An Update on Feline Calicivirus

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Eine Übersicht zum Felinen Calicivirus

Das Feline Calicivirus (FCV) ist weltweit einer der häufigsten viralen Erreger bei Hauskatzen. Der erste Bericht über FCV stammt aus dem Jahr 1957, als FCV aus dem Magen-Darm-Trakt von Katzen in Neuseeland isoliert wurde. Spätere Berichte fanden FCV als Ursache von Atemwegserkrankungen bei Katzen. Kleintierärztinnen und Kleintierärzte weltweit sind täglich mit FCV-Verdachtsfällen konfrontiert. Die stark mutagene Natur von FCV und seine hohe genetische Plastizität ermöglichen dem Virus ein erfolgreiches Überleben in der Katzenpopulation und stellen eine besondere Herausforderung hinsichtlich der Diagnose, Behandlung und Prävention von FCV-induzierten Erkrankungen dar. Erkrankungen der oberen Atemwege gelten als häufiges klinisches Zeichen einer FCV-Infektion. Eine Studie aus der Schweiz zeigte, dass orale Ulzerationen, Speichelfluss und Gingivitis-Stomatitis häufiger mit einer FCV-Infektion assoziiert waren als Erkrankungen der oberen Atemwege, und weniger als die Hälfte der Katzen bei denen der Verdacht auf eine FCV-Infektion bestand, war FCV-positiv. Zusätzlich fand eine Studie zu FCV-Isolaten aus der Schweiz Hinweise darauf, dass der genetische Hintergrund von Katzen ihre Anfälligkeit für eine FCV-Infektion beeinflussen könnte.Dieser Übersichtsartikel bietet eine umfassende Zusammenfassung der FCV-Literatur und integriert die Ergebnisse der jüngsten Forschung zu den genetischen Merkmalen von FCV, der zellulären und humoralen Immunität hervorgerufen durch eine FCV-Impfung oder -Infektion, der Diagnose von FCV, der FCV-Prävention/-Impfung, den Risikofaktoren einer FCV Infektion und den erforderlichen Hygienemassnahmen in FCV-verseuchten Bereichen. Nach jedem Abschnitt werden die wichtigsten Punkte zusammengefasst und relevante Informationen beschrieben, um Tierärzte bei der Diagnose, Behandlung und Prävention von FCV zu unterstützen.

Schlüsselwörter: Katzen, genetische Evolution, orale Ulzera, Risikofaktoren, Impfung, virulent-systemische Erkrankung

Summary

Feline Calicivirus (FCV) is one of the most common viral pathogens in domestic cats worldwide. The first report of FCV dates back to 1957, when FCV was isolated from the gastrointestinal tract of cats in New Zealand. Subsequent reports recognised FCV as a cause of respiratory disease in cats, and at present, feline practitioners worldwide are daily confronted with cats suffering from suspected FCV. The highly mutagenic nature of FCV and its high genetic plasticity enable the virus to successfully survive in the feline population, and pose a special challenge as regards the diagnosis, treatment, and prevention of FCV-induced disease. Upper respiratory tract disease has been considered a common clinical sign of FCV infection. A study from Switzerland demonstrated that oral ulcerations, salivation and gingivitis-stomatitis were more commonly associated with FCV infection than upper respiratory tract disease, and less than half of the cats suspected to have FCV infection were found to be FCV-positive. Furthermore, a study investigating FCV isolates from Switzerland found some evidence that the genetic background of cats might influence their susceptibility to FCV infection. This review article provides a comprehensive summary of the FCV literature, and integrates the results of recent research on FCV's genetic characteristics, the cellular and humoral immunity evoked by FCV vaccination and infection, the diagnosis of FCV, FCV prevention/vaccination, the risk factors associated with FCV, and the hygienic measures necessary in FCV-contaminated areas. After each section, the key points are summarised, and relevant information is outlined to help feline practitioners in FCV diagnosis, treatment and prevention.

Keywords: Cats, genetic evolution, oral ulceration, risk factors, vaccination, virulent-systemic disease

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The virus

FCV belongs to the order of *Picornavirales* and the family of *Caliciviridae*. The name is related to the electron microscopic appearance of "cup (from Latin calix)-shaped depressions" on the virion's surface.[138] The family *Caliciviridae* consists of 11 genera, i.e., *Bavovirus*, *Lagovirus*, *Minovirus*, *Nacovirus*, *Nebovirus*, *Norovirus*, *Recovirus*, *Salovirus*, *Sapovirus*, *Valovirus* and *Vesivirus*.[138] Members of the genera *Lagovirus*, *Norovirus*, *Nebovirus*, *Recovirus*, *Sapovirus*, *Valovirus*, and *Vesivirus* infect mammals; members of the genera *Bavovirus* and *Nacovirus* infect birds; and members of the genera *Minovirus* and *Salovirus* infect fish. FCV belongs to the genus *Vesivirus*, together with the vesicular exanthema of the swine virus. Other caliciviruses relevant to veterinary practice include European brown hare syndrome and rabbit hemorrhagic disease virus, both of which are members of the genus *Lagovirus*.[138] Some caliciviruses found in dogs, sea lions and minks have not yet been classified, but are considered vesivirus-like viruses.[138] The virions of vesiviruses are non-enveloped with an icosahedral symmetry, and between 27 and 40 nm in diameter.[138] FCV is a single-stranded RNA virus with a positive polarity.[138] The viral genome is about 7,7 kb in length and divided into three open-reading frames (ORF).[138] ORF 1 encodes a polyprotein that is post-translationally cleaved into non-structural proteins, such as the NTPase enzyme or the viral protein genome (VpG)-linked, the viral protease and polymerase complex, and the RNA-dependent RNA polymerase.[106] ORF2 encodes the major capsid protein VP1 and ORF3 encodes for the minor capsid protein (VP2), both of which are essential for binding to the host cell and the production of infectious virus, respectively.[19; 125] The VpG linked at the 5' end acts as a primer during viral RNA synthesis.[138] The poly-A tail present on the 3' end of the genome is important for viral RNA stability and translation. [72] The capsid gene is divided into six regions, A–F.[87] The region E is divided into the 5' prime hypervariable region (HVR), the central conserved region and the 3' HVR. The 5' HVR contains epitopes for neutralising monoclonal antibodies,[52] and the whole of HVR E is considered a target for immune evasion during persistent FCV infections.[108] The capsid protein is synthesised as a precursor protein, which is cleaved by the viral protease into the small leader capsid protein and the larger major VP1 capsid protein.[126] The leader capsid protein has been found to be essential for the production of viruses able to induce a cytopathic effect in feline kidney cell culture.[2]

The cellular receptor junctional adhesion molecule 1 (JAM 1) has been identified as a functional receptor for FCV attachment, entry, and further downstream events.[78,79] In cats, the feline JAM 1 (fJAM 1) receptor is mainly localised at the cell–cell junctions of epithelial and endothelial cells, and the ulcerative and vesicular lesions observed after FCV infection reflect the disruption of intercellular junctions.[96] However, differences have been identified between FCV isolates as regards the interaction of receptors, as the virulent-systemic (VS)-FCV isolates and isolates from kittens with pneumonia were inactivated after incubation with the fJAM 1 ectodomain *in vitro,* and the FCV F9 vaccine isolate was resistant to receptor-mediated inactivation by fJAM 1.[91]

