GUIDELINE for Feline Morbillivirus infection

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Key points

- Feline Morbillivirus (FeMV) is an enveloped, single-stranded RNA virus, detected in 2012 in renal tubular cells and lymph nodes of two cats from Hong Kong, affected by tubulointerstitial nephritis. Two distinct genotypes of FeMV are known. Genotype 1 is found worldwide in cats and genotype 2 has been detected in Germany. The importance of genetic diversity of FeMVs in determining the clinical outcome of infections is not clear. In addition to domestic cats, the host spectrum of FeMV infection includes wild felids, dogs, and some noncarnivores mammals.
- Spontaneous transmission routes and possible interspecies transmission have not been proven.
- The respiratory route is the most probable way of transmission, and urine is likely an important source of infectious virus as FeMV is frequently and chronically shed in urine.
- Epidemiological investigations mostly evaluated urine and kidney samples by reverse-transcriptase (RT)-PCR for detecting viral RNA with the aim of studying associations between FeMV RT-PCR positivity and kidney disease. FeMV has been found in both healthy and sick cats and tissues.
- Experimental infections provided feline models of FeMV acute infection and documented virus lymphotropism and epitheliotropism. The acute disease consisted in transient mild fever with leukocytosis or leukopenia, acute kidney injury, and mild hepatic lesions.
- Seroconversion occurred two weeks post infection and antibodies did not prevent kidney infection and viral urinary shedding.
- In spontaneous infection, acute disease can be observed and acute kidney injury, febrile syndrome, leukopenia, and encephalitis, have been described.
- Chronic course of FeMV infection can be associated to chronic kidney disease, feline lower urinary tract disease, and hepatobiliary disease.
- FeMV diagnostic investigation is currently restricted to research laboratories. In acute disease diagnosis is confirmed by detection of viraemia by RT-PCR and seroconversion. In chronic infections high levels of positivity are more frequently measured by RT-PCR in urine and kidney tissues.
- The management of cats with urinary positivity to FeMV relies on addressing concurrent CKD if present.
- Control of infection is challenging in case of multicat environment and in free-roaming cats.
- Data available do not support a risk of infection for humans.

Agent properties

The *Morbillivirus* genus (family *Paramyxoviridae*) comprehends well-known RNA viruses of humans and animals including measles virus,

canine distemper virus (CDV), rinderpest virus (globally eradicated in 2011), peste des petits ruminants viruses and viruses affecting marine mammals (Nambulli et al., 2016). CDV and related morbilliviruses have been shown to naturally infect wild and captive large felids (Appel et al., 1994; Roelke-Parker et al., 1996; Myers et al., 1997; Daoust et al., 2009; Meli et al., 2010; Terio and Craft, 2013) and disease outbreaks associated with these viruses are a significant threat to wildlife conservation. CDV infection has never been documented in domestic cats, although limited viral replication was observed in macrophages in asymptomatic experimentally infected cats (Bart et al., 2000).

Scarce data are available for feline paramyxovirus infections, apart from their susceptibility to highly pathogenic zoonotic paramyxoviruses of *Henipavirus* genus (Hendra virus and Nipah virus) belonging to the *Orthoparamyxovirinae* subfamily, which have never been reported in Europe (Eaton et al., 2006). In 2018 a new hepadnavirus, named domestic cat hepadnavirus (DCH), has been detected in a cat in Australia and, since then, it has been also found in Asia (Japan, Hong Kong, Malaysia, Thailand, and Turkey), Europe (Italy and UK), and the Americas (USA and Chile) (Shofa et al., 2022; Choi et al., 2023). Feline infection with DCH seems to be related to hepatic diseases with higher prevalences observed in cats with chronic hepatitis and hepatocellular carcinoma (Shofa et al., 2022). A paramyxovirus-like agent was isolated in 1981 in Australia from a cat with demyelinating lesions in the central nervous system (CNS) and intracytoplasmic inclusion bodies in glial cells (Cook and Wilcox, 1981).

In 2012, the new paramyxovirus, feline morbillivirus (FeMV), was isolated from stray cats in Hong Kong (Woo et al., 2012). The virus was detected in renal tubular cells and lymph nodes in two cats affected by tubulointerstitial nephritis (TIN). –

FeMV is an enveloped, single-stranded RNA virus, with six genes encoding six structural and two non-structural proteins (Woo et al., 2012; Marcacci et al., 2016). Three of the structural proteins (nucleocapsid N, phosphoprotein P, and protein L) are found in the nucleocapsid. A matrix protein (M) is located between the nucleocapsid and the envelope. The glycoproteins H and F play an important role in the interaction with the host cell membrane and are responsible for viral host spectrum, tissue tropism, and pathogenesis (Conceicao and Bailey, 2021; De Luca et al., 2021). It has been shown that FeMV is phylogenetically distinct from other morbilliviruses (Seki and Takeda, 2022), and genetic analysis has demonstrated the presence of two distinct genotypes of FeMV sharing a genomic nucleotide sequence identity of approximately 78.2% (Sieg et al., 2018). Genotype 1 (GT1) was first identified in 2012 in Hong Kong (Woo et al., 2012) and is found worldwide in cats, with detection confirmed in all studies conducted. In Asia, beyond Hong Kong, FeMV-GT1 has been identified in Japan, Thailand, Malaysia, and China (Furuya et al., 2014; Chaiyasak and Techangamsuwan, 2017; Mohd Isa et al., 2019; Chaiyasak et al., 2020; Ou et al., 2020). In Europe, FeMV-GT1 has been detected in Germany, Italy, and Turkey (Sieg et al., 2015; Lorusso et al., 2015; Yilmaz et al., 2017; Donato et al., 2019; Muratore et al., 2021). In the Americas, FeMV-GT1 has been reported in the USA and Brazil (Sharp et al., 2016; Darold et al., 2017; Balbo et al., 2021). Genetic heterogeneity of FeMV-GT1 isolates was found, and phylogenetic analysis of 29 publicly available whole genome sequences suggested the existence of two clades of FeMV-GT1 (De Luca et al., 2021). One clade, containing three clusters, includes the GT1 isolates from China, Japan, Thailand, Germany, Italy, Brazil, and the USA. The second clade includes only the GT1 strains from Italy (De Luca et al., 2021). Genotype 2 (GT2) was identified in Germany in 2018 (Sieg et al., 2018). One important question is how important genetic diversity of FeMVs is in determining the clinical outcome of infections.

Thermal sensitivity and stability of FeMV have been investigated *in vitro* by incubating viral stocks at various temperatures and measuring the viral replication capacity (Koide et al., 2015). Viral infectivity was reduced by exposure to high temperatures with incubation at 70 °C inactivating FeMV in two minutes. In contrast, FeMV was stable at 4 °C, retaining infectivity for at least 12 days (Koide et al., 2015). This stability at low temperatures may allow indirect transmission to susceptible individuals, but viral drying on contaminated surfaces should also be considered in further studies.

