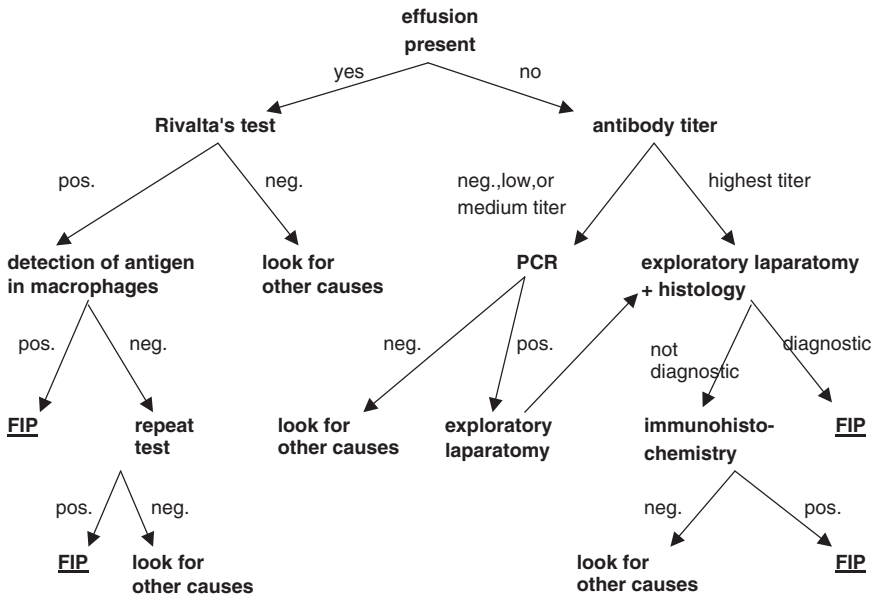

Fig. 7. Algorithm for the diagnosis of FIP.

Treatment of healthy feline coronavirus antibody–positive cats

There is no indication that any treatment of a healthy antibody-positive cat would prevent development of FIP [26]. Treatment with corticosteroids can conceivably prevent clinical signs from occurring (once the mutation has occurred) for a certain period of time, but immune suppression might have the opposite effect and precipitate clinical FIP because it can increase the risk of mutation (if the mutation has not occurred yet). Thus, immune suppression is contraindicated as long as the cat is only infected with harmless FCoV. Because stress is an important factor in the development of FIP [95], avoidance of unnecessary stress, such as rehoming, elective surgery, or placement in a boarding cattery, may be beneficial. IFNs (eg, feline IFN-ω, which is available commercially in Europe and Japan) have been discussed in this situation, but controlled studies are missing to date.

Treatment of cats with feline coronavirus–induced enteritis

Most cases of diarrhea caused by nonmutated FCoV are self-limiting. Cats with chronic diarrhea that have antibodies against FCoV, in which other possible causes have been eliminated or in which FCoV has been detected in the feces by electron microscopy, can only be treated supportively with fluid and electrolyte replacement and dietary intervention [20]. Treatment with lactulose or living natural yogurt may be beneficial because it regulates the intestinal bacterial flora and increases passage time. No specific antiviral treatment has yet been demonstrated to cure this condition. These cases can be a challenge because they are sometimes difficult to distinguish from cats with FIP, which can manifest solely as granulomatous changes in the intestines leading to diarrhea. FIP diarrhea can only be treated with immune suppression if it is identified, which, conversely, is contraindicated in harmless FCoV infection. In both cases, cats usually have antibodies and sometimes high titers but can only be differentiated by exploratory surgery, which should be avoided in cats with harmless intestinal FCoV infection.

Symptomatic treatment of cats with feline infectious peritonitis

Treatment for FIP is almost invariably doomed to failure, because cats with clinical FIP eventually die. Some cats with milder clinical signs may survive for several months and enjoy some quality of life with treatment, however. Once clinical signs become debilitating and weight and appetite decline, the owner must be prepared for the reality that the cat is dying.