FCV is a highly mutagenic virus, and the evolution rates of a strain within an individual and a strain circulating within a population have been indicated to be $1{,}32\times10^{-2}$ to $2{,}64\times10^{-2}$ and $3{,}84\times10^{-2}$ to $4{,}56\times10^{-2}$ substitutions per nucleotide per year, respectively.[25] This is one of the highest identified evolution rates for RNA viruses. Sequence analyses revealed a broad genetic heterogeneity among related isolates, and therefore it is thought that FCV exists as a so-called quasispecies within the host.[108] Using nucleotide and amino acid analyses of the HVRs of various FCV isolates, FCV has been classified into two genogroups, but isolates belonging to genogroup II originate only from Japan.[114] Based on studies into FCV genetic diversity and viral evolution, the level of genetic distance that allows strain differentiation is generally accepted to be 20 %.[22,121] Epidemiologically unrelated isolates differ by more than 20 % on the nucleotide and amino acid level in the variable regions C and E of the capsid gene, and are therefore considered separate strains. Epidemiologically related isolates, such as those found in outbreaks of acute and virulent-systemic disease, are around 99 % identical, and are considered variants of the same strain.[22,105,107] In FCV-endemic cat colonies, the viral variation within one strain can be up to 18 %.[25] At the spatial and temporal level, FCV strains show high genetic and antigenic strain complexity, with no single field strain dominating over the others.[22,130] Viral evolution is therefore not only based on competition among the different isolates, but rather long-term survival within a susceptible population or individual is ensured through the progressive accumulation of random mutations within one isolate, sequential reinfection, and recombination.[24,25,27] Concurrent infection of one cat with two distinct FCV strains has been described,[107] and the recombination of two distinct but co-circulating FCV strains within a cat shelter has been observed.[27] With these strategies, the genetic variability of FCV strains can increase until new strains emerge, and this high genetic plasticity may contribute to immune evasion.[25] Even though genetic heterogeneity also leads to antigenic heterogeneity, there seems to be sufficient genetic relatedness between the strains to ensure some cross-protection through vaccination.[88,101]

Key points:
- FCV is a highly mutagenic RNA virus;
- FCV has been classified into two genogroups, but all as-yet identified isolates belonging to genogroup II originate from Japan;
- The long-term survival of FCV within a susceptible population or an individual is ensured through the progressive accumulation of random mutations within an isolate, recombinations between different isolates, and the sequential reinfection of cats.

Pathogenesis of FCV

The understanding of FCV molecular pathogenesis has benefitted in the past from the fact that, unlike other members of the family of *Caliciviridae*, it is cultivable in cell culture.[106] FCV has served as a model organism to study the viral pathogenesis and disinfection methods of human noroviruses or sapoviruses, which have not as of yet been cultivable.[106]

FCV is host-specific for animals of the family *Felidae*, and no zoonotic potential or changes in the host-range have been observed for FCV.[104] FCV-like particles have been isolated from dog diarrhoea samples, but it remains unclear whether these particles are responsible for the clinical signs or if they only represent the gastrointestinal passage.[94] Cats can be infected with FCV directly, from cat to cat, or indirectly via fomites and possibly by aerosols.[127] The infection occurs via the nasal, oral or conjunctival route, and the capsid protein is responsible for attachment to the permissive host cell. The feline junctional adhesion molecule A (fJAM-A), also named fJAM 1 in some studies, and α-2,6 sialic acid, act as receptors for the entry of FCV into host cells.[94] fJAM-A is an immunoglobulin-like protein, important for the assembly and maintenance of tight junctions of epithelial and endothelial cells.[96] The α-2,6 sialic acid was identified as an additional receptor component, but it is insufficient to mediate infectious entry alone.[132] The entry process of FCV requires acidification in endosomes, and FCV is able to infect cells via clathrin-mediated endocytosis.[131] The vesicular disease (i.e., oral, lingual or cutaneous ulcerations) caused by FCV mainly reflects the disruption of tight junctions of the epithelial cells. The fJAM-A receptor is additionally found on feline platelets and peripheral blood leukocytes.[96] The receptor's presence in blood cells increases the likelihood of a haematogenic distribution within the host. RNAemia in FCV infection has previously been described, but mostly in the context of VS-FCV disease, and it has been thought that FCV presents a local disease manifestation, whereby neighbouring cells will be infected progressively.[94] However, FCV RNA has been detected in the blood of cats experimentally infected with an FCV field strain that caused oral ulcerations, fever and reduced general condition but not VS-FCV.[129] The presence of FCV RNA in the blood opens up new possibilities of viral dissemination in the cat population, and in rare cases FCV might be transmitted by blood-sucking arthropods, bites, or blood transfusion, but whether the sole presence of FCV RNA in the blood is sufficient to infect naïve cats via the haematogenic path has not yet been investigated.

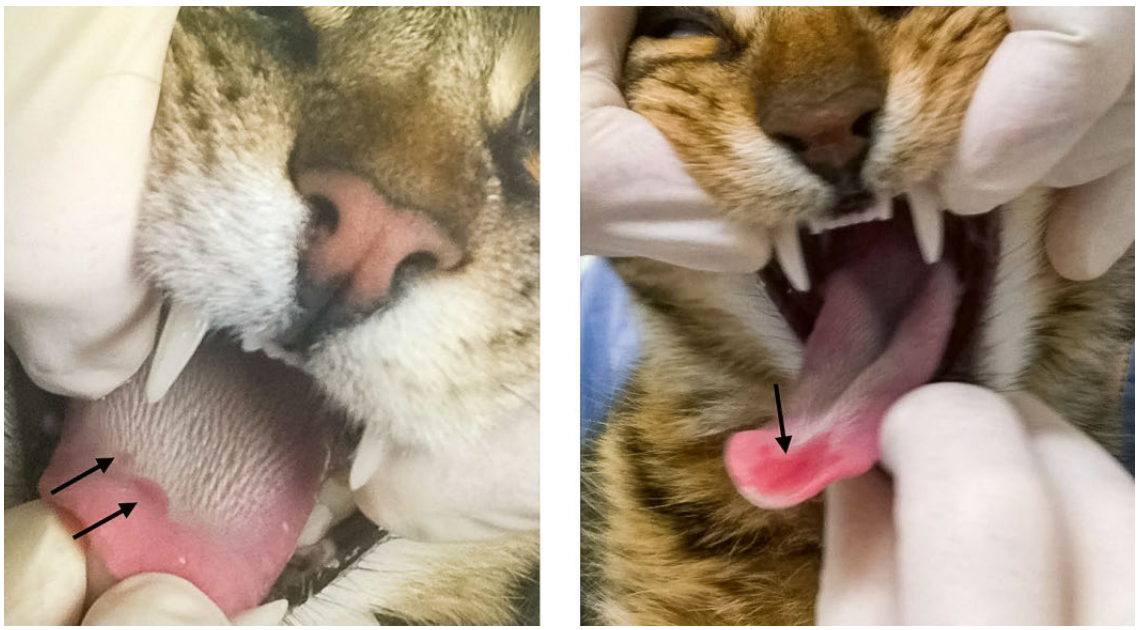

Figure 1: Lingual ulcerations (black arrows) in cats experimentally infected with FCV.

