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Review

An update on feline infectious peritonitis: Diagnostics and therapeutics

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Niels C. Pedersen *

Center for Companion Animal Health, School of Veterinary Medicine, University of California, One Shields Avenue, Davis, CA 95616, USA

ABSTRACT

This review is concerned with what has been learned about feline infectious peritonitis (FIP) diagnostics and therapeutics since the publication of an extensive overview of literature covering the period 1963–2009. Although progress has been made in both areas, obtaining a definitive diagnosis of FIP remains a problem for those veterinarians and/or cat owners who require absolute certainty. This review will cover both indirect and direct diagnostic tests for the disease and will emphasize their limitations, as well as their specificity and sensitivity. There is still no effective treatment for FIP, although there are both claims that such therapies exist and glimmers of hope coming from new therapies that are under research. FIP has also been identified in wild felids and FIP-like disease is now a growing problem among pet ferrets.

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Introduction

Feline infectious peritonitis (FIP) is a coronaviral disease that can affect cats of any age, but is most prevalent among cats <3 years of age and especially from 4 to 16 months of age (Pedersen, 2009). FIP occurs commonly in catteries (pedigreed cats), shelters, kitten foster/rescue facilities and dense free-roaming colonies. Typical of an enzootic infection, the incidence of FIP can vary widely over time. The mortality is extremely high once clinical signs appear, although some cats can live with the disease for weeks, months or, rarely, years. A detailed clinical description of FIP can be found in earlier comprehensive reviews and will not be covered herein (Addie et al., 2009; Pedersen, 2009; Drechsler et al., 2011).

FIP virus (FIPV) arises through specific mutations in a common feline enteric coronavirus (FECV) that is ubiquitous in cats throughout the world and not in itself an important pathogen (Pedersen, 2009). FECV is shed in the feces of most apparently healthy cats in large multi-cat environments (Pedersen et al., 2004) and transmission results from direct ingestion of feces or contaminated litter and other fomites. Kittens usually become infected at around 9 weeks of age (Pedersen et al., 2004, 2008). Mutants of FECV capable of causing FIP are probably generated in large numbers during this initial infection, when levels of FECV replication are extremely high (Pedersen et al., 2008; Vogel et al., 2010). However, only a small proportion of cats exposed to these mutant viruses will develop FIP. Resistance to FIP is complicated and involves genetic susceptibility, age at the time of exposure and a number of stressors that occur at

the same time as infection and have a negative impact on the ability of the infected cat to eliminate the virus. The time period between initial FECV exposure and clinical signs of disease can be as short as 2–3 weeks, as long as several months or, rarely, years. This period could reflect the time it takes for mutant FIPVs to evolve, or for the disease to progress from a subclinical to clinical state. Subclinical infections are usually limited to the mesenteric lymph nodes and can resolve or progress (Pedersen and Black, 1983; Legendre and Bartges, 2009; Pedersen, 2009). The onset of overt disease is a signal that the cat's battle with the virus has been lost and a return to normal health is extremely uncommon. There are rare occasions when a cat will make an apparent recovery, only to have clinical signs recur months and even years later (Legendre and Bartges, 2009).

The disease course between onset of clinical signs and death is also variable, but is generally shorter in younger cats and cats with effusive disease than in older cats and cats with non-effusive disease. Some cats, even with effusive FIP, can live for many months and the author has worked with a Birman cat that died of dry FIP at 6 years of age; based on its extensive clinical history, the cat appeared to have subclinical disease for its entire life. In one study concerning mainly cats with relatively mild presenting signs of non-effusive disease, the 1 year survival rate was only 5%.[1]

Owners that have acquired a kitten or young cat often become deeply attached to the animal before the first signs of FIP occur. The diagnosis of FIP, especially with its extreme mortality rate and lack of any effective treatment, has a great psychological effect on many owners. It also is the trigger for an owner communication most feared

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[1] See: http://www.vetmed.ucdavis.edu/ccah/research/FIP%20and%20PI%20info%20page.cfm (accessed 11 May 2014).

by both breeders and shelter managers. Because some cats with FIP are still reasonably well at the time of diagnosis and can often live weeks or months longer with only symptomatic treatment, owners might be reluctant to accept the diagnosis or the fact that there is no effective treatment. This can lead to a series of additional tests that often purport to be highly sensitive and specific, but seldom provide the desired answer and might even further cloud the diagnosis. The lack of an effective therapy often complicates matters, and some owners will go to great lengths to research the disease on the Internet and other sources. This can lead them to individuals who claim to have found treatments for the disease that are either curative or will prolong life. These claims are frequently supported by anecdotal statements from owners who have found such treatments beneficial. Unfortunately, due to problems with interpreting available diagnostic tests, not all cats diagnosed with FIP actually have the disease. If these cats have a self-limiting condition other than FIP, they will appear to respond well to almost any non-harmful treatment that is administered. Such cases give credibility to a particular treatment when none is deserved.

The purpose of this review is to update the knowledge of FIP diagnostics and therapeutics since the subjects were last reviewed (Pedersen, 2009). A number of studies concerning these subjects have appeared over the last 5 years and our knowledge of FIP has greatly increased. However, there still is no easy way to prevent the disease, no simple way to diagnose it definitively and no way to treat it effectively. Hopefully, this will change with our increasing knowledge of the factors causing FIP and drugs that target essential steps in FIP viral replication.

