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#### **FERRETS**

# Ferret Systemic Coronaviral Disease (FSCD)

## BASIC INFORMATION



# **DEFINITION**

Ferret systemic coronaviral disease (FSCD) is a chronic, lethal disease of domestic ferrets. It is caused by a coronavirus initially designated as ferret systemic coronavirus (FSCV). Microscopic lesions in affected ferrets are identical to those seen in cats with the dry form of feline infectious peritonitis (FIP). The first cases of FSCD were seen in 2002.

# **SYNONYMS**

- Granulomatous inflammatory syndrome (GIS) of ferrets
- Systemic coronavirus-associated disease
- · Ferret systemic coronavirus infection
- · FIP-like disease of ferrets

#### **SPECIAL SPECIES** CONSIDERATIONS

The disease is seen only in domestic ferrets

# **EPIDEMIOLOGY**

#### SPECIES, AGE, SEX

- FSCV can infect ferrets of any age and sex, but young ferrets (<1 year old) are more commonly affected. This age-related susceptibility may be due to immune suppression in ferrets that have been recently weaned, neutered, vaccinated, descented, and shipped to pet shops and private pet homes.
- The epidemiology of FSCD follows patterns similar to those of FIP, with

outbreaks usually followed by a return to the endemic form of the disease

#### **RISK FACTORS**

- · Post-weaning stress and immune suppression due to surgeries, vaccination, overcrowding, and poor husbandry and shipment
- Failure to quarantine newly introduced young ferrets
- The role of fomites is unknown.

#### CONTAGION AND ZOONOSIS

- Transmission routes are unknown, but it is believed that the virus spreads by the same fecal-oral route as the FIP virus.
- No zoonotic potential is known.

# GEOGRAPHY AND SEASONALITY

- The disease has been reported only in Europe and the United States.
- No seasonality is known.

#### ASSOCIATED CONDITIONS AND DISORDERS

- FSCV and ferret enteric coronavirus (FECV) are different but related viruses. However, it is unknown if there is a relationship between them as has been proposed in cats with FIP and feline enteric coronavirus.
- · Many ferrets with FSCD have diarrhea days to months before the development of other signs.

# **CLINICAL PRESENTATION DISEASE FORMS/SUBTYPES**

• The disease is progressive, chronic, and lethal.

- · Ferrets die or are euthanized days to months after the diagnosis. Average survival time after diagnosis is about 2 months.
- · The disease is similar to the noneffusive (dry) form of FIP in cats. Lesions of FSCD resembling the effusive (wet) form of FIP have not been reported in

# HISTORY, CHIEF COMPLAINT

- Diarrhea may be the first clinical sign and can progress from brown-yellow to green-hemorrhagic.
- Weight loss, lethargy, anorexia, and hind limb weakness are common signs.
- Inability to gain weight is seen in growing animals.
- · Less common clinical signs include vomiting, cough, sneezing, decreased consumption of water, and bruxism.
- Nasal discharge and rectal irritation have also been reported. Seizures may be observed before death.

#### PHYSICAL EXAM FINDINGS

- · Common physical exam findings include palpable intraabdominal masses and splenomegaly. Intraabdominal irregular masses correspond more often with mesenteric lymphadenopathy, although the kidneys may also be enlarged.
- Fever greater than 40° C (104° F) can occur in some ferrets, but most animals show normal rectal temperature (39.3° C/102.7° F).
- Systolic murmurs, greenish urine, jaundice, and dehydration have rarely been reported.

# ETIOLOGY AND PATHOPHYSIOLOGY

- FSCV infection
- Host response to FSCV infection is polyclonal hypergammaglobulinemia that results in systemic granulomatous inflammation

# **DIAGNOSIS**



## **DIFFERENTIAL DIAGNOSIS**

- Aleutian disease (see Aleutian Disease)
- Does not always cause mesenteric lymphadenopathy and hypergammaglobulinemia, and when present, these are less marked than in FSCD.
- Lymphoma (see Lymphoma)
  - Can produce gross lesions identical to FSCD, but lymphoma has not been linked to hypergammaglobulinemia in ferrets. Lymphocytosis and abnormal lymphocytes may be seen in some cases of lymphoma, but not in FSCD.
- Proliferative bowel disease
  - Produces diarrhea; mesenteric lymphadenopathy may be seen in rare cases as the result of extraintestinal translocation of colonic mucosa into regional lymph nodes. Hypergammaglobulinemia is not seen. Proliferative bowel disease is less commonly observed now than in the past. It generally affects ferrets younger than 16 weeks old, and the affected large bowel is usually thickened at palpation.
- Eosinophilic gastroenteritis
  - Produces diarrhea; in chronic cases, mesenteric lymphadenopathy occurs. Hypergammaglobulinemia has not been reported, but it might occur because of antigenic stimulation. Peripheral eosinophilia is commonly seen in cases of eosinophilic gastroenteritis.