Key points:
- Infection can occur directly from cat to cat, indirectly via fomites, and possibly via aerosols;
- The vesicular disease (i.e., oral, lingual or cutaneous ulcerations) caused by FCV mainly reflects the disruption of tight junctions of the epithelial cells;
- FCV RNA can also be found in the blood of cats affected by non VS-FCV, thus the sole presence of FCV RNA in the blood does not represent proof of VS-FCV.

Clinical signs

FCV-induced disease has various manifestations, and can be categorised into ulcerative disease (Figure 1), gingivo-stomatitis, limping syndrome and virulent-systemic disease. The disease manifestation depends on various factors, such as the FCV strain involved, the host immune response, and the co-infections present. Most commonly, cats are affected by ulcerative upper respiratory tract disease, with such clinical signs as oral ulcerations, gingivitis-stomatitis, fever and lethargy.[11,17,53] Oral ulcerations, gingivo-stomatitis, hypersalivation and fever are more often associated with FCV than classical upper respiratory disease, which is indicated by sneezing and ocular and nasal discharge.[9] In the field, cats are often not infected with FCV alone, and co-infections with feline herpesvirus (FHV), *Chlamydia felis* and *Mycoplasma felis* are common. The presence of *Mycoplasma felis* was found to be associated with FCV positivity,[69] and FHV, *Mycoplasma* species and *Chlamydia felis* were found to be the main contributors to upper respiratory tract disease.[6] The combination of co-infections influences the presentation of clinical signs. FHV and *Chlamydia felis* predominantly cause ocular disease with conjunctivitis and keratitis, and FHV can reduce the mucociliar clearance of the lungs and impair the local immune defence, resulting in focal alveolitis progressing to exudative and proliferative interstitial pneumonia.[84] Alveolar macrophages have been shown to be the main target and replication site for FCV in cats with FCV-associated pneumonia.[85] Nevertheless, primary FCV-induced pneumonia in adult cats and kittens is still uncommon, and the disease's presence may have been overestimated in the past because experimental infections with FCV used the aerosolisation route of infection.[106] Oronasal inoculation, used in more recent studies, better reflects the natural route.[129]

The role of FCV in the pathogenesis of feline chronic gingivo-stomatitis (FCGS) is not fully understood, but there is a strong suspicion that viral and/or bacterial components might be involved.[38,40] In several studies, FCV was more commonly found in cats suffering from FCGS than in control cats,[7,42,86] and in another study, FCV was strongly associated with gingivo-stomatitis.[47] A metatranscriptomic next-generation RNA sequencing approach detected a strong association of FCGS with FCV in oral mucosal swab samples, and puma feline foamy virus was identified in the majority of cats that were refractory to the treatment of FCGS with tooth extraction or mesenchymal stem cells.[49] However, no association between FCV load and the severity of caudal and alveolar stomatitis was found, and only lingual ulcerations were significantly correlated with the FCV load.[43] Interestingly, a greater prevalence of FCV antibodies in cats with FCGS compared to control cats was found, indicating that, beside the involvement of pathogens, FCGS could be an immune-mediated disease.[7] FCGS has not as of yet been experimentally induced in laboratory cats,[67] and FCV could not be detected via immunohistochemistry in FCGS lesions.[111]

A further but meanwhile rather uncommon clinical presentation of FCV is limping syndrome.[30,134] FCV is known to affect several tissues, and the synovial membranes of joints can also be affected. FCV could be isolated from the joints of affected cats,[30] and immunocomplexes were detected in synovial macrophages.[8] Limping syndrome has also been identified in kittens after vaccination with certain FCV vaccine strains.[31]

The most severe form of FCV-induced disease is the virulent-systemic manifestation. Cats affected by the virulent-systemic form suffer from a systemic inflammation response with internal organ involvement, jaundice, disseminated intravascular coagulation and severe skin and mucous membrane ulcerations. Highly contagious and epizootic outbreaks of VS-FCV have been reported worldwide.[26,48,60,88,92,109,115,116] The morbidity and mortality rate in virulent-systemic disease outbreaks can be very high, at up to 67 %,[104] with a fast onset of severe clinical signs and rapid epizootic progression. Particularly in multicat environments, such as shelters, breeding catteries and animal hospitals, VS-FCV can cause high numbers of deaths. A clinical picture similar to VS-FCV, named "paw and mouth disease", was first described by Cooper and Sabine in 1972.[21] A young cat presented with paw oedema, oral ulcerations and cutaneous lesions on the feet, and calicivirus could be isolated from the tongue and paw lesions, but the cat maintained a good general condition.[21] More cases of non-epizootic forms resembling VS-FCV were described afterwards.[140] The affected cats presented with cutaneous ulcerative lesions, cutaneous oedema and/or inner organ involvement, but with varying mortality rates.[140] VS-FCV therefore does not present as a clear picture, but rather as a continuum of possible clinical signs with varying morbidity and mortality rates. It is thought that VS-FCV strains emerge independently, and no genetic relationship has been identified so far between reported outbreaks.[140]

To date no conclusive genetic fingerprint on the nucleotide or amino acid level has been identified to molecularly characterise VS-FCV. One study implicated sequence changes in the capsid protein to characterise the VS-FCV phenotype,[1] and another study identified two amino acids in the hypervariable region of the capsid protein as a potential unique signature for the VS-FCV strain.[112] However, other studies could not find a correlation between overall sequence data and disease manifestation.[103,140] Some highly virulent FCV isolates might have increased viral fitness based on a higher replication efficiency *in vitro* compared to less-virulent isolates.[90,95]

A recent study analysed amino acid properties to characterise VS-FCV and non-VS-FCV isolates.[13] Seven remarkable residue positions in the capsid protein were found to be distinctive for the VS-FCV pathotype.[13] The study represents an interesting approach and opens up a new path for viral sequence analyses. The analyses of more VS-FCV isolates from different geographic locations are needed to further determine whether certain amino acid properties are distinctive for the VS-FCV pathotype.

FCV RNA can be detected by RT-PCR in faeces of cats with enteritis.[36] The enteric FCV isolates were found to be more resistant to bile acid treatment, digestion enzymes and low-pH conditions compared to non-enteric isolates.[36] The role of FCV in feline gastrointestinal diseases remains unclear, but enteric tropism could be possible, as other members of the family *Caliciviridae* (e.g., human norovirus) also cause gastrointestinal disease.