The host spectrum of FeMV has been studied *in vitro* by the evaluation of viral replication in cell lines derived from 13 different mammalian species (including humans). These studies revealed that only cell lines derived from cats and, less efficiently, African green monkeys were permissive to FeMV replication (Sakaguchi et al., 2015). The feline cell lines that supported FeMV-GT1 replication included renal, fibroblastic, lymphoid, and glial cells (Sakaguchi et al., 2015). The feline cells that allowed *in vitro* replication by FeMV-GT2 included renal cells, epithelial lung cells, lymphocyte subsets, monocytes, and primary cells from the cerebrum and cerebellum (Sieg et al., 2019). Virus tropism for different cell types has also been studied using immunohistochemistry (De Luca et al., 2020). FeMV antigens were detected in inflammatory cells residing in the blood vessels of the kidney and brain, in respiratory epithelial cells, alveolar macrophages, and to a lesser extent, the CNS (De Luca et al., 2020). These data suggest that systemic infections can occur with FeMV and that clinically relevant genotype differences in tropism may exist.

The cellular receptors involved in FeMV infection have been studied (Nambulli et al., 2022; Nikolin et al., 2022). FeMV infection of immune and epithelial cells is mediated by the same cell receptors used by other morbilliviruses to attach to the viral haemagglutinin. The signalling lymphocyte activation molecule family member 1 (SLAMF1 or CD150) is a set of primary cell receptors for morbilliviruses expressed on subsets of immune cells (Nikolin et al., 2022). SLAMF1 was the host cell entry receptor used by a US strain of FeMV-GT1 in vitro (Nambulli et al., 2022). The amino acid sequences of SLAMs differ amongst mammalian species and are likely to influence the host spectrum of morbilliviruses. Human, canid, and feline SLAMF1 amino acid sequences are different. Although both canine and feline

SLAMF1-expressing cells were permissive to FeMV replication, feline SLAM cells were more permissive, such that massive syncytium formation was observed in the feline SLAM cells (Nikolin et al., 2022).

Unlike other morbilliviruses, the mechanism for FeMV-induced cell-to-cell fusion depends on cathepsin, a protease that is expressed in infected cells (Nambulli et al., 2022). Interestingly, this cathepsin dependence of FeMV is shared with the zoonotic henipaviruses that infect cats and the DCH (Nambulli et al., 2022). The reduced availability of cathepsin on feline lymphocytes, compared to monocytes, may explain the less severe lymphodepletion observed with acute FeMV-GT1 infection in feline experimental models compared to CDV infection in ferret experimental models (Nambulli et al., 2022). The epithelial cell receptor that binds the viral haemagglutinin protein (H glycoprotein) appears to be nectin-4, similar to other morbilliviruses (Nambulli et al., 2022). In support of this, a FeMV-GT1 study found that the H protein amino acids that were conserved included all those important for the H receptor/nectin-4 binding and function (Nambulli et al., 2022). However, further investigations are needed to confirm the H glycoprotein/nectin-4 interaction in FeMV infection. Moreover, different cell receptors may be involved and explain the larger excretion of FeMV in feline urine compared to the respiratory tract.

In addition to domestic cats, the host spectrum of FeMV infection includes wild felids, such as the *Leopardus guigna* in Chile (Sieg et al., 2020) and the *Panthera pardus* in Thailand (Piewbang et al., 2020). Azotaemia and TIN have been reported in two black leopards with FeMV infection in Thailand and FeMV could be a threat for susceptible endangered host species (Piewbang et al., 2020).

Susceptibility of dogs to FeMV infection has been also described in Thailand. Nasal and oral swabs from dogs with respiratory disease were tested reverse transcriptase–polymerase chain reaction (RT-PCR) positive for FeMV RNA, and FeMV-GT1 was subsequently isolated from swabs and lung samples of a dead dog (Piewbang et al., 2022). The FeMV-GT1 sequences obtained in this study showed 97.5–99.2% identity with sequences derived from domestic cats in Thailand, Hong Kong, and Japan. An FeMV prevalence of 12.4% (14/113) was found in dogs in this study, and six of the PCR-positive dogs were co-infected with other respiratory viruses (comprising canine corona-, canine herpesvirus, and/or CDV). Moreover, immunohistochemistry (IHC) confirmed the presence of the virus in two of 22 lung samples collected from necropsied animals that had died from respiratory disease, and FeMV antigen was demonstrated in the kidney, lymphoid, and brain tissues of two fully necropsied dogs (Piewbang et al., 2022). The role of FeMV co-infection with other canine respiratory viruses has to be further investigated, but these data suggest that FeMV could be a significant canine respiratory pathogen.

The host spectrum of FeMV includes also noncarnivore species. Indeed, in Brazil, FeMV RNA was detected in a synanthropic marsupial, the white-eared opossum (*Didelphis albiventris*), and an FeMV strain from an opossum was isolated in Crandell Rees feline kidney lineage cells (Lavorente et al., 2022). On phylogenetic analysis, the FeMV opossum strain clustered with FeMV-GT1 but formed a new branch (Lavorente et al., 2022).

It is clear that the host spectrum and tropism of FeMV go beyond the domestic cat and the kidney. A major implication of a wide host spectrum for FeMV is of course the potential for interspecies transmission, with possibility of transmission between dogs and cats that, if confirmed, would be of great concern in the field of companion animal infectious diseases.

Epidemiology

Prevalence

Many prevalence studies of FeMV RNA have been performed in samples collected from live and necropsied cats, following the initial report documenting FeMV in stray cats from Hong Kong in 2012 (Woo et al., 2012) (Table 1). It is not easy to compare the reported geographical prevalences as varied analytical methods have been used in the studies and the populations tested have differed with respect to their demographic characteristics, husbandry, lifestyle, and health status. However, higher prevalence of urinary FeMV RT-PCR positivity was found in older cats (Donato et al., 2021), in male cats compared to females (Mohd Isa et al., 2019), and in entire compared to neutered males (Park et al., 2016). A very high (52.9%) urinary RT-PCR positivity was detected in cats from a cat shelter (Darold et al., 2017), although another study reported a higher prevalence in pets compared to shelter cats (Mohd Isa et al., 2019). The urine of cats from suburban and rural areas were more frequently FeMV RT-PCR-positive than those from urban areas (Donato et al., 2021), and cats with outdoor access more frequently tested FeMV RT-PCR-positive than indoor cats (Ylmaz et al., 2017; Donato et al., 2021). Similarly, a higher prevalence was detected in cats in stray colonies compared to owned household cats (De Luca et al., 2017). Foundling cats and cats living in rescue catteries more frequently tested positive than non-foundling cats and owned multi-cat household cats, respectively, in another study (Donato et al., 2021). It is difficult to explain the differences seen with demographic data; however, male and entire cats usually have more aggressive interactions and a higher risk for infections transmitted by bites and mating. Similarly, outdoor access favours cat-to-cat interactions and contact with soil potentially contaminated with FeMV-containing urine. In the case of shelters and rescue catteries, intra-species interactions depend on the management of facilities. When cats live indoors in a multi-cat environment, in addition to the risk of direct transmission of many infections, susceptibility to disease is generally increased by the chronic stress status of cats that can favour viral replication and shedding (Möstl et al., 2013).