Because FIP is an immune-mediated disease, treatment is aimed at controlling the immune response to FCoV, and the most successful treatments consist of relatively high doses of immunosuppressive and anti-inflammatory drugs. Immunosuppressive drugs, such as prednisone (4 mg/kg administered orally every 24 hours) or cyclophosphamide (2.5 mg/kg administered orally for four consecutive days every week), may slow disease progression but do

not produce a cure. Some cats with effusion benefit from tapping and removal of the fluid and injection of dexamethasone (1 mg/kg) into the abdominal or thoracic cavity (every 24 hours until no effusion is produced anymore). Cats with FIP should also be treated with broad-spectrum antibiotics and supportive therapy (eg, subcutaneous fluids) for as long as they are comfortable. A thromboxane synthetase inhibitor (ozagrel hydrochloride), which inhibits platelet aggregation, has been used in a few cats and has led to some improvement of clinical signs [148].

Some veterinarians prescribe immune modulators (eg, *Propionibacterium acnes*, acemannan) to treat cats with FIP, with no documented controlled evidence of efficacy. Immune modulators and IFN inducers are widely used and induce synthesis of IFNs and other cytokines. It has been suggested that these agents may benefit infected animals by restoring compromised immune function, thereby allowing the patient to control viral burden and recover from the disease. Nonspecific stimulation of the immune system is contra-indicated however in cats with FIP, because clinical signs develop and progress as a result of an immune-mediated response to the mutated FCoV.

Antiviral chemotherapy in cats with feline infectious peritonitis

The search for an effective antiviral treatment for cats with FIP, unfortunately, has not been successful, although several studies have been performed.

Ribavirin

Ribavirin, 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide (RTCA), is a broad-spectrum triazole nucleoside that has marked in vitro antiviral activity against a variety of DNA and RNA viruses, including FCoV. Ribavirin is a nucleoside analogue, but in contrast to the most common antiviral compounds, which act primarily to inhibit polymerases, ribavirin allows DNA and RNA synthesis to occur but prevents the formation of viral proteins, most likely by interfering with capping of viral mRNA. In vivo, therapeutic concentrations are difficult to achieve because of toxicity, and cats are extremely sensitive to the side effects.

Although active against FCoV in vitro [149,150], ribavirin was not effective in the treatment of cats with FIP. In one study, ribavirin was administered (16.5 mg/kg orally, intramuscularly, or intravenously every 24 hours for 10 to 14 days) to specific pathogen-free kittens 18 hours after experimental challenge exposure with an FIP-causing virus. All kittens, including ribavirin-treated and untreated kittens, succumbed to FIP. Clinical signs of disease were even more severe in the ribavirin-treated kittens, and their mean survival times were shortened [151]. The most common side effect in cats reported in several studies (already using a low dose of 11 mg/kg) is hemolysis. This develops as a result of sequestration of the drug in red blood cells. In addition, a dose-related toxic effect on bone marrow occurs, primarily on

megakaryocytes (resulting in thrombocytopenia and hemorrhage), and erythroid precursors. Later on or at higher dosages, neutrophil numbers are suppressed. Liver toxicity has also been reported [152,153]. Weiss et al [151] tried to decrease the toxicity of ribavirin by incorporating it into lecithin-containing liposomes and giving it intravenously at a lower dose (5 mg/kg) to cats challenged with an FIP-causing virus. They were, however, not able to reach a therapeutic concentration with this regimen.

Human interferon-α

Human IFNα has immunomodulatory and antiviral activity. IFNα is active against many DNA and RNA viruses, including FCoV. IFNα has a direct antiviral effect by inducing a general "antiviral state" of INFα-containing cells that protects against virus replication. It is not virucidal but merely inhibits viral nucleic acid and protein synthesis. It binds to specific cell receptors that activate enzymes, inhibiting synthesis, assembly, and release of viruses. Human IFNα is marketed as a recombinant product (rHuIFNα) produced by a cloned human IFNα gene expressed in *Escherichia coli*. There are two common treatment regimens for use of human IFNα in cats: subcutaneous injection of high-dose IFNα (10^4 to 10^6 IU/kg every 24 hours) or oral application of low-dose IFNα (1–50 IU/kg every 24 hours). When given parenterally in high doses, application leads to detectable serum levels. When given parenterally to cats, it becomes ineffective after 3 to 7 weeks because of the development of neutralizing antibodies against the human IFNα, which limits its activity. In a study in which cats were treated with human IFNα subcutaneously, cats became refractory to therapy after 3 or 7 weeks, respectively, depending on whether a high (1.6×10^6 IU/kg) or a lower (1.6×10^4 IU/kg) dose was used [154].