FCV has been discussed as playing a potential role in feline urinary tract disease, and it has been isolated from urine and tissue samples of cats affected by idiopathic feline lower urinary tract disease (FLUTD).[71] However, the role of FCV in the pathogenesis of these conditions remains unclear, and it is probable that factors other than viral ones play major roles in FLUTD syndrome.[71]

Despite the wide range of clinical signs caused by FCV, seemingly healthy cats can also shed FCV.[9,23] After recovering from transient acute disease, some cats remain persistently infected and become FCV carriers.[25,62,70,108] The virus might deploy immune-protected sites, and the epithelium of the tonsils and the surrounding tissues have been shown to harbor FCV in asymptomatic carriers.[139] However, tonsillectomy did not eliminate the FCV carrier state.[102] *In vitro*, the persistent infection of T-lymphoblastoid cells for at least one month has been demonstrated.[66] Another factor contributing to persistence in an individual is the continuous viral evolution resulting in immune-escaping variants. Viral evolution occurs mainly in the FCV capsid region, which is highly variable and the main target for neutralising antibodies.[52] However, viral evolution is probably not the sole factor contributing to viral persistence, as substantial antigenic changes in the capsid might be prevented by structural restrictions,[122] and certain capsid residues have been identified to be crucial for binding to the cellular receptor, as well as for infection.[20,78] Interestingly, some cats seem to be resistant to FCV infection. In a long-term study in a UK cat shelter, some cats were never found to be FCV-positive despite continuous exposure to FCV.[23] The study found some evidence that cats younger than three years were more likely to become FCV-positive than cats older than three years, and the resistance to FCV shedding could be based on age-related and acquired immunity. Additionally, genetic factors are important, as most non-shedder cats in the UK study were British Shorthairs.[23] Furthermore, a phylogenetic study documented a lack of FCV genetic divergence in Maine Coon cats.[130] As regards other members of the family *Caliciviridae*, i.e., human norovirus, genetic resistance based on the variability of the ABH histo-blood group antigen in gut cells has been identified.[77] Therefore, a cat's genetic background may ground an increased susceptibility or resistance to FCV infection.

Key points:
- Oral ulcerations, gingivo-stomatitis and hypersalivation have been more commonly associated with FCV than upper respiratory tract disease;
- No conclusive genetic fingerprint on the nucleotide or amino acid level has been identified so far to molecularly characterise VS-FCV;
- Apparently healthy cats can shed FCV.

Immune response

Acquired humoral and cellular immunity

In experimental challenge studies, the homologous and heterologous FCV antibody response correlated well with clinical protection against FCV disease.[101] Neutralising antibodies following the vaccination or experimental infection of naïve cats appeared by day eight to 14 post-vaccination or post-infection, and homologous antibodies were detected earlier than heterologous antibodies.[65,67,128] The magnitude of the antibody response can vary considerably between individuals.[128] A peak in class-specific anti-FCV IgM antibodies was detected after the start of FCV shedding and after the onset of clinical signs.[67] The appearance of IgM antibodies was then closely followed by rising levels of IgG antibodies, correlating with the onset of the virus-neutralisation response. This finding indicates that IgG antibodies contribute to the majority of neutralising antibodies, but IgM antibodies might be important for an early neutralising response. Furthermore, salivary and serum IgA antibodies were investigated, and peak IgA values

were reached earlier in saliva than in serum.[67] Therefore, the local immunity represented by IgA antibodies on mucosal surfaces acts synergistically in the humoral defence against FCV. It has been demonstrated that a previous FCV infection can induce cross-neutralising antibodies and local immunity, and that clinical signs and FCV shedding can be reduced upon heterologous FCV challenge.[67,127,129]

Even though antibodies are considered pivotal for protection, no relationship between the cessation of virus shedding or the termination of clinical signs and the arising of an antibody response could be detected, and the antibody titre related to clinical protection remains unidentified.[67] In a neutralisation study, a titre of 1:16 or higher was considered to be protective, whereas a titre of 1:7 or lower indicated susceptibility to heterologous FCV challenge.[101] In another study, the presence of any anti-FCV antibodies was shown to be protective, independent of the titre.[73] However, cats without detectable antibodies were also found to be protected from disease, indicating that immune mechanisms other than antibodies are also of importance.[76,99,100] Cell-mediated, FCV-specific immunity following inactivated FCV vaccination has been described,[135] and FCV-specific CD4+ cells were detected in the spleens of FCV-vaccinated cats.[34] Additionally, cell-mediated immunity in MLV FCV F9 vaccinated cats against the vaccine virus was detected, and cell-mediated cross-reactive immunity against an FCV field strain was observed.[128] Interestingly, the cross-reactivity was limited to cellular immunity, as no cross-neutralising antibodies were detected against the FCV field strain.[128]

Innate immune mechanisms

Innate immune mechanisms – such as the upregulation of mRNA expression of the myxovirus resistance gene 1 (MX1) or of type I IFNs – were found to have an antiviral inhibitory effect on FCV *in vitro* and *in vivo*.[110] MX1 and proteins that help in the elimination of virus-infected cells, such as perforin and granzyme B, were elevated after MLV FCV F9 vaccination and experimental FCV infection.[128] The study further demonstrated that even though adaptive immunity was already present in vaccinated cats, innate immune mechanisms seem to be important in the early defence against FCV infection. Furthermore, levels of the acute phase protein serum amyloid-A (SAA) were found to increase significantly after experimental FCV infection, and in asymptomatic FCV-infected cats high SAA values could be detected in the short term.[129]

Maternally derived immunity

Kittens in the first weeks of life are protected by maternally derived antibodies (MDA), given that the mother will have acquired immunity before giving birth. The half-life of MDA has been determined as approximately 15 days, and MDA were found to persist up to 13 weeks.[63] However, the transfer of MDA to kittens can vary considerably within a litter and between different litters.[98] MDA might interfere with the formation of vaccine immunity, as MDA are able to neutralise the vaccine virus before adaptive immunity is built.[32,98] MDA are not routinely measured before vaccination in kittens, and it is not known which antibody titre interferes with the building of vaccine immunity. Given that the MDA level varies greatly between kittens, most vaccination guidelines recommend starting the first FCV vaccination at around eight weeks of age.[33,59] A second vaccination should follow two to four weeks later, but not before 12 weeks of age.[33,59] In a situation of high FCV risk, or when high MDA levels are expected, a third injection at 16 weeks of age and another booster at 40 to 64 weeks of age are recommended for all cats.[33,59] With this vaccination series, most cats will receive at least one vaccination outside the MDA period (Figure 2). In high FCV risk situations and when MDAs are likely to be low, an early commencement of FCV vaccination at six weeks of age can be considered.[32] Johnson and Povey, 1984, described the course of FCV infection in kittens born from persistently FCV-infected queens.[64] The kittens became FCV-infected between three and nine weeks of age, and shed FCV up to 11 weeks of age.[64] Clinical signs, such as depression and tongue ulcers, were observed in some kittens, but no severe respiratory disease developed.[64] MDAs were detected in all kittens, and anti-FCV antibody titres started to increase one to three weeks after infection, indicating a mild but immunising infection of the kittens.[64] However, FCV-infected kittens can also suffer severe pneumonia, but in these cases, co-infections are very common. In particular, FHV is able to induce severe primary lesions, thus facilitating a secondary infection with FCV and/or bacteria of the respiratory tract.[84]

Key points:
- Cellular immunity and humoral immunity, as well as innate immune mechanisms, are important in resistance to FCV infection;
- MDA might interfere with the formation of vaccine immunity, as MDA are able to neutralise the vaccine virus before adaptive immunity is built.