Most frequently tested samples were urine and kidney tissues, with the aim of studying associations between FeMV RT-PCR positivity

and kidney disease. However, wide ranges of urinary (range: 0.8–50.8%) and kidney (range: 7.4–80.0%) RT-PCR positivity have been detected in both healthy and sick cats (see Table 1).

Table 1. Worldwide FeMV prevalence

Data from cats reported in chronological order and in relation to the country studied, the characteristics of the cat population sampled, and the sample types tested by reverse transcriptase–polymerase chain reaction (RT-PCR).

Country (Year)	Cat Population	Number of Cats Sampled	Sample/Tissue (% of Positive RT-PCR)	Overall % of Positive RT-PCR [a]	Reference
Hong Kong (2012)	Strays	457	Urine (11.6)	12.3	Woo et al., 2012
			Blood (0.2)		
			Rectal swabs (0.8)		
Mainland China (2012)		16	Oral swabs (6.2)	6.2	
			Rectal swabs (6.2)		
Japan (2014)	Admitted to clinics	82	Urine (6.1)	n. r.	Furuya et al., 2014
		10	Blood (10.0)		
		10	Kidney (40.0)		
Japan (2014)	Client-owned	13	Urine (23.1)	n. e.	Sakaguchi et al., 2014
Japan (2016)	Admitted to clinics	166	Urine (15.1)	n. e.	Furuya et al., 2016
USA (2016)	n. r.	327	Urine (3.0)	n. e.	Sharp et al., 2016
Japan (2016)	Strays/client-owned	100	Urine (17.0)	22.0	Park et al., 2016
			Kidney (18.0)		
Brazil (2017)	Multi-cat household °	17	Urine (52.9)	n. e.	Darold et al., 2017
	Client-owned	35	Urine (8.6)		
Turkey (2017)	Client-owned	96	Urine (3.1)	5.4	Yilmaz et al., 2017
		15	Kidney (26.0)		
			Lymph nodes (13.0)		
			Lung (6.0)		
			Spleen (6.0)		
			Intestine (6.0)		
			Liver (6.0)		

UK (2018)	Client-owned geriatric	40	Urine (12.5)	n.e.	Mc Callum et al., 2018
Italy (2019)	Strays	6	Urine (16.7)	3.2	Stranieri et al., 2019
	Client-owned	59	Urine (0.0)		
	n. r.	27	Kidney (7.4)		
Malaysia (2019)	Sheltered °/client-owned	124	Urine (50.8)	39.4	Mohd Isa et al., 2019
		93	Blood (0.0)		
		25	Kidney (80.0)		
Germany (2019)	n. r.	723	Urine (0.83)	n.e.	Sieg et al., 2019
Italy (2020)	Colony	69	Urine (31.8)	n.e.	De Luca et al., 2020
	Client-owned	127	Urine (8.6)		
	Colony	7	Kidney (57.1)	22.8	
			Urinary bladder (14.2)		
			Spleen (28.5)		
			Lymph nodes (14.2)		
	Client-owned	28	Kidney (10.7)		
			Urinary bladder (10.7)		
			Spleen (3.5)		
			Brain (3.5)		
Mainland China (2020)	n. r.	64	Urine (9.3)	n.e.	Ou et al., 2020
Thailand (2020)	Sheltered °*	31	Urine (19.3)	11.9 (Sheltered: 29.5; Client-owned: 6.5)	Chaiyasak et al., 2020
	Client-owned [§]	100	Urine (13)		
	Sheltered °*	61	Blood (19.6)		
	Client-owned [§]	100	Blood (0.0)		
Brazil (2021)	Client-owned	56	Urine (26.7)	n.e.	Darold et al., 2021
	Multi-cat household	82	Urine (28.0)		
	Sheltered	138	Urine (42.0)		
	Total	276	Urine (34.7)		

Italy (2021)	Client-owned	127	Urine (3.9)	n.e.	Muratore et al., 2021
	Cattery	23 [&]	Urine (26)		
	Total	150	Urine (7.3)		
	Client-owned	40	Kidney (7.5)	n.e.	
	Cattery	10	Kidney (10.0)		
	Total	50	Kidney (8.0)		
Italy (2021)	Outdoors	111	Urine (18.9)		Donato et al., 2021
	Indoors	106	Urine (14.2)		
	Total	223	Urine (16.1)		
	Outdoors	111	Blood (2.7)	18.5	
	Indoors	100	Blood (2.0)		
	Total	211	Blood (2.4)		
	Indoors/Outdoors	10	Kidney (10.0)		
			Urinary bladder (10.0)	10.0	
			Mandibular lymph nodes (10.0)		

Antibody positivity prevalence of FeMV has been investigated in cats from many countries by enzyme-linked immunosorbent assay (ELISA), immunofluorescence assay (IFA), or western blot (WB) (table 2).

Table 2. Worldwide anti-FeMV antibody prevalence

Data from cats reported in chronological order and in relation to the country studied, the characteristics of the cat population sampled, and the serological technique used. WB: Western blot; IFA: immunofluorescence assay; ELISA: enzyme-linked immunosorbent assay; *: sera tested with two different assays developed for genotypes 1 (GT1) and 2 (GT2) of FeMV; 30% of cats were antibody positive to both genotypes, and in total, anti-FeMV antibody prevalence was 63%; **: sera tested with two different assays developed for FeMV-GT1 and FeMV-GT2; 15% of cats were antibody positive to both genotypes, and in total, the anti-FeMV antibody prevalence was 49%.

Country (Year)	Cat Population	Number of Tested Cats	Prevalence (%)	Assay	Reference
China (2012)	Strays	457	27.8	WB	Woo et al., 2012
Japan (2014)	Client-owned	13	23.1	WB	Sakaguci et al., 2014
Japan (2016)	Strays/client-owned	100	21.0	IFA	Park et al., 2016
Japan (2017)	Not reported	100	22.0	ELISA	Arikawa et al., 2017
UK (2018)	Client-owned geriatric	72	31.0	WB	McCallum et al., 2018

Italy (2020)	Colony	69	21.7	IFA	De Luca et al., 2020
	Client-owned	127	17.3		
	Total	196	18.9		
Chile (2021)	Rural free-roaming	112	54.0 39.0	GT1-IFA * GT2-IFA *	Busch et al., 2021a
Germany (2021)	Admitted to hospital	380	26.0 8.0	GT1-IFA ** GT2-IFA **	Busch et al., 2021b
Italy (2021)	Outdoors	103	18.5	IFA	Donato et al., 2021
	Indoors	90	10.0		
	Indoors + Outdoors	193	14.5		

Similar to RT-PCR positivity, antibody positivity prevalences vary widely (8.0–54.0%), and again, this could be due to the differing characteristics of the tested population and analytical methods used. The presence of serum antibodies against recombinant viral N protein has been investigated by WB (Woo et al., 2012; McCallum et al., 2018) and against recombinant viral P protein by ELISA (Arikawa et al., 2017). Additionally, high levels of antibodies against FeMV F protein were also detected by IFA (Sharp et al., 2016). Different patterns of antibody reactivity against FeMV proteins have also been seen when feline sera were tested by whole-virus immunoblot analysis (Sakaguchi et al., 2014). Thus, tests evaluating antibodies against single proteins might underestimate antibody prevalence.