In vitro, antiviral activity of human IFNα against FIP-causing FCoV strains was demonstrated. Combination of IFNα with ribavirin in vitro resulted in antiviral effects significantly greater than the sum of the observed effects from ribavirin or IFNα alone, indicating synergistic interactions [149]. Human IFNα treatment was used in 74 cats (52 treated cats, 22 controls) with experimentally induced FIP that received IFNα, *P acnes*, a combination, or placebo. The prophylactic and therapeutic administration of high doses (10^4 or 10^6 IU/kg) of IFNα did not significantly reduce the mortality in treated versus untreated cats; only in cats treated with IFNα and *P acnes* at a dose of 10^6 IU/kg, the mean survival time was significantly prolonged by a few days [155].

Orally, human IFNα can be given for a longer period, because no antibodies develop. Given orally, however, IFNα is inactivated by gastric acid and, like other proteins, destroyed by trypsin and other proteolytic enzymes in the duodenum; therefore, it is not absorbed and cannot be detected in the blood after oral administration [156]. Thus, direct antiviral effects are unlikely after oral administration; instead, it only seems to have immunomodulatory activity. IFNα may bind to mucosal receptors in the

oral cavity, stimulating the local lymphoid tissue and leading to cytokine release on lymphatic cells in the oral or pharyngeal area, which triggers a cascade of immunologic responses that finally act systemically [157]. Tomkins [158] showed that orally administered IFNα induced cytokine responses in buccal mucosal lymph nodes, including upregulation of IFNγ expression and downregulation of interleukin-4. In studies in mice, it was shown that subcutaneous administration of murine IFNα had an antiviral effect, whereas oral administration caused an immunomodulatory effect. Infection of mice with encephalomyocarditis virus resulted in death in 100% of mice if not treated, in 40% survival of mice when treated with murine IFNα orally at a dose of 2×10^5 IU per mouse, and in 90% survival of mice when given the same dose intraperitoneally [159] confirming the immune modulatory effect after oral application. Therefore, low-dose oral IFNα treatment should not be used in cats with FIP because of its immunomodulatory activity, which may lead to progression of disease.

Feline interferon-ω

Recently, the corresponding feline IFN, feline IFNω, was licensed for use in veterinary medicine in some European countries and Japan. IFNs are species specific, and the human IFN clearly differs from the feline one not only regarding its antigenicity (thus causing antibody development in animals) but with respect to its antiviral efficacy in feline cells. Even if feline IFNω is used long term, cats do not develop antibodies. In addition, because it is the homologous species of IFN in cats, it is expected to be more effective than human IFNα. Feline IFNω is a recombinant product, which is produced by baculoviruses containing the feline sequence for this IFN that replicate in silkworms after infection; subsequently, feline IFNω is purified out of homogenized silkworm preparations [160]. Data on the efficacy of feline IFNω in cats with FIP are limited. FCoV replication is inhibited by feline IFNω in vitro [161]. In one study (not controlled and only including a small number of cats), 12 cats that were suspected of having FIP were treated with IFNω in combination with glucocorticoids and supportive care [162]. IFNω was given at a rate of 10^6 IU/kg subcutaneously every 48 hours initially until clinical improvement and, subsequently, once every 7 days. Glucocorticoids were given in the form of dexamethasone in case of effusion (1 mg/kg intrathoracic or intraperitoneal injection every 24 hours) or prednisolone (initially, 2 mg/kg administered orally every 24 hours until clinical improvement, then gradually tapered to 0.5 mg/kg administered every 48 hours). Although most cats died, 4 cats survived over a period of 2 years; all had initially presented with effusions. Even though there was no control group in this study and FIP was not even confirmed in the 4 surviving cats, these results are somewhat interesting (because cats with other effusion-associated diseases would not be expected to survive for 2 years without proper treatment), and further studies would certainly be interesting.