Viral evolution strategies and possible immune evasion

Viruses have evolved different strategies to evade host immune responses. Highly mutagenic RNA viruses, such as FCV, have an error-prone viral polymerase, and therefore constantly accumulate mutations (antigenic drift) in their genome.[25] Some mutations might be del-

eterious, but some increase viral fitness and can lead to immune evasion. Beside the constant accumulation of mutations, recombination between two different FCV has also been observed (antigenic shift).[27] Antigenic drift and antigenic shift can lead to significant antigenic changes and viral epitopes no longer being recognised by neutralising antibodies, or to an ameliorated binding capacity of the virus to the corresponding cell receptor, resulting in higher infectivity.[25]

The constant viral evolution of FCV poses a challenge to vaccine design, and the vaccine strains used over the decades may have become less effective, as suspected by some studies.[3,57,74] Geographic differences in the patterns of neutralisation to vaccine strains in FCV field isolates have also been identified.[56] However, the latest *in vitro* neutralisation results do not confirm any divergence of current continental European and UK FCV field isolates from the vaccine virus FCV F9.[5,123]

Another strategy used by FCV to evade the host immune response consists of the inhibition of host protein synthesis (known as host "shut-off").[51] Cells that undergo "shut-off" mainly produce viral proteins, and the host's protein synthesis is limited to proteins essential for viral replication.[141] It has been reported that some FCV isolates are unable to activate the IFN-β promotor[136] or suppressed type I IFN production of the host cell *in vitro*, resulting in an impaired antiviral host defence.[146] The proteinase–polymerase protein of FCV strain 2280 was shown to suppress the host gene expression using truncated proteins on the N-terminal end.[142] Interestingly, the same domain of the FCV strain F9 failed to suppress host genome expression.[142] Three key sites were identified as responsible for the host "shut-off" induced by FCV strain 2280, and the same amino acid residues were found in several other FCV strains.[142] Whether these amino acid residues are responsible for increased viral growth *in vitro* and virulence *in vivo* remains to be determined, but these findings are of interest for further investigating the viral properties of different FCV isolates.

Key points:
- The highly mutagenic nature of FCV could contribute to possible immune evasion;
- FCV F9 vaccine virus still induces a broad and cross-reacting immune response to a wide range of European FCV strains;
- Some FCV strains can induce host "shut-off", resulting in a weakened antiviral defence.

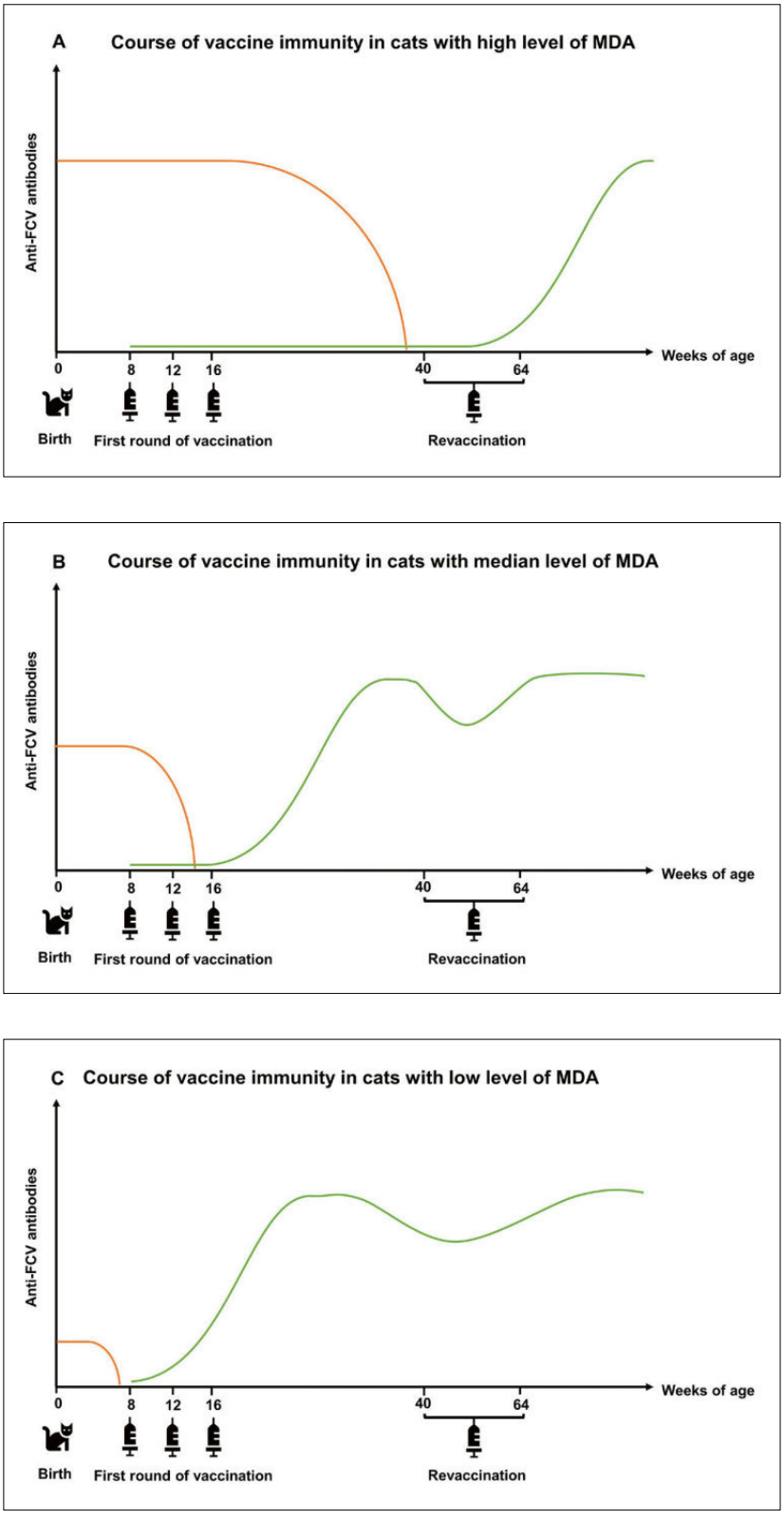

Figure 2: Course of maternally derived antibodies (MDA, orange line) and vaccine-derived (green line) anti-FCV antibodies in cats receiving a basic FCV immunisation at eight, 12, and 16 weeks and a revaccination at 40–64 weeks of age with a high level of MDA (A), median level of MDA (B), and low level of MDA (C). The figures were drawn using MS powerpoint and fontawesome icons (https://fontawesome.com).