The most widely used antibody testing technique is the IFA, which allows the detection of antibodies against all viral proteins (Park et al., 2016; Arikawa et al., 2017; Donato et al., 2018; De Luca et al., 2020; Donato et al., 2021; Busch et al., 2021a; Busch et al., 2021b;). However, genotype-specific IFAs are needed to evaluate the exposure of cats to specific genotypes. An IFA using two different cell lines infected with FeMV-GT1 and FeMV-GT2, respectively, was developed and validated for detecting antibodies against the two FeMV genotypes (Busch et al., 2021a). Additionally, cross-reactivity with CDV for FeMV-positive cat sera was excluded in this study (Busch et al., 2021a). A high antibody prevalence (63.4%; 71/112) was detected in adult free-roaming rural cats from central to southern Chile, and 30% of cats had antibodies against both GT1 and GT2 (Busch et al., 2021a). Antibodies directed against only FeMV-GT2 were more prevalent in male cats, but only 10 FeMV-GT2-positive cats were found (Busch et al., 2021a). The same two genotype-specific IFAs were then used in a large retrospective study (Busch et al., 2021b). The authors tested 840 serum samples from 380 cats admitted to a veterinary teaching hospital in Germany with different diseases (43.0% of them for urinary problems) (Busch et al., 2021b). Similar to the study conducted in Chile, a high antibody prevalence (45%) was found, with 26.0% of cats being FeMV-GT1 antibody positive, 8.0% FeMV-GT2 antibody positive, and 15.0% positive for both genotypes. In this study, sex was not correlated to FeMV antibody status, and cats aged 3–4 years old were more likely to be antibody positive than older animals. Interestingly, pedigree cats were more frequently antibody positive and FeMV-GT1 antibody-positive compared to domestic shorthair cats (Busch et al., 2021b). Virus neutralising (VN) antibodies were not measured in epidemiological studies but evaluated in experimental investigation and in a case report (Sieg at al., 2019; Nikolin et al., 2022).

Limited data regarding co-infection of FeMV with other feline pathogens exist. Feline immunodeficiency virus (FIV) antibody positivity was higher in cats shedding FeMV RNA in urine than in FIV-antibody-negative cats, and in another study, FeMV positivity was positively associated with both FIV and feline leukaemia virus (FeLV) infections (Darold et al., 2017; Donato et al., 2021). In five FeMV-positive cat carcasses, tissue samples were found positive for FeLV RNA (three cats), feline panleukopenia virus (four cats), feline coronavirus (FCoV) (one cat), and *Leishmania* spp. (one cat) (De Luca et al., 2020). Other infectious disease agents were detected in the cats of one large epidemiological study, but similar overall frequencies of these agents occurred in both FeMV-positive and FeMV-negative cats and between FeMV-positive genotypes (i.e., GT1, GT2, and both GT1 and GT2) (Busch et al., 2021b).

Transmission

Spontaneous transmission routes and possible interspecies transmission have not been proven. The respiratory route is the most probable way of transmission, and urine is likely an important source of infectious virus as FeMV is frequently (Table 1) and chronically (Sieg et al., 2019; De Luca et al., 2020; Donato et al., 2021) shed in urine, although there are no data about the infectiousness of FeMV excreted in urine. However, when considering the behavioural importance of both olfactory exploration of cats for detecting scent marks and the release of scent when they spray urine, it is easy to understand why a virus shed chronically in the urine with possibly a low

rate of acute lethality is a good candidate for endemic infections in feline populations (Crowell-Davis et al., 2004). Moreover, cat reciprocal facial rubbing and allogrooming behaviour (van den Bos, 1998) would favour transmission of infectious virus shed by mouth and nose, beyond shared bowls and litter trays.

Pathogenesis

Two different experimental infections with FeMV-GT1 and with FeMV-GT2, respectively, have provided feline models of FeMV acute infection (Nambulli et al., 2022; Nikolin et al., 2022).

The first experimental infection study delivered FeMV-GT2 Gordon strain intravenously to three groups of five young adult specific pathogen-free (SPF) cats sampled at different times for clinicopathological monitoring, detection of viraemia, viral excretion in urine and in nasal swabs (by RT-qPCR), and finally infected cats were euthanised after 14, 24, and 56 days, respectively (Nikolin et al., 2022). Some cats had a mild fever on days 3–5 post-infection (pi) and it was the only clinical sign detected. The complete blood counts (CBCs) and biochemical profiles were performed at different times in each group, providing data between day 14 and day 56 pi. Apart from a mild and transient leukocytosis, detected between days 20 and 49 pi, no other changes in CBC were found. However, one individual cat was severely leukopenic on day 56 pi. Occurrence of the lymphopenia that is often observed in morbillivirus infections and that has been reported in experimentally infected cats by Nambulli et al. (2022) was not investigated. A sporadic increase in aspartate aminotransferase (AST) was reported in six cats from day 20 pi onwards, but the severity was not described. Viraemia (from day 1 to 56 pi), virus urinary excretion (from day 7 to 56 pi), and nasal FeMV detection (from day 3 to 14 pi) were investigated at different times each (Nikolin et al., 2022). Viraemia was detectable with high viral loads in a variable number of cats in each group from day 1 to 49 pi (at around $10^{3.5}$ RNA copies/mL), with all cats tested on day 3 and day 5 found to be RT-quantitative (q) PCR positive. Peak viraemia (greater than 10^4 RNA copies/mL) was associated with mild fever in some cats but was not associated with any changes in cat behaviour. These findings suggest that the acute phase following natural FeMV infection could unlikely be detected by veterinarians, as owners would rarely have a reason to seek veterinary help for their animals. Urinary excretion occurred later than viraemia and it was found in some cats at all time points, with all tested cats found positive from day 20 to day 56 pi. Urinary viral loads were higher than in the blood from day 20 pi onwards, with concentrations of RNA copies greater than 10^4/mL up to day 49 pi as reported in natural infections of both a healthy cat and a cat with CKD (Sharp et al., 2016; De Luca et al., 2018).These findings confirm the field observations that have found lower percentages of positive blood samples compared to urine samples (Woo et al., 2012; Furuya et al., 2014; De Luca et al., 2018; Donato et al., 2021) or, indeed, an absence of positive blood sample test results (Mohd Isa et al., 2019; De Luca et al., 2020). Moreover, the duration of viraemia appeared to be variable, as suspected under natural conditions (Donato et al., 2021). Nasal swabs tested positive in some cats when viraemia peaked, but viral loads were mostly less than 10^3 RNA copies per swab and no signs of upper respiratory tract disease were observed (Nikolin et al., 2022). These data suggest that the risk of transmission via the respiratory route could be low. Similarly, in field studies Woo et al. (2012) did not find RT-PCR-positive nasal swabs in any of the 457 stray cats studied, while 53 of 457 urine samples tested positive (Woo et al., 2012). At present, scant information is available on mucosal FeMV positivity rates, and one field study found only 1/16 cats sampled by oral and rectal swabbing was positive in both samples (viral loads were not measured). Rectal swabs (4/457) also were less frequently positive compared to the urine samples (53/457) in stray cats (Woo et al., 2012). Moreover, intestinal samples of an FeMV-positive cat with severe necrotising enteritis tested RT-PCR positive, but IHC evaluation of the intestine was negative (Chaiyasak et al., 2022).