Prevention

Unfortunately, preventing FIP is extremely difficult. The only way to prevent the development of FIP is to prevent infection with FCoV. Vaccination prevents neither FIP nor FCoV infection effectively. Testing and removing strategies are ineffective. Management of FIP should be directed at minimizing the population impact and accurately diagnosing and supporting individual affected cats. Thus, veterinarians need to be knowledgeable regarding successful and unsuccessful strategies so as to provide useful counsel to their clients.

Management

Different situations have to be considered depending on the environment.

Management of a cat after contact

If a cat with FIP is euthanized and there are no remaining cats, the owner should wait approximately 3 months before obtaining another cat, because FCoV can stay infectious for at least 7 weeks in the environment. If there are other cats in the household, they are most likely infected with and shedding FCoV. In natural circumstances, cats go outside to defecate and bury their feces, in which case the virus remains infectious hours to days (slightly longer in freezing conditions). Domesticated cats have been introduced to litter boxes, however, in which FCoV may survive for several days, and possibly up to 7 weeks in dried-up feces. Thus, FCoV-shedding cats most likely have a better chance to eliminate the virus if allowed to go outside (optimum situation is in a fenced yard).

It is a common practice for clients to present a cat to the veterinarian that has been in contact with a cat with FIP or a suspected or known virus excretor. The owner may want to know the prognosis for the exposed cat or may want to obtain another cat and needs to know whether the exposed cat is shedding FCoV. It is likely that the cat is antibody-positive, because 95% to 100% of cats exposed to FCoV become infected and develop antibodies approximately 2 to 3 weeks after FCoV exposure. There are a few cats, however, that may be resistant to FCoV infection. It has been shown that a low number of cats in FCoV endemic multiple-cat households continuously remain antibody-negative [163]. The mechanism of action for this resistance is still unknown. The owner should be advised that the cat in contact is likely to have antibodies and reassured that this is not necessarily associated with a poor prognosis. Most cats infected with FCoV do not develop FIP, and many cats in single- or 2-cat households eventually clear the infection and become antibody-negative in a few months to years. Cats can be retested (using the same laboratory) every 6 to 12 months until the results of the antibody test are negative. Cats exposed only once often have a quicker reduction in antibodies. To exclude any risk at all, the owner should be advised to wait until antibody titers of all cats are negative before

obtaining a new cat. Some cats, however, remain antibody-positive for years. A rise in antibody titer or maintenance at a high level does not necessarily indicate a poor prognosis for the cat. In a study following cats with high titers, the titers of 50 of these cats remained at a high level on at least three occasions, yet only 4 cats died of FIP [26]. In contrast, in a situation of endemic infection, a constantly low titer is highly indicative that a cat is not going to develop FIP.

Management of multiple-cat households with endemic feline coronavirus

Households of less than 5 cats can spontaneously and naturally become FCoV-free, but in households of more than 10 cats, this is almost impossible, because the virus passes from one individual cat to another, maintaining the infection. This holds true for virtually all multiple-cat households, such as breeding catteries, shelters, foster homes, and other homes with more than 5 cats.

When a cat in a household develops FIP, all other cats in contact with that cat have already been exposed to the same FCoV. There is virtually nothing to prevent FIP in other cats that are in contact with the cat with FIP. Although the risk is only 5% to 10%, full-sibling litter mates of kittens with FIP have a higher likelihood of developing FIP than other cats in the same environment [164] indicating a certain genetic component.

