Ending FIP, Is There Hope?

A summary of Dr. Niels Pedersen's presentation to the Winn Feline Foundation Symposium in Chicago July 29th, 2017 by Carol Johnson DVM, Ph.D and Heather Lorimer Ph.D. Additional information from literature articles written by Dr. Pedersen have been added for clarification.

Feline infectious peritonitis (FIP) is one of the most complex infectious diseases and is grossly one of the worst diseases imaginable. It is caused by an RNA virus of the Nidovirales order Coronavirus family. Other RNA viruses that the reader may be more familiar with include Ebola virus, influenza, AIDS and rhinoviruses. Coronaviruses are named for the knob like projections that form a crown (or corona) when viewed by electron microscopy. Coronaviruses can cause disease in almost every animal species but overall coronaviruses are species specific: feline coronaviruses do not infect humans, dogs, or other animals.

Feline Enteric Coronavirus (FECV, also abbreviated as FCoV in the literature) normally stays in the intestinal tract, infecting the top layer of the cells lining the small intestine before settling in the colon. FECV may cause mild diarrhea and vomiting but is not considered a serious pathogen (disease causing agent) in the intestinal tract.

An FECV-infected cat may shed large numbers of virus and shedding may continue for months. Cats are obligate meat eaters and, as a result, have a very short intestinal tract. This feature may aid in the shedding of high concentrations of virus. Immunity to FECV is usually temporary and previously immune animals can be reinfected. This is one of the reasons that prevention by vaccine is difficult to impossible.

Specific mutations in the FECV virus allow it to leave the intestinal tract where it infects immune system cells called macrophages that normally help fight infection. This mutated version of FECV is referred to as FIPV (Feline Infectious Peritonitis Virus). Infected macrophages spread the disease throughout the cat's body in a manner similar to the spread of tuberculosis (TB) bacteria in humans or animals. Mutations associated with FIPV occur in three parts of the FECV genome, however the exact mutation can be unique to each cat. Up to 20% of FECV infections can result in subclinical infection of the macrophages, however relatively few cats go on to develop FIP. Similarly, up to 40% of the world's human population is infected by tuberculosis bacteria but few develop full blown TB. Unlike the TB bacteria, FIPV is not transmitted to other cats; transmission occurs via the unmutated FECV.

FIP is a disease associated with high density cat populations where kittens are part of the equation. Kittens are most susceptible to developing FIP and typically become infected with FECV at around 9 weeks of age. Worldwide, FIP can occur in dense urban or rural populations of free roaming cats. In the US, it is more common to see FIP in cats and kittens from high density conventional shelters and kitten/foster/rescue groups where kittens may be exposed to massive amounts of virus. The other source of FIP is pedigree catteries. In catteries there are not only a number of cats, but there may be genetic susceptibility, which can also play a part (up to 50% in some cases). Unfortunately, although genetic risk is clear, genetic analysis indicates that there are probably a large number of genes involved in the susceptibility. As a result, inbreeding is connected to susceptibility but genetic testing for

susceptibility is not currently possible. Overall, FIP occurs in 0.3% of cats, but can occur in 1-5% (or more) of cats in high density situations such as catteries or rescue groups.

FIP is on the rise probably due to increasing numbers of rescue operations where kittens may be bottle-fed, weaned early, and exposed to large amounts of FECV virus.

FIP is often categorized into dry and effusive (wet) forms but there can be mixtures and switches between types. In general, the effusive form, characterized by internal fluid secretions resulting in a swelling abdomen or fluid in the lungs along with other symptoms, has a rapid course and may kill a cat quickly (death is often due to euthanasia). The dry form may persist for months to about a year, sometimes longer.

Risk factors for developing FIP include the prevalence of cats that are FECV shedders, the magnitude of virus shedding, number of cats in the 4 to 29 month old (most susceptible) age range, and genetic predisposition (in pedigreed cats). Often FIP appears in young cats following a stressful event, such as neutering or spaying. In these cases, the cat may already have FIPV infected macrophages in the lymph nodes and the stress allows it to develop into FIP.

Older cats may also develop FIP. A typical history is that one (or more) cats in a multicat household die of old age and the owner feels that a remaining cat needs a new buddy and so gets a kitten from a rescue facility. The older cat lost immunity to FECV years before and now is susceptible to infection. Because of age, the older cat may have poorer immune responses than a younger animal and may be more likely to develop FIP.

Dr. Pedersen feels that FIP is usually easy to diagnose. Kittens or young cats with abdominal or thoracic mucinous yellow-tinged fluid have presumptive FIP. Dry form FIP can be more challenging, but usually a combination of observations in a young cat with chronic poor health, including weight loss, cyclic fever, characteristic bloodwork (anemia of chronic disease, decreased albumin, increased globulin, low albumin to globulin ratio, increased absolute neutrophils, decreased absolute lymphocytes, increased bilirubin, etc.), and a coronavirus titer $\geq$ 1:3200, helps steer towards a diagnosis of FIP. Dry FIP may present with neurological signs such as convulsions or characteristic “mutton fat” lesions in the eyes. In an autopsy, gross lesions and histology are stereotypic. Tissue or histology sections can be further tested with a variety of techniques such as polymerase chain reaction (PCR), immunofluorescence (IFA) (frozen tissue only), or immunohistochemistry (IHC)(formalin fixed tissue), but Dr. Pederson considers these tests simply confirmatory. He feels that in nearly all cases, FIP can be diagnosed by examination. Importantly, some diagnostic tools produce false negatives. PCR, a commonly used diagnostic test, has about 30% false negative results.