In the experimental model of Nikolin et al. (2022), antibody seroconversion was detected early and was associated with a declining viral load in blood; however, viraemia was observed up to day 49 pi (Nikolin et al., 2022), in line with the occurrence of naturally infected cats testing serum antibody positive, as well as RT-PCR positive in urine (Sieg et al., 2019; Donato et al., 2021).

Necropsies have been performed after cat euthanasia and gross lesions have not been observed (Nikolin et al., 2022). However, histopathological examination of kidney, liver, and spleen samples were performed, as well as immunohistopathology on kidney samples. Histopathological lesions in the kidney and liver and diffuse activation of lymphoid follicles in the spleen were reported at all time points (Nikolin et al., 2022). Importantly, renal tubular abnormalities were observed in all cats and immunohistology-localised FeMV nucleoproteins were detected at the apical surface of epithelial cells from the renal cortex as it has been described in naturally infected cats (Woo et al., 2012; De Luca et al., 2018; Donato et al., 2021; Sutummaporn et al., 2019; Chaiyasak et al., 2022). Multifocal tubular (hyaline or granular) casts were observed from day 14 pi with all cats affected later on, sometimes with degeneration of the lining of the epithelial tubular cells. Subsequently, multifocal tubular mineralisation and multifocal chronic TIN were found in some cats, and lesions observed on day 56 were in general considered more prominent. The above findings provide therefore evidence of acute kidney injury caused by FeMV and suggest that, under natural conditions, urinalysis with microscopic detection of urinary casts could provide early information regarding the acute tubular damage found in this experimental study, as well as the detection of a tubular pattern of proteinuria detectable by urine protein electrophoresis (UPE). Indeed, Crisi et al. (2020) found a tubular pattern of proteinuria frequently in a retrospective urinary sodium-dodecyl-sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) evaluation of FeMV-positive cats (Crisi et al., 2020).

Hepatic lesions were reported as mild in all experimentally infected cats, at all time points (Nikolin et al., 2022). Multifocal lymphoplasmacytic portal and interstitial hepatitis and hydropic degeneration of hepatocytes were detected. Most cats also showed multifocal acute portal haemorrhages, and at day 56 pi, portal biliary proliferation and fibrosis were observed in one cat. Importantly, hepatic lesions were similar to those reported in naturally infected cats with positive FeMV antigen IHC in hepatocytes and monocytes, but in the field study, some cats were also FCoV positive (Yilmaz et al., 2017).

Interestingly, in this experimental model the acute phase of infection was clinically irrelevant with no overt cat clinical signs nor gross lesions at necropsy, but most of these cats had already suffered from multifocal chronic TIN and mild hepatic lesions when euthanised. TIN is found in natural feline FeMV infection and is also the most common histopathological pattern of cat CKD with causative agents mostly undetected (McLeland et al., 2015). Overall, the experimental data from Nikolin et al. (2022) confirm a role for FeMV as a potential causative agent of feline TIN. A role for FeMV in cases of lymphoplasmacytic portal hepatitis merits further evaluation.

A second experimental model of feline FeMV infection focused on the early spread of the virus after airway transmission, which may be an infection route in natural infection (Figure 1). Two groups of three young domestic shorthair male cats (16–17 weeks old) were infected by intratracheal and intranasal routes with two recombinant viruses of an FeMV-GT1 unpassaged strain obtained from a chronically infected cat (Nambulli et al., 2022). Of note, a fluorescent protein-expressing recombinant FeMV was used to track virus spread during necropsy and to identify infected cells. In the first group, individual cats were sampled (blood, urine, and throat and nasal swabs) at different time points and euthanised at days 7, 14, and 28 pi. The second group of cats was sampled on days 2, 5, 6, and 7 pi, when all cats were euthanised to focus on the peak of early acute infection. Increased temperatures occurred at around day 5 pi in both groups with lymphopenia peaking at the same time. The cats then underwent progressive recovery. Viraemia was confirmed by flow cytometry in white blood cells (WBCs) on days 6–10 pi and in lymph nodes and bronchoalveolar lavages (BAL) on day 7 pi. Virus was isolated from WBCs on days 4 to 14 pi, from urine on days 12 to 28 pi, and from lung samples on day 7 pi only and was never isolated from throat or nose swabs. All six studied cats were necropsied and post-mortem macroscopic bioimaging evaluation confirmed virus lymphotropism during the early acute phase (day 7 pi), when all lymph nodes, thymus, and tonsils were highly positive. IHC in lung and lymph node tissues showed that most of the infected cells were monocytes/macrophages. At the peak of virus detection in the respiratory tract (day 7 pi) the virus was detected in the BAL, the lung interstitium, bronchial tissue, and the bronchial-associated lymphoid tissue. Urinary FeMV isolation and the presence of renal lymphoplasmacytic lesions occurred later (days 14 and 28 pi) and were associated with positive IHC in the medullary tubular epithelium of kidney sections on day 28 pi. This FeMV-GT1 experimental model showed hallmarks typical of early morbillivirus infections in the infected cats, such as lymphotropism with viral detection in WBCs and lymphopenia (Nambulli et al., 2022).