Diagnostic tests for feline infectious peritonitis

The diagnosis of FIP is based first and foremost on consideration of the cat's age, origin, clinical signs and physical examination. Cats 4–36 months of age from high-density environments that manifest a persistent but undulating antibiotic unresponsive fever are immediate suspects for FIP. Very few infectious diseases other than FIP have this signalment. More specific signs of FIP observed by the owner or on physical examination will narrow the diagnostic choices even more. Abdominal distension with ascites, dyspnea with pleural effusion, jaundice, hyperbilirubinuria, discernible masses on the kidneys and/or mesenteric lymph nodes, uveitis and a range of neurological signs associated with brain and/or spinal cord involvement are all common in cats with either the effusive ('wet') or non-effusive ('dry') form of FIP. At this point, the diagnosis of FIP can be made with reasonable certainty. However, given the high mortality, many veterinarians and owners feel uncomfortable with a diagnosis based on 'reasonable certainty'.

The difficulty then becomes choosing tests that will either further increase the odds that the clinical signs are caused by FIP (indirect tests), or that might provide a definitive diagnosis (direct tests). It is important to remember that the sensitivity and specificity of any indirect test will vary greatly depending on the likelihood that the cat has FIP based on other parameters. That is to say, the positive predictive value of a test such as a complete blood count (CBC) or albumin:globulin (A:G) ratio to predict FIP will be far greater in cats that have a signalment compatible with FIP than for those with a signalment not typical of FIP. It is also important to mention that the results of additional indirect tests are just as capable of confusing the diagnostic process as strengthening it.

Indirect tests

Complete blood count, albumin, globulin and bilirubin

The diagnosis of FIP is usually achieved by weighing signalment, clinical findings, abnormalities present in common diagnostic procedures and, when possible, postmortem examination and histopathology (Sharif et al., 2010). Classic indirect tests for FIP include CBC, total serum protein, albumin and globulin levels, A:G ratio and basic blood chemistries (Addie et al., 2009; Pedersen, 2009; Drechsler et al., 2011). Common abnormalities usually include a chronic non-regenerative anemia (anemia of chronic disease), leukocytosis with an absolute increase in neutrophils and an absolute decrease in lymphocytes, elevated serum protein associated with high globulin and low albumin, and a low A:G ratio.

Hyperbilirubinemia and hyperbilirubinuria are common in cats with FIP, especially those with the effusive form. Elevations in serum and urine bilirubin (or biliverdin) are usually not associated with elevations in liver enzymes (Addie et al., 2009) and the liver is often spared in cats with FIP; evidence of cholestasis is not observed. Therefore, elevations in blood and urine bilirubin are not due to liver disease, as has been previously suggested, but rather are due to the increased destruction of RBCs in both lesions and in the circulation and difficulties in clearing hemoglobin breakdown products. Cats are notoriously poor at glucuronidation (Court and Greenblatt, 2000), thus limiting the rate that bilirubin and biliverdin are metabolized and recycled. If these common abnormalities are coupled with the usual signalment and clinical signs, a diagnosis of FIP can be made with high certainty. Even though many cats with FIP have characteristic CBCs, albumin and globulin levels and A:G, it is not reasonable to expect that every targeted parameter is always abnormal in the right direction. It is more important to look at the total picture and always in context of the signalment, clinical and physical features.

Analysis of effusions

The presence of a characteristic type of fluid in the peritoneal cavity or, less frequently, the pleural cavity is one of the most diagnostic features of the effusive (wet) form of FIP. Wet FIP predominates in most purebred and random bred cats, except for Birman and Burmese, which are more commonly diagnosed with the dry form. The fluid is usually yellow tinged due to the presence of bilirubin and, rarely, green-tinged due to the presence of biliverdin. As with hyperbilirubinemia and hyperbilirubinuria, the yellowish discoloration is a product of microhemorrhage and the breakdown of erythrocytes by macrophages.

FIP effusions are clear to moderately cloudy, viscous (egg-white consistency, often with threading) and high in protein (near serum level or higher). They often form partial clots when placed in a serum tube. FIP fluids are frequently labeled 'modified transudates' based on their perceived lack of cellularity. However, they are inflammatory exudates in the purest sense and do not meet the established physical or physiologic criteria for a modified transudate (Zoia et al., 2009). Most FIP effusions contain a fair number of cells (500–5000/µL), including macrophages, neutrophils and a low proportion of lymphocytes. FIP effusions are usually not outwardly hemorrhagic in appearance, with the exception of some pleural effusions. However, they often contain microscopic numbers of RBCs and visible fibrin tags. The exudate of FIP is unlike that seen in rare cases of bacterial peritonitis; the fluid accompanying bacterial peritonitis is clearly purulent in appearance, with very high neutrophil counts, and is not viscous or yellow-tinged. Transudates and modified transudates associated with liver and heart disease, lymphatic duct rupture and neoplasia do not have the same physical and cellular characteristics as FIP effusions.

Ultrasonography

The analysis of ascitic or pleural exudates in cats with FIP depends on the ability to realize the presence of such effusion and to obtain a fluid sample by simple centesis. Large pleural or peritoneal effusions often cause noticeable dyspnea or abdominal distension. However, there are many effusions that go unsuspected on initial physical examination or that are of minimal volume. In those cases,