Various tactics have been used to eliminate FCoV from a household. Reducing the number of cats (especially kittens less than 12 months old) and keeping possibly FCoV-contaminated surfaces clean can minimize population loads of FCoV. Antibody testing and segregating cats are aimed at stopping exposure. Approximately one third of antibody-positive cats excrete virus [10,11,130,165,166]; thus, every antibody-positive cat has to be considered infectious. After 3 to 6 months, antibody titers can be retested to determine whether cats have become negative. Alternatively, RT-PCR testing of (several) fecal samples can be performed to detect shedders. It is important to detect chronic FCoV carriers so that they can be removed. In large multiple-cat environments, 40% to 60% of cats shed virus in their feces at any given time. Approximately 20% shed virus persistently. Approximately 20% are immune and do not shed virus. Repeated PCR testing of feces should be performed at weekly intervals for 2 months or more to document carriers. If the cats remain persistently PCR-positive for more than 6 weeks, they should be eliminated from the cattery and placed in single-cat environments [164].

Early weaning and isolation

More than any other factor, management of kittens determines whether or not they become infected with FCoV. Kittens of FCoV-shedding queens should be protected from infection by maternally derived antibody until they are 5 to 6 weeks old. An early weaning protocol for the prevention of FCoV infection in kittens has been proposed by Addie and Jarrett [26],

which consists of isolation of queens 2 to 3 weeks before parturition, strict quarantine of queens and kittens, and early weaning at 4 to 6 weeks of age. This procedure is based on the findings that some queens do not shed the virus and some queens stop shedding after several weeks if not re-exposed. Even if queens do shed, young kittens have maternal resistance to the virus [7]. Early removal of kittens from the queen and prevention of infection from other cats may succeed in preventing infection in these kittens. Although straightforward in concept, isolation of queens and early weaning is not as simple as it may seem. The procedure requires quarantine rooms and procedures that absolutely ensure a new virus does not enter. It is an advantage when the isolated queens are not shedding FCoV, when they are shedding low levels, or when they can clear the infection early after being isolated. The single most important factor is the number of animals. The success of early weaning and isolation in FCoV control depends on effective quarantine and low numbers of cats (<5 cats) in the household. Also, human abodes do not easily allow adequate quarantine space for large numbers of queens and kittens, and the time and money required to maintain quarantine increase in proportion to the number of queens and litters under quarantine. In a study in large catteries in Switzerland in which the same protocol was followed, early weaning failed and viral infection of kittens as young as 2 weeks old was demonstrated [167]. It is clear that low FCoV exposure can delay infection, whereas high exposure can overcome maternally derived immunity at an early age.

There are two essential downsides of isolation and early weaning. It is not easy to do, and it fails if appropriate conditions are not maintained. Additionally, some breeders believe that early weaning exacts a social price on the kittens. In recognition of both concerns, it is recommended that early weaning not be undertaken without careful consideration. FCoV-free households do not require routine isolation and early weaning. When kittens are isolated with their queen, special care must be taken during the period from 2 to 7 weeks of age to socialize the kittens. The success of early weaning should also be monitored, and it should not be continued if it is not successful. Kittens that have been successfully reared free of FCoV should be antibody-negative at 12 weeks of age. Even if kittens can be raised free of FCoV, they may become infected sooner or later. Therefore, the objective of isolation and early weaning should not be to prevent infection but to delay it [164]. For early weaning to be effective, it is best for kittens to be taken to a new home (with no other cats) at 5 weeks of age. Even then, however, early weaning is not always successful.

Recommendations for breeding catteries

It has been suggested to maximize heritable resistance to FIP in breeding catteries. Genetic predisposition is not completely understood, however. It is known that susceptible cats are approximately twice as likely to develop FIP as other cats [168]. If a cat has two or more litters in which kittens develop

FIP, that cat should not be bred again. Particular attention should be paid to pedigrees of males, in which FIP is overrepresented. Because line breeding often uses valuable tomcats extensively, eliminating such animals may have a small but important effect on improving overall resistance [164].

Screening of a cattery for the presence of FCoV is important. If there are many cats housed in a group, a random sampling of 3 to 4 cats should indicate whether FCoV is endemic. If cats are housed individually, it may be necessary to test them all. Cats in households with fewer than 10 cats and no new acquisitions and cats that are isolated from each other in groups of 3 or less often eventually lose their FCoV infection [169]. Once they have been established, antibody-negative catteries can be maintained free of FCoV by monitoring new cats before they are introduced. Thus, cats should be screened before introduction, and antibody-positive cats should never be taken into the household. Cat breeders often also request that their cats be screened for FCoV antibodies before mating. If the cat is healthy and antibody-negative, it can be safely mated with another antibody-negative cat. If the cat is antibody-positive, it should not be mated with a cat from an FCoV-free environment [164].