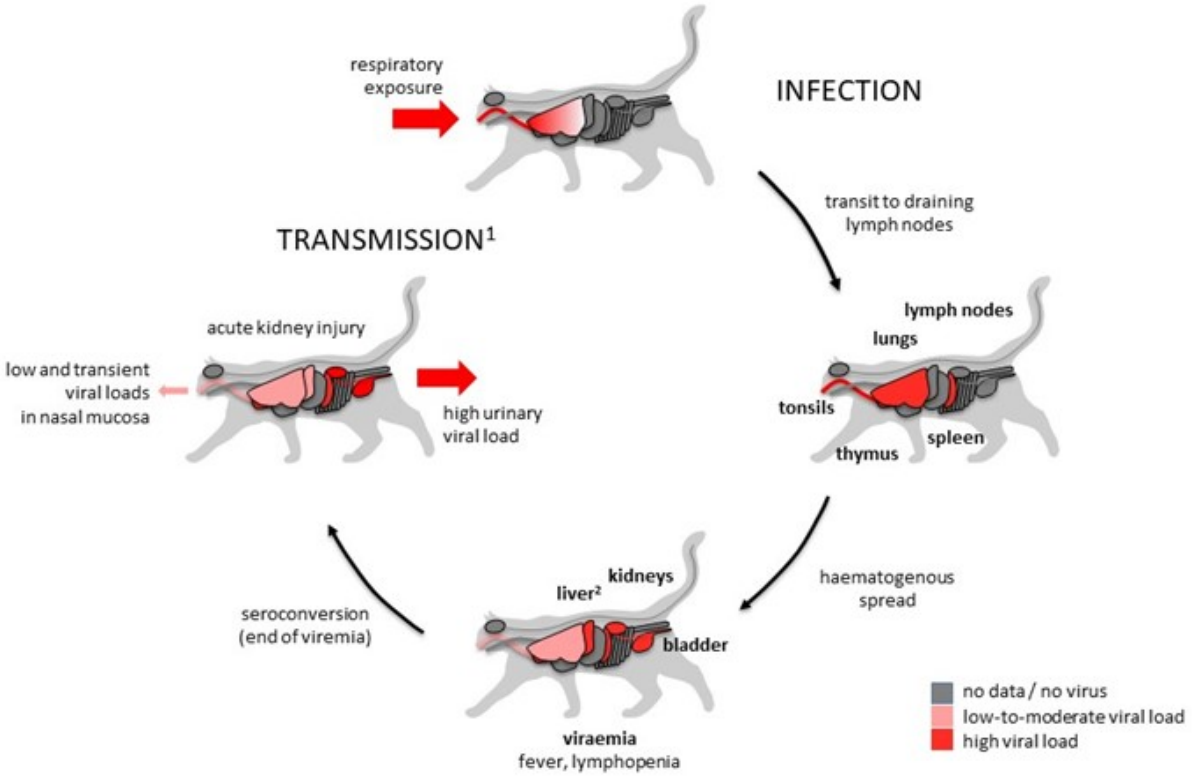

Fig 1: Feline model of acute feline morbillivirus (FeMV) respiratory infection with FeMV-GT1 (Nambulli et al., 2022) and intravenous infection with FeMV-GT2 (Nikolin et al., 2023). Main phases of the first weeks of infection are schematically represented with focus on tissues infected, clinical signs, seroconversion, kidney damage and viral shedding. [(1)] *Spontaneous transmission has not been studied.* [(2)] *The presence of virus in the liver is reported only by Nikolin et al., 2022.*

Experimental models of FeMV acute infection showed that both genotypes could not cause overt clinical signs despite fever and urinary and pathological demonstrations of AKI and the occurrence of lymphopenia (Nikolin et al., 2022; Nambulli et al., 2022). However, this could go differently in non-controlled situations where host and virus variables could lead to different outcomes. This gap of knowledge has been investigated by Ito et al. (2023) after the detection of FeMV in a cat that was subjected to an investigation of unknown viruses as part of a study in cats with fever using unbiased next-generation sequencing (Momoi and Matsuu, 2021; Ito et al., 2023). A retrospective controlled study was performed in an area endemic for the zoonotic severe fever with thrombocytopenia syndrome (SFTS) caused in East Asia by Huaiyangshanbanyang virus; most of the studied cats had fever, leukopenia, thrombocytopenia, and jaundice, but SFTS and parvovirus infections had been excluded by blood PCR (Ito et al., 2023). FeMV-GT1 (mostly of subtype A) was detected in 32 of 102 plasma samples (31.4%) by RT-qPCR (threshold cycle (Ct) value range: 27.4–39.0), and FeMV RNA was never found in 374 control samples from sick cats (Ito et al., 2023).

With respect to the post-mortem findings in cats suspected of acute FeMV disease, three case reports are available and are worthy of description (Chaiyasak et al., 2022; Ito et al., 2023). Various samples tested FeMV RT-PCR positive in a cat that had died about four days after the onset of lethargy and anorexia (Ito et al., 2023). Necropsy did not reveal the cause of death, but high viral loads in the spleen (Ct 17.7), lung (Ct 22.1), liver (Ct 23.3), urine (Ct 23.6), blood (Ct 24.4), rectal swab (Ct 24.5), kidney (Ct 25.3), oral swab (Ct 29.0), and lymph nodes (Ct 34.5) were detected. Unfortunately, FeMV IHC was only performed on the kidney, spleen, and lymph node samples. Immunopositivity was found in renal tubular cells, in macrophage and lymphocyte infiltrates surrounding positive tubules, in lymphoid follicles in the mandibular lymph node, and in macrophages and lymphocytes in splenic lymphoid follicles (Ito et al., 2023). The role of FeMV in the death of the cat was not proven, but the systemic viral dissemination was suggestive of acute infection (Ito et al., 2023). Viral systemic spread of FeMV was detected in another two cats that died with acute multifocal necrotising haemorrhagic cystitis associated with two different bacterial infections (*Escherichia coli* in one case and *Pseudomonas aeruginosa* in the other) and suspected septicaemia, detected at necropsy (Chaiyasak et al., 2022). Diffuse renal tubular vacuolation with mild or moderate segmental

multifocal membranous glomerulopathy were observed, as well as viral inclusion bodies in tubular epithelial cells (Chaiyasak et al., 2022). High viral loads were measured by RT-qPCR in the urine (Ct 24.8) and FeMV-GT1 infection was diagnosed in both cats. Interestingly, kidney infection was confirmed by RT-qPCR (Ct 34.2) and IHC evaluation, but no associated inflammatory infiltrates were observed within the renal tissue. Lung viral load was lower (Ct 37.4) than urinary bladder and small intestine loads (Ct 34.8), and the cytoplasm of various epithelial cells (transitional, tracheal, bronchial, and bronchiolar), macrophages, and lymphoid cells in the spleen and lymph node occasionally tested IHC positive. Liver and brain samples were also RT-PCR positive, and astroglia and oligodendroglia cells were FeMV positive by IHC. Epitheliotropism (particularly in renal tissue), lymphotropism, and neurotropism of FeMV were observed in these two young cats, but a role in their death was not evident (Chaiyasak et al., 2022). Data from these necropsied cats confirmed that systemic spread of FeMV occurs in field cases as described in experimental models. Experimental studies have not investigated the CNS of infected cats, and FeMV neurotropism seems to be associated with less extensive viral replication compared to epithelial and inflammatory cells (De Luca et al., 2020; Nambulli et al., 2022; Nikolin et al., 2022). However, brain glial cells of both cats and dogs and dog neurons were found to be FeMV positive by IHC in natural disease (Piewbang et al., 2022; Chaiyasak et al., 2022). An additional confirmation of FeMV neurotropism and the association with fatal encephalitis have been provided by the retrospective detection of FeMV in brain tissue of a 2-month-old Bengal cat euthanised few days after the onset of neurologic signs suggestive of acute encephalitis (Dawson et al., 2023).