Traditional treatments do not work. Immunosuppressants such as corticosteroids may make the cat feel better but ultimately does not alter the course of the disease. Biologics do not work. Vaccines do not work because the kitten is usually infected with FECV before vaccination and because immunity is transient. The most common cause of death for felines with FIP is euthanasia, due to the loss of quality of life as the disease inevitably progresses. Although the effusive form of FIP is often rapidly fatal, some cats can live longer than one might imagine (weeks or months) with supportive care. Pulmonary fluids

need to be drained, but abdominal fluids typically should not be drained. Cats with the dry form may stay alive for months or more. Some spontaneous remissions can occur, but usually all cats ultimately succumb to FIP.

Hope may come in the form of newer antiviral drugs. RNA viruses share many of the same types of genes and so offer similar targets for drug development. This means that drugs designed to block one type of RNA virus may prove useful for treating a different type. Two possible drugs that may work on FIP are protease inhibitors and nucleoside analogs (NUCs) that specifically target viral enzymes. RNA viruses often make one very large protein that is cut by a very specific proteases into individual viral proteins needed to assemble new viruses. Drugs that inhibit specific proteases have been developed as anti-viral medications for a variety of viruses. NUCs used to prevent HIV genome replication (reverse transcriptase inhibitors) for AIDS patients may also block the RNA-dependent RNA polymerases that replicate the coronaviruses genome. Cats, like all mammals, do not have a RNA-dependent RNA polymerase, so this is a virus specific enzyme. Protease inhibitors work late in the infection of the cell while the NUCs work when the virus first infects a cell.

GC376, a protease inhibitor, was the first drug of this type investigated in cats. Dr. Pedersen collaborated with a team of veterinarians and chemists at Kansas State and Wichita State Universities to treat cats experimentally infected with FIP, then felines with natural infections. Twenty naturally infected symptomatic cats with FIP were treated. Thirteen eventually died, often relapsing after a remission and dying of neurological FIP in the brain. Seven cats survived and appear to remain disease free as of now, one as long as 1 year following treatment. The study in symptomatic, naturally infected cats established drug safety and established the optimal time of treatment to be 12 weeks. However, cats with neurological symptoms did not benefit from treatment, most likely because the drug does not cross the blood brain barrier. The drugs had few adverse effects; one of the most notable was inhibiting the formation of adult teeth, a known side effect of this class of drugs. The limiting factor in the study was the finite amount of drug manufactured.

EVO984 is a nucleoside analog reverse transcriptase inhibitor created by Gilead Sciences. NUCs may have some advantage over protease inhibitors as they work earlier, when the virus first infects the cells. Gilead provided a series of NUCs that Dr. Pedersen screened for efficacy against FIPV in vitro, followed by a pharmacokinetic study, and finally a study in experimentally FIP-infected cats. UC Davis required extensive documentation prior to treating client's pets with natural FIP infections, but that study is currently underway. The drug appears to be safe, has reversed symptoms of FIP including effusions, and has put some cats into remission. Like GC376, EVO984 does not work with neurological FIP because it does not cross the blood brain barrier well. Though this trial has been underway for only a few months, it looks more promising than G376. So far the trial is only 12 weeks along but all 24 cats in the trial are currently alive.

Next Steps: Although the studies are promising, there remain many unanswered questions. Dr. Pedersen feels that if his study is successful, it will probably be necessary for a second party to replicate his results. It was pointed out that additional funding via the Winn Foundation's Bria Fund may be

necessary and they encouraged everyone to donate to future FIP research. Gilead is excited about the interim results, but the company develops human drugs and does not have an animal health division. Gilead indicated to Dr. Pederson that if the results remain hopeful, that they might pursue it or, alternatively, look for a partner that specializes in animal health products. Because the overall prevalence of FIP world-wide is small, the drug may not be attractive to large pharmaceutical companies. However, Dr. Pedersen mentioned that there may be a way forward using provisions set by FDA's Minor Use and Minor Species Animal Health Act of 2004.

Questions and Answer session:

A question was asked why more cats can't receive treatment through the study. The drugs are experimental and in limited supply and Dr. Pedersen feels that he needs only about 20 cats to reach conclusions, as this is normally a fatal disease. He also said that at times desperate owners offered him large amounts of money to enter into his studies. He said it was unfortunate but they needed to observe strict criteria for entry onto the trial and it was not possible to accommodate all possible patients.

When questioned about genetic susceptibility and whether it was possible to select purebred cats for resistance to FIP, Dr. Pedersen relayed his experiences with random bred cats experimentally infected with a highly lethal laboratory FIPV strain. Despite infection, about 20% of the cats did not develop FIP. When the surviving cats were bred together, a smaller percentage (only about 10%) of the kittens did not develop FIP. When the 2nd generation of surviving cats were bred together, all of their kittens developed FIP. Dr. Pedersen feels that these results support the concept that the most resistant cats are outcrossed cats, where many immune system genes are heterozygous (have two different versions of each gene) and so the cat's immune system can respond to and attack a broader range of pathogen targets. He believes that when cats become inbred, that the cat's immune system becomes more homozygous (have two copies of the same version of each gene) reducing the variety of targets that the immune system can respond to. Since the mutations that change FECV to FIPV vary, cats with a broader ability to respond to small viral changes are probably better protected. Breeders should minimize using males that have produced kittens that have died of FIP. Why males? Because individual breeding males generally produce more offspring than breeding females do and therefore have more influence on the next generation of cats.