Laboratory diagnosis of FCV infection

Reverse transcription quantitative polymerase chain reaction (RT-qPCR)

The successful molecular detection of FCV starts with choosing the optimal sampling site and method. In swabs of the oropharynx and the tongue, FCV detection by RT-qPCR was more likely, compared to using conjunctival swabs,[117] but the direct sampling of an FCV-associated lesion did not increase the likelihood of FCV detection.[117] Even though FCV has high tenacity and can be stable for a long time in the environment, molecular viral RNA detection can be influenced by storage and transport conditions. The levels of RNA detection on dry swabs at 4 or -20 °C were similar, but the viral burden was maintained for a longer time when viral transport media were used.[83] Additionally, the viral burden of dry swabs dropped to an RT-qPCR undetectable level after four days at room temperature.[83] Ideally, samples for FCV diagnosis should be transported in viral transport medium, at ≤4 °C, and should be processed as soon as possible, with a maximum of four days of storage. In routine diagnostics, RT-qPCR is a sensitive method for detecting FCV. However, the plasticity of the FCV genome poses a challenge to primer and probe design. In a recent study, neither of the two well-established and optimised RT-qPCR assays were able to detect all FCV strains.[83] The combination of these two RT-qPCR assays with virus isolation on cell culture achieved the highest sensitivity (96 %).[83] However, virus isolation on cell culture requires specialised laboratory equipment, and the results are time-delayed and therefore not usable for routine diagnostics. Quantitative Real-time PCR assays are preferred over conventional PCR assays due to their higher sensitivity, and additionally, the cycle of threshold (ct)-value provides semiquantitative information about the viral RNA load.[46] Less variable sections on the viral genome, such as the proteinase/polymerase complex in ORF 1, should be used when designing the primer and probes for FCV RT-qPCR. This ensures that a broad range of FCV isolates can be detected, and the combination of different assays has been shown to increase the sensitivity.[83] However, some FCV infections may be missed by RT-qPCR, leading to false negative results. Therefore, if there is a strong suspicion of FCV due to the clinical presentation of the cat, a negative RT-qPCR result should be queried, and hygienic measures to prevent viral spreading should be taken. Multiplex PCR assays to simultaneously detect various infectious agents have been described, but these assays might lack sensitivity.[133]

Cell culture

Cell culture is a sensitive method for detecting replication-competent FCV. If replication-competent FCV are present, a characteristic cytopathic effect is visible on the cell monolayer after a period of some hours to some days. Cell cultures have the advantage of not being influenced by the high genetic variability of FCV; however, cell cultures may also fail due to the low number of virions in the sample, virus inactivation during sample transport and storage, or the presence of antibodies in extracellular fluids, which hamper viral replication in the cell culture.[104]

Electron microscopy and immunohistochemistry

In tissue samples, the characteristic cup-shaped virions of FCV can be observed via electron microscopy, and FCV antigens can be detected via immunohistochemistry.[26,85] These methods are not used for routine diagnostics as they require a specialised sample preparation process and sophisticated laboratory equipment, and the time between sample submission and the derivation of results make it inutile for routine diagnostic.

Antibodies

Antibodies against FCV can be measured either by immunofluorescence[14], enzyme-linked immunoassay (ELISA)[10,39] or neutralisation assays.[3] The results of the immunofluorescence and ELISA assays reflect the presence of anti-FCV antibodies, and are dependent on the FCV strains used for plate coating and the cross-reactivity of the cat serum. On the other hand, neutralisation assays assess the capacity of the serum to neutralise a certain FCV strain (biological activity). The prevalence of anti-FCV antibodies is very high in the feline population, and differentiation between antibodies of maternal origin, or those derived from an infection or from vaccination, is not possible. Therefore, when diagnosing FCV infection, antibody measurement is not suitable, as antibodies only indicate the contact of the cat with the antigen, and not whether the infection is still present. The detection of class-specific antibodies, such as early serum IgM or mucosal IgA, has been described, but is not routinely used to diagnose FCV infection.[113]

Key points:
- Samples for FCV RT-qPCR diagnosis should be transported in viral transport medium, at ≤4 °C, and should be processed as soon as possible, with a maximum of four days of storage;
- In rare cases, FCV infections can be missed by RT-qPCR due to their high genetic variability, resulting in a primer or probe mismatch.

Diagnosis of VS-FCV

To date, no laboratory method has been able to distinguish between the classical and the VS course of FCV infection. The molecular characterisation of isolates causing VS-FCV has not revealed a clear genetic finger-

print that can be used to design variant-specific molecular assays, and no RT-qPCR can distinguish between VS-FCV and non-VS-FCV isolates.[140] VS-FCV does not present as a clear clinical picture, and the clinical signs of cats infected with the same FCV strain within the same VS-FCV outbreak might present with varying degrees of severity. The diagnosis of VS-FCV is similar to a jigsaw, where different diagnostic pieces, such as the clinical presentation, the epidemiological situation and the molecular diagnostic results, must be matched together. Therefore, a severe clinical presentation, the presence of FCV in ulcerative lesions, blood and, if possible, affected organs, and the detection of VS-FCV in multicat environments with epizootic spreading and high mortality rates, should raise the suspicion of VS-FCV.

The acute-phase protein SAA could help to determine the degree of inflammation in FCV-infected cats. A short-term increase in SAA has been observed in cats with a non-VS-FCV disease course, and cats with less severe clinical signs had significantly lower values of SAA compared to the group of cats with more severe clinical signs.[129] However, cats with an asymptomatic FCV infection also displayed short-term increases in SAA levels.[129] In general, SAA can be useful to determine the severity of inflammation in both VS-FCV and non-VS-FCV cases.

Key point:
- No molecular or laboratory diagnostic tool can distinguish between VS-FCV and the classical FCV pathotype.