Feline models of chronic FeMV infection are not available. The high percentages of RT-PCR-positive cats detected worldwide since the discovery of FeMV (Table 1) are supportive of a chronic course of infection. Some positive cats have been followed up longitudinally to monitor changes in their health status and the duration of urinary excretion (Sharp et al., 2016; De Luca et al., 2018; Sieg et al., 2019; De Luca et al., 2020; Donato et al., 2021), but information available is scarce and fragmentary. The tendency for FeMV to persist *in vivo* was repeatedly reported in both healthy cats (Sharp et al., 2016) and cats with CKD (De Luca et al., 2018; Sieg et al., 2019). The Ct values and sequences of FeMV-GT1 in the urine samples of five cats were unchanged during an epidemiological study that lasted 8–10 months (De Luca et al., 2020). Similarly, long-term shedding of FeMV-GT2 was observed in two cats (Sieg et al., 2019).

Since the discovery of FeMV in 2012 (Woo et al., 2012), in the renal tubular cells and lymph nodes in two stray cats affected by TIN, research studies have focused on the role of FeMV in feline kidney pathology and in CKD. This 2012 study also included a case-controlled prospective investigation that provided evidence for a significant association between FeMV infection and TIN (Evidence-based level I) (Lloret et al., 2009; Woo et al., 2012). Thereafter, kidney tissues have been often studied with a higher percentage of positive samples found (ranging from 7.4 to 80.0%) compared to other tissues and urine (Woo et al., 2012; Park et al., 2016; Yilmaz et al., 2017; De Luca et al., 2018; Mohd Isa et al., 2019; Stranieri et al., 2019; De Luca et al., 2020). Kidney histological and IHC evaluation, performed in some studies, aimed to detect associations between any pathological changes, the detection of FeMV, and the occurrence of FeMV in any lesions (Woo et al., 2012; De Luca et al., 2018; Sutummaporn et al., 2019; De Luca et al., 2020). However, field studies had used different approaches and given contradictory results. As in the first study (Woo et al., 2012), FeMV detection can be associated with tubular damage and the presence of inflammatory infiltrates and intralesional FeMV detected by IHC (Woo et al., 2012; Park et al., 2016; Yilmaz et al., 2017; Sutummaporn et al., 2019). The tissue injury scores of tubular lesions were higher in FeMV-positive tubular sections, as well the severity scores of glomerulosclerosis and capillary thickness (Sutummaporn et al., 2019). Conversely, in other studies, the lesions observed were similar to those detected in FeMV-negative cats (Yilmaz et al., 2017; De Luca et al., 2020). This does not exclude a role for FeMV in the pathological changes observed, as the virus could have been cleared from tissues prior to examination. It should be remembered that TIN is the most common diagnosis in feline kidney pathology and the most common cause of feline CKD (Muratore et al., 2021). When tubular injury involves the basement membrane (tubulorrhexis), inflammation spreads to the interstitium, and focal TIN occurs (Spencer et al., 2021). Feline tubular cells typically accumulate lipids in the cytoplasm, and leakage of lipids into the interstitium in the case of tubulorrhexis enhances the inflammatory response (Quimby et al., 2022). Interestingly, a few weeks after experimental infection with FeMV-GT2, multifocal chronic TIN was observed in some cats, similar to what had been seen in feline experimental models of renal ischaemia (Nikolin et al., 2022; Quimby et al., 2022). Indeed, AKI-to-CKD transition is usually triggered by hypoxia regardless of the cause of AKI (Spencer et al., 2021). This may explain why a few clinical surveys (Sieg et al., 2015; Arikawa et al., 2017; Donato et al., 2021) have demonstrated an association between FeMV RT-PCR positivity and CKD, while no associations have been found in many other investigations (Yilmaz et al., 2017; McCallum et al., 2018; Mohd Isa et al., 2019; Stranieri et al., 2019; Chaiyasak et al., 2020; Muratore et al., 2021; Darold et al., 2017, 2021; De Luca et al., 2020). A limitation of some studies is due to the criteria used to select CKD and control cases, and in some reports, only a low number of cats have been tested. Moreover, in cross-sectional studies detecting viral RNA in urine samples, there is a risk of negative RT-PCR results despite infection because of possible intermittent urinary shedding. Finally, cats examined in field studies can be exposed to a wide range of infectious and noninfectious causes of CKD (Roura, 2023), and these confounding factors are not easily investigated and/or recognised. For example, Crisi et al. (2020) compared the clinical, haematological, and urinary parameters in cats with positive urine FeMV RNA RT-PCR results, cats with CKD, and healthy cats (Crisi et al., 2020). No cats in the CKD group tested FeMV positive; however, some degree of early renal damage, less severe than in the CKD group cats, was demonstrated in those cats testing FeMV RT-PCR positive in urine. Of note, this study performed UPE as well, and FeMV-positive cats showed a frequent tubular pattern of proteinuria, and the three necropsied cats were diagnosed with TIN (Crisi et al., 2020). This clinical study showed similarities, with the results

obtained in the experimental infections described above showing early kidney damage caused by FeMV (Crisi et al., 2020; Nikolin et al., 2022; Nambulli et al., 2022). Interestingly, transient proteinuria and cylindruria were documented in the FeMV RNA-positive urine of a cat diagnosed and treated for cholangiohepatitis in another study (Stranieri et al., 2019).

Fewer data on pathology are available for infected organs other than kidney. Liver involvement is definitely of high clinical relevance. Lymphocytic cholangiohepatitis is a common inflammatory hepatobiliary disease in cats histologically characterised by lymphocyte infiltration in the portal region with various degrees of fibrosis and bile duct proliferation (Jaffey, 2022). It is often subclinical with variable biochemical parameter abnormalities, and the causes triggering the aberrant inflammatory process are unknown (Jaffey, 2022). Sometimes, liver FeMV positivity (by RT-PCR and/or IHC) was associated with kidney positivity in cats affected by diffuse cholangiohepatitis, as seen in experimental infection (Yilmaz et al., 2017; Nikolin et al., 2022).

Data on spleen, lymph node, lungs, intestine, urinary bladder, infections, and associated pathology are very sparse in field studies and case reports (De Luca et al., 2020; Chaiyasak et al., 2022), and further investigation is needed.

FeMV infection (confirmed by both RT-PCR and IHC) of tubular cells without inflammatory reactions has been seen in some cases (Donato et al., 2021; Chaiyasak et al., 2022), and factors promoting inflammation and associated damage to tissues (primarily in the kidney and liver) remain unknown. It has to be considered that TIN and lymphocytic cholangiohepatitis are common feline kidney and liver pathologies, respectively, that occur worldwide; FeMV is just one possible cause (McLeland et al., 2015; Jaffey, 2022). For instance, DCH is a further viral candidate as liver pathogen for cats (Shofa et al., 2022).

Immunity

There are important gaps in knowledge concerning cat immunity to FeMV. The role of cat nonadaptive immune response to FeMV is unknown as well as of adaptive cell-mediated immunity.

