

PURRsuing FIP and WINNING

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This past November, the Winn Feline Foundation brought experts on feline infectious peritonitis (FIP) from around the world to the campus of the University of California–Davis School of Veterinary Medicine for a two-day symposium. Their goal was to discuss the latest advances in the detection, treatment, and prevention of FIP. In a series of short lectures and round-table discussions, leading clinicians, researchers, and advocates shared information with in person and online participants, covering a wide range of topics that included the pathogenesis of the FIP virus, diagnosing FIP, breakthroughs in the treatment of FIP, and the prevention of FIP through future vaccines and environmental management.

FIP Pathogenesis

The symposium kicked off with a presentation by Dr. Niels Pedersen, who is arguably the leading authority today on the topic of FIP, and on FIP pathogenesis. (Pathogenesis is the origin and biological processes that lead to the diseased state). Thanks to the efforts of Dr. Pedersen and other researchers around the world, the pathogenesis of FIP is now well understood.

Dr. Pedersen explained that FIP is a relatively new disease and that there were no documented cases before the 1950s. It is a double-stranded RNA virus, and currently the largest RNA virus known to science. There are two viruses involved in the pathogenesis of FIP: the feline enteric corona virus (FECV), and feline infectious peritonitis virus (FIPV).

Corona viruses are ubiquitous in the environment, extremely adaptable, and can infect multiple species of animals. Examples

of corona virus that can cause disease in humans are the Middle East respiratory syndrome virus (MERS) and the severe acute respiratory syndrome virus (SARS). While human corona viruses attack the respiratory system, FECV is strictly a virus inhabiting the digestive tract. It is shed in the feces of an estimated 40–60% of healthy cats, particularly in multi-cat environments where cats share litter boxes. The FECV virus has a very narrow tropism (type of tissue that supports the growth and replication of the virus), infecting only a very specific type of epithelial cell primarily located in the large intestine and colon. It may cause a mild diarrhea in cats, but for the most part it enters its host through a fecal–oral route and resolves itself without causing disease of any kind. Healthy cats typically can raise an immune response to the virus, but the immunity is not permanent, and a cat can become re-infected when antibodies to the virus drop off.

Kittens receive FECV antibodies from their mother's colostrum, which are absorbed into their system and provide protection for approximately the first 11 weeks of their lives. They also receive antibodies in their mother's milk. These are not absorbed into their system, but provide a passive immunity by coating the oral pharynx of the kitten—the entry point of the enteric corona virus—thereby providing an additional layer of immunity as long as the kitten is nursing. At approximately 12 weeks, the kittens begin to produce their own antibodies. It is important to understand this timeline, as it is the reasoning behind early weaning and separation of new kittens from their mother and other adults in some catteries. It also provides a rationale for separating non-nursing kittens less than 12 weeks old

from other adults in shelters. Additionally, it provides some insights as to why bottle-fed kittens are more susceptible to FIP than kittens who nurse normally.

Dr. Pedersen also explained that since antibodies in a cat or kitten drop off as the virus levels drop, multi-cat households or shelters are in a constant state of reinfection, passing the virus back and forth to one another through shared litter pans. Typically, this does not cause any issues in the cattery; at most, there could be mild diarrhea from time to time.

So, how does a corona virus infection progress to FIP? Dr. Pedersen emphasized that FIP is not a rare form of a corona virus infection, as was once thought. FECV produces a mild enteric infection, FIPV causes FIP. Researchers discovered that FECV was mutating into a new virus that was structurally 99% the same as the FECV, but instead of merely residing inside the large intestine, the mutated virus attacked



Dr. Niels Pedersen

macrophages, a type of white blood cell that is the most primitive and basic level of the body's immune response. Macrophages lining the walls of the large intestine clean up the FECV as the cat's immune system fights the foreign invaders. If the virus happens to mutate inside the macrophage, the macrophage now becomes infected. Macrophages can travel through the body, spreading the virus throughout the host. Worse, the virus interferes with the cell's ability to self-destruct when infected with a virus. Typically, cytokines (a type of protein) inside a cell will rapidly trigger a self-destruct message to the macrophage when it becomes infected with a virus, but in the case of FIPV, the self-destruct response is delayed until the macrophage is filled with pockets of virus, giving it a characteristic foamy appearance under a microscope. Fluid drained from the abdomen of a cat with FIP will typically contain these foamy macrophages. Eventually the cytokines do trigger, but too late, and the virus is spread and infects other macrophages, attacking other parts of the body.

Dr. Pedersen also discussed the epizootiology, which is the study of disease patterns in a population, of FIP. He noted that FIP is primarily a problem of multi-cat environments, and that foster rescues were suffering the most. He noted some possible contributing factors; e.g., lack of milk immunity from early weaning or possibly stress from early spay-neuter. He said the environments need to be further studied as they may provide answers. He also stated that the incubation period for FIPV is unknown as yet, and that some kittens or cats are infected immediately, while others exhibit a sub-clinical stage then exhibit disease due to

some stress factor. Males seem slightly more susceptible than females.

The presentation closed with a brief discussion on FIP incidence rates. According to Dr. Pedersen, 100% of cats are exposed to FECV—there isn't much you can do about it. At least 10% of cats will develop a mutant form of the virus capable of producing FIP. Out of those cats, only one in ten will develop actual FIP, meaning most cats are able to develop an immunity to it. Why some are unable to do so is not yet known.