Treatment

The treatment of cats suffering from upper respiratory tract disease caused by an FCV infection consists of supportive care via intravenous fluids, anti-inflammatory drugs, feeding with highly palatable food and inhalation, and if secondary or co-infections are present, antimicrobial and antiviral treatment must be considered.[46] Recombinant feline interferon omega (FeIFN-ω) has been described to reduce clinical signs, inflammation, and FCV replication or pain in cats suffering from FCGS and FCV infection.[55,81] Recombinant FeIFN-ω has an indirect anti-viral effect as it binds to the IFN receptors of virus-infected cells, and induces the inhibition of the cell–internal protein synthesis mechanism, but there can be variation between strains as regards sensitivity to recombinant FeIFN-ω.[89]

No direct antiviral drug against FCV has been commercially available so far. One study screened the antiviral effects of 19 compounds against a panel of recently collected feline calicivirus field strains *in vitro*.[82] Mefloquine was the most potent compound, and it significantly reduced the viral replication in cell culture; however, the extent of the reduction was different between the strains tested.[82] The combination of recombinant FeIFN-ω and mefloquine resulted in an additive antiviral effect.[82] A recent study documented the antiviral activity of nitazoxanide and mizoribine *in vitro* using different FCV strains, and a synergistic effect of these two substances was observed.[28] Furthermore, *in vivo* nitazoxanide reduced clinical signs as well as the viral load in the trachea and in the lungs, and viral shedding was reduced in experimentally infected cats.[28] In future, nitazoxanide could be considered as a potential antiviral agent to treat FCV infection.[28] In a clinical study, cats suffering from upper respiratory tract disease were treated with the hyperimmunised sera of horses containing, among others, FCV-neutralising antibodies (marketed as Feliserin). The cats of the treatment group underwent a faster improvement of clinical signs compared to the cats of the control group, but by the seventh day after the start of the study, both groups displayed equal clinical signs.[50]

Key points:
- Supportive care consisting of rehydration, inhalation and feeding of highly palatable food, along with anti-inflammatory treatment and pain management, are the main therapy options for cats suffering from FCV infection;
- Antimicrobial treatment is recommended if secondary bacterial infections are present;
- No antiviral treatment against FCV is licensed but some compounds such as nitazoxanide were efficient under experimental conditions.

Vaccination

FCV vaccination was found to be a protective factor for FCV infections, and vaccination is therefore a mainstay for managing FCV in the feline population.[9,69] FCV vaccination is considered essential, and thus every cat should receive it.[33,59,118] The protective effects of the commercially available FCV vaccines have been shown in several studies,[12,65,93,120] and a recent FCV vaccination and challenge study using FCV field strains further demonstrated that FCV-vaccinated cats suffered from less severe clinical signs and less inflammation, shed lower FCV RNA loads from the oropharynx, and had a shorter duration of FCV RNAemia than unvaccinated control cats.[129] Several feline vaccination guidelines are available, but no standard vaccination procedure can be applied to all cats.[33,45,58,59,118,119] For the decision regarding vaccination intervals and vaccine types, the cat's age, health status, lifestyle and housing condition, and the related risk of FCV infection, should be taken into ac-

count.[59] In Europe, one widely used FCV vaccine is the modified-live F9 vaccination, which is often used in combination with either FHV alone or FHV and feline panleukopeniavirus.[104] More recently, an inactivated, non-adjuvanted double-strain FCV vaccine was marketed that contained the inactivated FCV strains 431 and G1. These vaccine strains are used in combination with either modified-live FHV alone, or modified-live FHV and feline panleukopenia in combination.[99] The inactivated strain FCV 255 has been used in Europe in combination with inactivated FHV, feline panleukpenia, feline leukemiavirus and *Chlamydia felis*, but this vaccine's production has been discontinued recently. Intranasal modified-live FCV vaccines are used in the US, but no product is currently licensed in Europe. The fast onset of local mucosal immunity after a single administration, mediated by IgA, is the main advantage of this vaccine type, and the interference with maternally derived antibodies is less than with subcutaneously applied vaccines.[33] However, mild respiratory clinical signs and the oronasal shedding of vaccine virus are possible after intranasal vaccination.[33] Beside modified-live and inactivated vaccines, other vaccine types, such as protein subunit vaccines,[68] virus-like particles vaccines,[37] recombinant feline herpesvirus-1 (FeHV-1) expressing an FCV capsid protein,[143–145] and DNA vaccines,[124] have been tested experimentally, but they offered only partial protection, and have never been licensed for commercial use.[97] Inactivated vaccines, in contrast to MLV vaccines, require an adjuvant to elicit a sufficient immune response. The use of adjuvants in feline vaccination is controversial because of the unique propensity of cats to develop injection-site sarcoma.[18] Inactivated but adjuvanted vaccines containing rabies, FeLV, FPV, FHV or FCV have been cited as a possible cause for feline injection-site sarcoma in the past, but the pathogenesis of these sarcomas has remained unclear until now.[137] The development of sarcomas and tumorigenesis in general has been linked with prolonged inflammation, which can also be caused by non-adjuvanted vaccines, by the injection of other substances, such as antibiotics or anti-inflammatory drugs, or by the presence of suture material or microchips.[16,29,137] Feline injection-site sarcomas are very invasive, and their tentacle-like spreading in adjacent tissue makes them extremely difficult to remove completely. If the removal is not complete after the first attempt, the relapsing tumor will become even more aggressive, invading the adjacent tissue. Highly invasive surgery is needed to remove this type of sarcoma. Therefore, the commonly used injection sites between the shoulders or in the neck are not recommended anymore, because the complete removal of sarcoma at these locations is almost impossible. Alternative injection sites, such as the distal legs or the tail, are therefore promoted.[54] The amputation of a limb or a part of the tail is a less invasive means to remove a sarcoma. Besides the improvements that have been made in therapy for sarcoma, efforts are being undertaken to reduce the inflammation caused by vaccine injections. It has been shown that the lower injection volume of a feline multivalent vaccine induces less local events while maintaining immunogenicity.[61]

The use of modified-live vaccines is more critical in the face of possible vaccine strain circulation in feline populations, thus contributing to the building of immune-evasive variants or vaccine virus-induced diseases in immunocompromised animals.[74] FCV F9-like variants have been detected in cats via phylogenetic analyses, but the role of the circulating FCV F9 virus in the feline population remains unclear.[22,130] FCV can be shed from the oropharynx of cats after an inadvertent spilling of a subcutaneous vaccine and subsequent oral uptake due to self-grooming, or if a subcutaneous vaccine is applied intranasally by mistake.[93] Commercially available semi-quantitative in-house antibody tests are used to assess whether a revaccination in adult cats is needed.[39] However, for FCV, the measuring of antibodies as part of the decision to vaccinate is still controversial, and antibody testing is not recommended to replace routine FCV vaccination.[10] The detection of any FCV-specific antibodies via ELISA or virus neutralisation has been shown to be predictive for protection against disease, independently of the titre in FCV-vaccinated cats;[73] however, other studies have not confirmed this finding.[101,128] It is not conclusively understood which antibody titre correlates with disease protection *in vivo*. Furthermore, cats without detectable neutralising antibodies against FCV can be protected from disease, indicating the role of cellular immunity.[76,99,100] Anti-FCV antibodies act directly on free virions and enhance cytotoxic activity via antibody-mediated cytotoxicity. However, to eliminate virus-infected host cells, cytotoxic cell-mediated immunity is required. The assessment of anti-FCV antibody levels can therefore not be used alone to determine the need for revaccination.

Key points:
- FCV vaccination is a mainstay in managing FCV infection in the feline population;
- The cat's lifestyle, housing conditions, age, and reproductive and health status should be considered when choosing the FCV vaccination strategy;
- Spilling or leakage, or inadvertent intranasal administration of subcutaneous MLV vaccines must be avoided, as this could lead to vaccine virus shedding and spreading in the feline population;
- Pre-vaccination antibody testing cannot replace routine FCV vaccination, as it is unknown which antibody titre confers protection, and cats without detectable antibodies can be protected by cell-mediated immunity.