Experimental infection with FeMV-GT2 resulted in antibody production in all infected cats (Nikolin et al., 2022). Seroconversion was detected from day 7 pi by semiquantitative IFA, and all cats were considered strongly positive from day 14 pi (Nikolin et al., 2022). Serum samples of some of these cats were also tested for virus neutralizing antibodies. From day 7 pi onwards these cats tested VN positive ($\geq$512) and at the end of the study (day 56) all tested cats had VN titers > 1024 (Nikolin et al., 2022). However, antibody positive cats shed viral RNA in urine and tubular renal cells were found infected at post mortem investigations, therefore antibodies are not able to control renal infection and urinary FeMV shedding (Nikolin et al., 2022). Antibody response was associated with a declining viral load in blood, but some antibody positive cats were still viraemic up to day 49 pi (Nikolin et al., 2022). Similarly, naturally infected cats had neutralising antibodies (Sieg et al., 2019) or tested serum antibody positive by IFA (Donato et al., 2021), and shed FeMV-GT2 and FeMV-GT1 RNA in urine respectively.

Interestingly, antibody seroconversion was not observed in four cats positive in urine samples for 21–360 days that were followed up in a field trial (Donato et al., 2021). Moreover, one additional cat that was followed up for six months converted to an antibody-negative status associated with the cessation of FeMV RNA urinary shedding (Donato et al., 2021).

Clinical signs

A wide spectrum of clinical outcomes appears to be possible in FeMV infected cats, from subclinical infections to acute and/or chronic disease and lethal outcomes (Sharp et al., 2016; Crisi et al., 2020; Donato et al., 2021; Ito et al., 2023; Dawson et al., 2023).

A disease associated with acute infection can develop and FeMV could be causing AKI when clinicopathological abnormalities suggest this diagnosis in a cat and no other cause is found (Crisi et al., 2020; Nambulli et al., 2022; Nikolin et al., 2022). Similarly, FeMV infection can be considered in cases of acute febrile syndrome, panleukopenia, and encephalitis of unknown origin (Ito et al., 2023; Dawson et al., 2023).

The most clinically relevant presentations of chronic course of FeMV infection seem to be associated with CKD, FLUTD, and hepatobiliary disease development (Woo et al., 2012; Yilmaz et al., 2017; Donato et al., 2018: Stranieri et al., 2019; 2Busch et al., 2021b; Donato et al., 2021: Nikolin et al., 2022).

Diagnosis

Currently, FeMV diagnostic investigation is restricted to research laboratories. It is recognised that CKD can be clinically diagnosed months or even years after a pathogen triggered the pathological process that led to the development of TIN. Since the infection could have resolved in the meantime, based on current knowledge, ABCD does not recommend routine screening of FeMV infection in healthy cats, nor in those with CKD.

Laboratory changes

Information available is fragmentary and scarce. Clinically relevant laboratory abnormalities reported in FeMV infected cats can be observed in the CBC, and in some serum biochemical markers.

Acute infection can be associated with leukocytosis, leukopenia, lymphopenia, and thrombocytopenia (Nikolin et al., 2022; Ito et al., 2023).

Abnormalities in renal disease markers values include increased serum SDMA and creatinine concentrations, mild tubular proteinuria and low urine specific gravity (Donato et al., 2018; Crisi et al., 2020; Donato et al., 2021). AST values over the reference range have been transiently reported in some experimentally infected cats (Nikolin et al., 2022).

Detection of the infectious agent

Direct detection

Urine and kidney tissue are the best samples for RNA detection by PCR in chronically infected cats and nested reverse transcriptase (RT)-PCR assays (targeting L, N or H genes) have been largely used (Woo et al., 2012; Furuya et al., 2016; Sieg et al., 2015; Park et al., 2016; Darold et al., 2017; Yilmaz et al., 2017; Mc Callum et al., 2018; Sieg et al., 2019; Stranieri et al., 2019). Quantitative real time RT-PCR (qPCR) for FeMV was developed by Sharp et al. (2016) by using L gene primers (Sharp et al., 2016). De Luca et al. (2018) developed a real-time RT-PCR targeting on a conserved region of FeMV P/V/C gene and it was found more sensitive than a RT-PCR targeting the L protein encoding gene of morbilliviruses (De Luca et al., 2018).

In the first days after infection, RT-PCR assay is more sensitive in blood than in urine and blood should be preferably tested in case of suspected cases with febrile syndrome (Nambulli et al., 2022; Nikolin et al., 2022; Ito et al., 2023).

In case of post mortem investigations, histopathology with IHC evaluation of renal lesions associated with FeMV infection shoul be performed. In cats dead following an acute disease, virus is systemically spread and can be detected by RT-PCR and IHC in spleen, lymph nodes, SNC and other organs (Nambulli et al., 2022; Nikolin et al., 2022; Chaiyasak et al., 2022; Ito et al., 2023; Dawson et al., 2023).

Indirect detection

The most widely used antibody testing technique is the IFA, which allows the detection of antibodies against all viral proteins (Park et al., 2016; Arikawa et al., 2017; Donato et al., 2018; De Luca et al., 2020; Donato et al., 2021; Busch et al., 2021a, 2021b). However, genotype-specific IFAs are needed to evaluate the exposure of cats to specific genotypes. An IFA using two different cell lines infected with FeMV-GT1 and FeMV-GT2, respectively, was developed and validated for detecting antibodies against the two FeMV genotypes (Busch et al., 2021a, 2021b). Cross-reactivity with CDV for FeMV-positive cat sera was excluded in this study (Busch et al., 2021a).

Immunoblot assay was used to evaluate antibody response to FeMV, but cross-reactivity between CDV and FeMV was documented (Sakaguchi et al., 2014).

Antibody detection (by IFA detecting both GT1 and GT2 strains) can support acute disease diagnosis when seroconversion is evidenced, as seen in experimental models (Nambulli et al., 2022; Nikolin et al., 2022).

Disease management and treatment

The management of cats with urinary positivity to FeMV relies on addressing concurrent CKD, if present, according to the IRIS guidelines for the diagnosis, staging and management of CKD in cats (www.iris-kidney.com).

In case of diseases associated with acute FeMV infection, supportive and symptomatic medical therapies are indicated.

Prognosis

FeMV infection has been reported in clinically healthy cats and factors triggering inflammatory reactions associated with viral detection are not known. The proportion of cats that develop long-term life-threatening renal disease after FeMV infection is unknown, as are the risk factors that drive a poor prognosis for kidney function.

Prognosis has therefore to be considered case by case on the basis of clinical and clinicopathological findings associated with FeMV positivity. In particular, the prognosis of cats with urinary positivity to FeMV relies on that of a concurrent CKD or hepatobiliary disease.

Vaccination

No information is available about prevention of FeMV infection or the development of associated clinical disease by cat vaccination.

Disease control in specific situations

There is an important gap of knowledge about infectivity of virus shed with cat urine or other biological fluids, and of contaminated fomites. Similarly, routes of transmission in natural conditions have to be proven.

Infected urine is probably the main source for transmission of FeMV infection between cats, particularly in catteries where cats are sharing litter trays. FeMV infection control is challenging in case of multicat environment and in free-roaming cats.

More studies are needed to understand the possibility of inter-species transmission, particularly between dogs and cats.

Zoonotic risk

Data available do not support a risk of infection for humans.

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