Recommendations for shelters

Prevention of FIP in a shelter situation is virtually impossible unless cats are strictly kept in separate cages and handled only by means of sterile handling devices (comparable to isolation units). Isolation is often not effective because of the ease with which FCoV is transported on clothes, shoes, dust, and cats. Comparison of shelters with different types of handling revealed a significant correlation between an increase in the number of handling events outside the cages and an increase in the percentage of antibody-positive cats. In a study in which feral cats were tested at the time they were brought into local shelters (in which multiple cats were kept together) and at 1-to 2-week intervals thereafter, only a low number of cats had antibodies at the time point of entering, but the percentage increased rapidly until virtually all cats in the shelters were infected with FCoV [40].

Shelter managers should use education and communication to minimize adverse effects of FIP in cat populations. Shelter managers should have written information sheets or contracts informing adopters about FCoV and FIP. They should understand that FCoV is unavoidable in multiple-cat environments and that FIP is an unavoidable consequence of endemic FCoV. Shelters need to optimize facilities and husbandry so that the facilities can be cleaned easily and virus spread is minimized. It is essential to decrease viral load and stress levels [164].

Vaccination

There have been many attempts to develop effective vaccines, but, unfortunately, most have failed, mainly because of ADE [75,78,170,171].

Nevertheless, a vaccine was licensed (Primucell, Pfizer Animal Health) incorporating a temperature-sensitive mutant of the FCoV strain DF2-FIPV, which can replicate in the cool lining of the upper respiratory tract but not at higher internal body temperatures [172–175]. This vaccine, administered intranasally, produces local immunity (IgA antibodies) at the site where FCoV first enters the body (the oropharynx) and also induces cell-mediated immunity. The vaccine has been available in the United States since 1991 and has been introduced in many European countries. The concerns of such a vaccine are safety and efficacy. Safety concerns focus on whether the vaccine could cause FIP or produce ADE. Although some experimental vaccine trials with vaccines that never appeared on the market have recorded ADE on challenge [176,177], field studies have demonstrated that this intranasal vaccine is safe. In two extensive placebo-controlled double-blind field trials there was no development of FIP or ADE [178–180]. There were a few immediate side effects after application, such as sneezing, vomiting, or diarrhea, which were not statistically different in the vaccinated group and the placebo group [178].

The efficacy of this vaccine is questioned constantly, however. Experimental studies have reported preventable fractions between 0% [176,177] and 50% to 75% [175,181], depending on the investigator. In a survey of 138 cats belonging to 15 cat breeders in which virtually all the cats had antibodies, no difference was found in the development of FIP between the vaccinated group and the placebo group [178]. Thus, vaccination in an FCoV endemic environment or in a household with known cases of FIP is not effective. In one of the placebo-controlled double-blind trials that was performed in Switzerland in a group of cats that did not have contact with FCoV before vaccination, a small but statistically significant reduction in the number of cats that developed FIP was noted [178,182]. Because the vaccine is ineffective when cats have already had contact with FCoV, antibody testing may be beneficial before vaccination. One disadvantage is that most cats develop antibodies after vaccination, thus making the establishment and control of an FCoV-free household difficult. In conclusion, study results do not clearly identify whether vaccination has no effect versus a small effect. Although only marginally if at all efficacious, the vaccine is at least safe and does not induce ADE.

Public health considerations

Concerns have arisen about a possible danger of FCoV to people because there is a close antigenetic relation between coronaviruses of different domestic animal species (eg, CCV, TGEV) and a coronavirus deriving from animals in close contact with humans recently caused the so-called "severe acute respiratory syndrome" (SARS) that seemed to be a threat to thousands of people. There is, however, no indication that people can be infected with FCoV.

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