FIP Diagnosis

Dr. Emi Barker and Dr. Katrin Hartmann discussed the importance of getting the diagnosis of FIP correct and some of the tools available to the veterinary clinician to obtain a diagnosis. FIP can mimic many types of disease states, and the diagnosis is not certain unless virus can be recovered from tissues, which is extremely difficult in the dry form of FIP. Now that promising treatments are becoming available, it is more important than ever to get the diagnosis right. A false negative diagnosis, and the disease can progress rapidly before therapy can be initiated. A false positive diagnosis, and the patient many spend thousands of dollars on an ineffective treatment.

Following their remarks, they participated in a roundtable discussion with other clinicians, moderated by Dr. Leslie Lyons. The focus was the challenge of diagnosing FIP. There was general agreement that the Rivalta test, a quick and easy test vets can do in their office, should be the first step in cases where there is an accumulation of

abdominal fluid and wet FIP is suspected. Acetic acid is mixed in a test tube with water, and a drop of the fluid exudate is carefully dropped on the surface. If the drop disappears and is dissolved into the solution, the test is negative, and if a milky white precipitate forms, the test is positive. A positive test does not mean the cat has FIP—other diseases can cause the milky precipitate, which is produced by an abnormal increase in certain proteins in the abdominal fluid. However, a negative test means that it is very unlikely the cat has FIP and other diagnoses should be considered. This simple test can save a client thousands of dollars on unnecessary testing and ineffective treatments.

If the test is positive, then additional laboratory testing usually needs to be done to attempt to confirm a diagnosis of FIP. With effective but expensive treatments now available to those who choose to pay for them, it is critical to try and confirm the diagnosis. No matter how competent a veterinarian is, it was also thought a good idea to get a second opinion on complex cases, given the difficulty in making an accurate diagnosis. Some veterinarians rarely see a case of FIP, so the second opinion by one who does see them more frequently can be helpful.

Treatment of FIP

Considerable time was dedicated to emerging treatments. Most people in the cat fancy have heard whispers of "black market" cures. Are they real, do they work, can we really call them a "cure?" Why aren't these drugs available to U.S. veterinarians legally? Dr. David Bruyette pointed out that while FDA processes are somewhat slow and cumber-

Speakers Dr. Katrin Hartmann (left) and Dr. Emi Barker (right)





some, “they aren’t always the bad guy.” There are pharmaceuticals in human clinical trials that could be effective in fighting FIP, but the patent owners will not license for animal trials. If toxicity is discovered in animal trials, it could cause the human trials to fail. He also explained that cost is a factor; the costs involved in researching and manufacturing a new drug could make the cost of the drug to consumers prohibitively high.

Dr. Pedersen offered some insights into treatment strategies, stating that there are only two approaches: boosting the immunity of the host so that the host fights off the virus, or attacking the virus itself. Until recently, the only treatments available were those that boosted the immune system of the host, and while they could make the patient more comfortable and sometimes prolong the inevitable, most patients were dead in less than a year.

Two drugs are now in clinical trials: GC 376 at Kansas State University and GS 441524 at UC-Davis. While most researchers involved stop short of calling these drugs “cures,” the majority of cats treated in the trials have recovered and remain disease-free. As of the date of the symposium (November 16, 2019) Dr. Pedersen noted that more than 3000 cats had been treated—95% successfully—across the world. The long-term toxicity of the drugs is unknown, as is their long-term effectiveness. However, multiple attendees stood up and shared stories of

their now healthy cats after treatment with the new drugs. Dr. Pedersen predicted the rise of many new drugs which he believed necessary to prevent the virus from becoming resistant. He also hoped that clinicians would never treat for corona virus, as that could hasten drug resistance challenges.

Also discussed at length was the ability of desperate U.S. pet owners to get a form of the new drugs overseas, and why researchers and clinicians were unable to help obtain or administer the drugs, citing U.S. law as the main barrier. Veterinarians who obtain unlicensed drugs for clients risk sanctions and the loss of their licenses. However, the panelists encouraged those cat owners who chose to obtain the drug overseas and administer it themselves to find a veterinarian who would help monitor their cat, even if he or she cannot help with the actual treatment.

FIP Prevention

While Dr. Pedersen stated that there was little that could be done to prevent exposure to FECV or prevent the mutation of the virus in a host, there was considerable discussion around preventing the mutated virus from becoming FIP disease. While a cure is a wonderful achievement, even better is preventing the disease through vaccination. Researchers were hopeful that a vaccine would be come available in the next

few years—ideally, one that would remain effective despite virus mutations.

Stress was also discussed as a risk factor for FIP. While no direct connection has yet been proven, cats in what might be considered stressful situations had a higher incidence of FIP (as noted earlier) but why this is so is not understood. It is hard to ignore stress as a factor, though, as shelters that worked to reduce the stressful conditions in their facility noted reduced incidence of FIP and other diseases in the general population.

While trying to maintain a corona virus-free cattery may seem like one way to avoid FIP, one researcher who had made multiple cattery visits over the years noted that there was not a clear connection between a clean cattery and what he classified as a dirty cattery. He saw healthy, robust kittens running around the dirty cattery and weak, sickly kittens running around the clean cattery.

While the participants stopped short of saying there was a cure for FIP, they repeatedly called the disease “curable.” And thanks to the efforts of the Winn Foundation, the Bria Fund, research facilities such as the UC-Davis and Kansas State University Veterinary Schools, and the countless brave pet parents who fight to save their fur-babies from this awful disease, we can now look forward to the day when no cat or kitten need ever die from FIP again.