Control of Enzootic Feline Coronavirus Infection in Closed Multi-Cat Environments and Cons of Using Antivirals

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It is important in discussing feline coronavirus (FCoV) infection in multi-cat environments to understand correct nomenclature. The term FCoV is a collective term for two historically named viruses. A coronavirus was ultimately identified as the cause of feline infectious peritonitis (FIP) in cats and named FIP virus or FIPV (Ward, 1970; Zook et al., 1968). FIPV was subsequently found to be a mutant form of FCoV that occurred within the body of cats infected with widespread and minimally pathogenic enteric coronavirus and named feline enteric coronavirus (FECV) (Pedersen et al., 1981). To avoid confusion, this author prefers to refer to the form of FCoV is applicable to the discussion at hand. Therefore, it is appropriate to use the term FIPV when discussing the form of FCoV that is found within a specific type of white blood cell (monocyte/macrophage) in diseased tissues and fluids of cats with FIP. The term FECV is used when referring to the form of FCoV that causes chronic and intermittent infections of epithelium in the lower bowel of healthy cats and is shed in the feces in large amounts. Enzootic is the correct term for infections that maintain themselves at a low and variable level in a population of animals, while endemic is the corresponding term used for humans. Epizootic refers to a sudden and significant outbreak of new infection, usually with rapid direct spread to animals of all ages. The human correlate of epizootic is epidemic. Clinical "signs" are what veterinarians and physicians observe in a physical examination or relayed by owners/parents, while symptoms are what people recognize in themselves and relate to their doctors.

FECV, like other mucosal pathogens of cats, is maintained in a population as a persistent or recurrent unapparent infection (i.e., an enzootic). FECV is first shed in feces starting at around 9-10 weeks of age coincident with the loss of maternal immunity (Pedersen et al., 2008). Infection is by the fecal-oral route and targets the intestinal epithelium, and primary signs of enteritis are mild or unapparent, transient, and only rarely chronic or severe (Pedersen et al., 2008; Vogel et al., 2010). Subsequent fecal shedding is from the colon, and usually ceases after several weeks or months (Herrewegh et al., 1997; Pedersen et al., 2008; Vogel et al., 2010) with the development of immunity. The resultant immunity is notoriously short-lived, and recurrent infections are common (Pearson et al., 2016; Pedersen et al., 2008. A stronger immunity appears to develop over time and cats older than 3 years appear less likely to be re-infected and become fecal shedders (Addie et al., 2003).

FIP is caused by specific mutants of FECV that evolve during the course of infection (Poland et al., 1996; Vennema et al., 1995).[1] As such, the ultimate risk factor for FIP in a multi-cat environment is the proportion of cats with high feline coronavirus antibody titers and fecal virus shedding (Foley et al., 1997). FIP-causing mutants evolve in 10% or more of FECV infections, but only a fraction of these end up causing disease (Poland et al., 1996). The actual incidence of FIP in a population with enzootic FECV infection appears to vary from less than 1 in 100 to 10 in 100 or more cats, with cases occurring at unpredictable intervals and varying from single cases to small clusters (Addie et al., 1995b; Foley et al., 1997). The actual incidence appears to be conditioned on a number of host and environmental factors that compromise the immune system in some manner and increase FIP risk.[1]

Considering the direct relationship between FECV presence and FIP, the logical way to prevent FIP would be to minimize FECV exposure. A vaccine would be the simplest approach to controlling FECV infection, but no vaccine can produce better immunity than recovery from a natural infection, something shown for SARS-CoV-II vaccines (Li et al., 2019). Based on what is known about the weakness and short-lived nature of natural FECV immunity (Pearson et al., 2016; Pedersen et al., 2008), coupled with significant serotype and strain variations between various populations and regions (Addie et al., 1995b; Liu et al., 2019), it is unlikely that effective vaccines against FECV will be developed.

Although enzootic FECV infection does not easily lend itself to vaccination, it is possible to eliminate FECV from a contained group of cats with vigorous testing for carriers and strict quarantine (Hickman et al., 1995). However, FECV is so ubiquitous in nature and easily spread both by direct and indirect cat-to-cat contact and on fomites carried on personages, the strictest of quarantine facilities and procedures are needed to keep it out. How strict must the quarantine be? Experience with test and removal coupled with quarantine to eliminate and prevent FECV infection is limited to one report (Hickman et al., 1995). FECV was eliminated from a specific pathogen free cat breeding facility at UC Davis by removing virus shedders and seriously increasing quarantine procedures for the remaining colony (Hickman et al., 1995). Nevertheless, FECV re-entered this colony after several years despite all attempts to keep it out (Pedersen NC, UC Davis, unpublished, 2022). The only example of an effective quarantine for FECV was described for cats on the Falkland Islands (Addie et al., 2012). These islands in the distant South Atlantic Ocean have fortuitously remained free of FECV, presumably from their extreme isolation. Steps have been initiated to prevent future inadvertent introduction of FECV to the islands (Addie et al., 2012). Based on these experiences, it is unlikely that FECV can be kept out of any group of cats kept in home type environments with anything less than the strictest isolation and infection prevention procedures.