FCV disinfection, hygienic measures and management considerations

In multicat situations, such as cat shelters, breeding catteries or feral cat populations, FCV is of special concern, and group housing with four or more cats, as well as intact reproductive status, have been identified as risk factors for FCV.[9] In the past, several reports have been published about virulent and non-virulent epizootic outbreaks affecting multicat communities.[48,60,92,115,140] A multicat situation represents an ideal condition for FCV, as the cats live closely together–sometimes with overcrowding–causing high levels of stress. Particularly in shelters and animal hospitals, the continuous influx of new cats with unknown immune, vaccine and disease status, together with the long (environmental) stability and tenacity of FCV, poses a risk. Therefore, basic hygiene rules should be followed in each multicat situation, and, if possible, the group size should be reduced.[9] The "FCV control evaluation tool" from the European Advisory Board On Cat Diseases (ABCD) provides a scoring system to evaluate the FCV risk status of multicat communities, and helps to identify areas for improvement.[44] FCV lacks an envelope of phospholipid bilayers that can easily be destroyed, e.g., by a detergent, and therefore the tenacity of FCV is high.[138] One case report of an VS-FCV outbreak demonstrated the fomite transmission of an animal caretaker to a housecat.[115] Contaminated items should be washed at ≥60°C, and virucidal disinfection must be applied to non-washable items.[104] Sodium hypochlorite (bleach diluted at 1:32), potassium peroxymonosulfate and chlorine dioxide are effective against FCV.[4] Sodium bicarbonate (baking soda) at a 5 % concentration is FCV-virucidal, with the advantage of not being toxic or corrosive, but it is not effective against other pathogens.[80] Virucidal disinfection agents against human norovirus are also effective against FCV, as both viruses have similar viral properties.[80] However, different FCV strains are not equally susceptible to certain biocides.[35] The environmental stability of FCV can be very long–up to several weeks, depending on the environmental conditions.[41] The stability of FCV is greater in a less humid (30 %) environment, compared to a more humid one (70 %).[15] FCV RNA has been detected by RT-qPCR in the environment of FCV-infected cats up to 28 days after the cessation of shedding, but no replication-competent virus could be found at any timepoint.[127] The environmental stability might also be FCV strain-dependent, and some FCV strains were more resistant to changes in pH and disinfection with biocides containing either alcohol or chlorine than other strains.[35,75]

Key points:
- FCV has a high tenacity;
- Contaminated items should be washed at ≥60 °C and virucidal disinfection must be applied to non-washable items;
- Disinfection products useful against human norovirus are effective against FCV.

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Conflict of interest

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An Update on Feline Calicivirus

A. M. Spiri

Une mise à jour sur le calicivirus félin

Le calicivirus félin (FCV) est l'un des agents pathogènes viraux les plus courants chez les chats domestiques dans le monde. Le premier signalement de FCV remonte à 1957, lorsque le FCV a été isolé du tractus gastro-intestinal de chats en Nouvelle-Zélande. Des rapports ultérieurs ont reconnu le FCV comme une cause de maladie respiratoire chez les chats et, à l'heure actuelle, les praticiens félins du monde entier sont quotidiennement confrontés à des chats suspectés de FCV. La nature hautement mutagène du FCV et sa haute plasticité génétique permettent au virus de survivre avec succès dans la population féline et posent un défi particulier en ce qui concerne le diagnostic, le traitement et la prévention de la maladie induite par le FCV. La maladie des voies respiratoires supérieures a été considérée comme un signe clinique courant d'infection par le FCV. Une étude réalisée en Suisse a démontré que les ulcérations buccales, la salivation et la gingivite-stomatite étaient plus fréquemment associées à une infection à FCV qu'à une autre maladie des voies respiratoires supérieures et moins de la moitié des chats suspectés d'avoir une infection à FCV se sont avérés positifs pour le FCV. De plus, une étude portant sur des isolats de FCV en Suisse a trouvé des preuves que le profil génétique des chats pourrait influencer leur sensibilité à l'infection par le FCV. Cet article de synthèse fournit un résumé complet de la littérature sur le FCV et intègre les résultats de recherches récentes sur les caractéristiques génétiques du FCV, l'immunité cellulaire et humorale évoquée par la vaccination et l'infection au FCV, le diagnostic du FCV, la prévention/vaccination contre le FCV, les facteurs de risque associés avec le FCV et les mesures d'hygiène nécessaires dans les zones contaminées par le FCV. Après chaque section, les points clés sont résumés et des informations pertinentes sont décrites pour aider les praticiens félins dans le diagnostic, le traitement et la prévention du FCV.

Mots clés: Chats, évolution génétique, ulcération buccale, facteurs de risque, vaccination, maladie systémique virulente

Un aggiornamento sul Calicivirus Felino

Il Calicivirus felino (FCV) è uno degli agenti patogeni virali più comuni nei gatti domestici in tutto il mondo. La prima segnalazione di FCV risale al 1957, quando il FCV fu isolato dal tratto gastrointestinale di gatti in Nuova Zelanda. Rapporti successivi hanno riconosciuto il FCV come la causa delle malattie respiratorie nei gatti, e attualmente, gli studi veterinari per piccoli animali in tutto il mondo sono confrontati quotidianamente con gatti che soffrono di un sospetto FCV. La natura altamente mutagena del FCV e la sua elevata plasticità genetica permettono al virus di sopravvivere con successo nella popolazione felina e rappresentano una sfida particolare per quanto riguarda la diagnosi, il trattamento e la prevenzione della malattia provocata da FCV. La malattia del tratto respiratorio superiore è considerata un segno clinico comune di infezione da FCV. Uno studio svizzero ha rilevato che ulcerazioni orali, salivazione e stomatite gengivale erano più comunemente associate all'infezione da FCV rispetto alle malattie del tratto respiratorio superiore, e meno della metà dei gatti sospettati di avere un'infezione da FCV erano positivi al FCV. Inoltre, uno studio sugli isolati di FCV, provenienti dalla Svizzera, ha trovato alcune evidenze che il profilo genetico dei gatti può influenzare la loro suscettibilità all'infezione da FCV. Questo articolo fornisce una sintesi completa della letteratura riguardante il FCV e integra i risultati delle recenti ricerche sulle caratteristiche genetiche del FCV, sull'immunità cellulare e umorale indotta dalla vaccinazione o dall'infezione da FCV, sulla diagnosi del FCV, sulla prevenzione/vaccinazione del FCV, sui fattori di rischio di infezione da FCV e sulle misure igieniche necessarie delle aree contaminate da FCV. Dopo ogni sezione, vengono riassunti i punti chiave e vengono descritte le informazioni rilevanti per assistere i veterinari nella diagnosi, nel trattamento e nella prevenzione della FCV..

Parole chiave: Gatti, evoluzione genetica, ulcerazione orale, fattori di rischio, vaccinazione, malattia virulento-sistemica

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