An interesting approach to either preventing or delaying FECV infection in kittens in pedigreed catteries was referred to as “early weaning and isolation” (Addie et al., 1995a). This approach was based on the finding that kittens born to FECV exposed or infected queens conferred maternal immunity to the infection up 9-weeks of age (Pedersen et al., 2008). Therefore, kittens weaned several weeks prior to the loss of this immunity (4-6 weeks of age) are usually free of infection and if removed from their mother and isolated from other cats they could theoretically be kept free of the virus. This procedure was popular at first, but the facilities and quarantine practices necessary to prevent entry of the virus are difficult to maintain in catteries with larger number of breeding cats (≥ 5 queens, Hartmann et al., 2005). Therefore, eliminating FECV from kittens by early weaning and isolation was doomed for failure in most conventional homes/catteries given the persistent direct and indirect FECV exposures to infected cats. Another problem with early weaning and isolation is the need to segregate virus free kittens from the rest of cats in a large group. This problem could be circumvented if all the cats were freed of infection at the same time. This can be done by serial fecal testing for FECV shedding over a period and elimination of all shedders coupled with strict quarantine. However, because a significant proportion of cattery cats involved in an FECV enzootic are fecal shedders (Foley et al., 1997; Herrewegh et al., 1997), eliminating cats can have a serious effect on the gene pool (Hickman et al. 1995). This begs the question – is there a way to eliminate FECV from all cats in a group at the same time?

Interestingly, the relatively recent discovery of effective antivirals against FIP (Pedersen et al., 2018, 2019 has also provided a theoretical method to eliminate all virus shedders at once. The first studies on such use of antivirals, although quite preliminary in nature, indicated that FECV can be cleansed from a closed group of cats with relatively short treatment (Addie et al., 2023). Assuming that FECV can be

eliminated as an enzootic from a group of cats using specific antiviral drugs, what are the pitfalls of such a practice? The first pitfall involves the duration of immunity to reinfection that might be induced by a short bout of antiviral drug treatment. A follow-up study of cats successfully treated for FIP with GS-441524 showed a return of unapparent FECV shedding in 5/18 individuals within 3-12 months (Zwicklbauer et al., 2023), indicating that treatment, like recovery from natural infection, does not confer long-lasting immunity. The second pitfall is the costs of the antiviral drugs to treat primary and secondary infections, frequent fecal testing to monitor fecal shedding, and creation and maintenance of reasonable quarantine facilities and practice. Therefore, home-orientated facilities with weak barrier containment procedures to maintain this group of cats free of FECV for extended periods of time are doomed to failure. A third pitfall concerns the normal activities involved with pedigreed cat breeding and showing. Pedigreed cat breeding involves frequent interaction between kittens and older cats, as well as people in contact with cats and with each other. It is also difficult to conceive that a pedigreed cat breeder and avid show participant would forego all the joys of raising and displaying their cats by avoiding all such interactions. The ultimate question is - "now that cats are freed of FECV, what should now be done with them?" What are the chances they will remain FECV free for any period after leaving a controlled environment? They will have no immunity to FECV and will be highly susceptible to the smallest of exposures. The same will be true of the group of cats from which they originated. Finally, and of greatest concern, is that the constant antiviral drug treatment required to maintain a group of cats free of FECV infection will generate drug resistance. We now know that resistance to GS-441524 can occur in cats treated for FIP, and researchers at both UC Davis[1] and Cornell University[3] agree that the acquisition of drug resistance in enzootic FECV infections would outweigh any potential benefit of such treatment on the incidence of FIP. FIP is now curable in over 90% of cases, [3] and even when antiviral drug resistance occurs, it is contained largely to the affected cat. It can be argued that HIV-1 infection of humans is now being prevented with antiviral drugs, with no advertised concern with drug resistance. However, HIV-1 prevention treatment is not a monotherapy, but involves several drugs of different classes. Multi-drug therapy is not done to increase the efficacy of the treatment, but rather to prevent drug resistance. If a virus develops resistance to one drug in a cocktail of drugs, it will be prevented from replicating by the others.

In conclusion, and to paraphrase, "just because something can be done, should it be done?" The author believes that much larger and better designed studies, done over a long period of time, are needed before the practice of treating asymptomatic FECV infection with antivirals as a means to prevent FIP is seriously considered. The overall incidence of FIP in smaller and well-maintained pedigreed catteries, shelters, and research breeding colonies with enzootic FECV infection is often low, and it is now possible to cure over 90% of FIP cases that might arise (Pedersen et al., 2019).[3] Keeping the numbers of breeding cats and resultant kittens low, maintaining more older cats, not breeding individuals and bloodlines that have produced FIP cases, and minimizing the stresses of frequent introductions of new cats and housing/re-housing changes, is a practical way to lower FIP incidence.[1] Isolation and early weaning may also be useful in smaller catteries (Addie et al., 1995a). The problem with FIP in foster/rescue situations poses a greater problem, as most of the cats originate from the feral population and are often very young when accessed. They often suffer from malnutrition, a number of other diseases, and are exposed to a high level of stress associated with capture, routine treatments, dietary changes, adaption to a new environment, and ultimately rehoming.[1,3]

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Footnotes

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