#### **INITIAL DATABASE**

- · Blood biochemistry
  - o Total protein and protein electrophoresis: mild to moderate hyperproteinemia can be observed in about 50% of cases. Hypergammaglobulinemia is seen in most, if not all, cases. Globulins are usually higher than 4.2 g/dL, representing about 80% of total proteins. Gammaglobulins are usually higher than 18 g/L, representing between 35% and 60% of total proteins. This gammopathy is polyclonal.
  - Remaining serum chemistry: nonspecific and dependent on the development of lesions in a particular organ
- · Hematologic examination

- Mild to moderate nonregenerative anemia is seen in about 50% of cases.
- Mature neutrophilic leukocytosis, thrombocytopenia, and lymphopenia can be observed in some cases.
- Imaging
  - Loss of lumbar musculature, decreased peritoneal detail, presence of mid-abdominal soft-tissue masses and splenomegaly are the most significant radiographic signs.
  - Peritonitis, abdominal lymphadenopathy, splenomegaly, abdominal soft-tissue masses, nephromegaly, and changes in renal cortex echogenicity are potential ultrasonographic findings.
  - Ultrasound is superior to radiology when abdominal contrast is reduced, as frequently occurs in FSCV.

# ADVANCED OR CONFIRMATORY TESTING

- Histopathologic examination
  - Multiple angiocentric granulomatous lesions can be observed in visceral organs and brain. These include diffuse granulomatous inflammation on serosal surfaces, and granulomas with or without neutrophils and necrosis. Observation of these microscopic lesions confirms FSCD.
  - If performing an exploratory laparotomy or laparoscopy, aim to biopsy abdominal organs (e.g., lymph nodes, spleen, liver, kidneys, small intestine, large intestine) that are nodular or that have pale, discolored foci on their surface.
- Immunohistochemistry on paraffinembedded tissues is a confirmatory technique.
  - The monoclonal antibody FCV3-70 detects the presence of antigen in the cytoplasm of macrophages in different types of granulomatous lesions.
- Reverse-transcriptase PCR (RT-PCR)
  - Initially used for detection and characterization of the virus on some fresh-frozen tissues. Its usefulness for diagnostic purposes is unknown.
- Electron microscopy
  - Macrophages containing multiple intracytoplasmic virions, both within cytoplasmic membrane-bound vacuoles and free in the cytoplasm
- Virus isolation in cell culture has been unsuccessful.
- Necropsy
  - Multiple, white, irregular nodules or foci of white discoloration (0.5 to 3 cm) can be observed on the surface and within the parenchyma of different organs: lymph nodes, spleen, liver, kidneys, mesentery, lungs, and heart. Splenomegaly, renomegaly, hepatomegaly and lymph node enlargement can also

be seen. Ascites/abdominal effusion has been observed only in a small number of cases.

# TREATMENT



#### THERAPEUTIC GOALS

- Supportive therapy aimed at alleviating clinical signs is indicated.
- Specific treatment is directed at reducing the inflammation typical of the disease.
- Therapeutic protocols are based on those described to treat FIP in cats.
- Euthanasia should be considered.
- Progression to fatal FSCD may be the direct consequence of immune suppression.

#### **CHRONIC TREATMENT**

- Nonsteroidal antiinflammatory drugs (NSAIDs) reduce inflammation and do not cause marked immune suppression (e.g., carprofen 1 mg/kg PO q 12-24 h; meloxicam 0.2 mg/kg PO on first day, then 0.1 mg/kg SID PO).
- Antivirals such as ribavirin (50 mg/kg/d based on cat dose) may be effective, if combined with interferon (IFN). Whereas ribavirin is strongly inhibitory of FIP virus and SARS coronavirus in vitro, it is not effective against these viruses in vivo.
- The combination of a type I IFN (interferon alpha or beta) and a type II IFN (interferon gamma) may be helpful.
  Low doses should be used to avoid causing immune suppression.
- Corticosteroids are better used for a short period (e.g., prednisone 1 mg/ kg PO q 24 h 7-14 d) once antiviral drugs have been administered to control viral replication.
- Antibiotics are indicated to control secondary infection.

#### **DRUG INTERACTIONS**

- Cytotoxic agents such as azathioprine, methotrexate, and cyclophosphamide could be used to control the immunopathologic consequences of viral infection, but they cause immune suppression.
- The most important side effect of these cytotoxic agents is marrow suppression. Owing to the high turnover of neutrophils, patients most frequently suffer neutropenia rather than thrombocytopenia or anemia. Neutropenia, as well as impaired humoral and cellular immune mechanisms, is responsible for increased susceptibility to bacterial, viral, or parasitic disease during immune suppressive therapy.

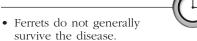
# POSSIBLE COMPLICATIONS

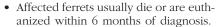
Doses of ribavirin >100 mg/kg/d in ferrets are immune suppressive.

## RECOMMENDED MONITORING

- Complete blood count should be monitored for nonregenerative anemia if the antiviral ribavirin is used.
- Protein electrophoresis is important to assess decrease of inflammation.

# PROGNOSIS AND OUTCOME





#### **CONTROVERSY**

As in FIP, initial recoveries in ferrets treated for FSCD may be related not to effectiveness of treatment, but to the normal course of the disease.

# PEARLS & CONSIDERATIONS



#### **COMMENTS**

 FSCD is a recently described disease in ferrets, and information available on this condition is still scarce. Consequently, little is known about FSCV. However, partial sequencing of the coronavirus spike gene revealed that it is related to FECV. Hence, it has been proposed that a recent mutation in FECV could result in this disease, similar to the deletion mutation that occurs in feline coronavirus preceding the development of FIP.

 Extrapolation from FIP seems to be the most appropriate way to explain characteristics still unknown about FSCD.

## **PREVENTION**

- Vaccination and noninvasive diagnostic testing are currently unavailable.
- Quarantine all animals, particularly young ferrets from an unknown origin.
- Avoid situations that combine poor hygiene, overcrowding, and stress in young ferrets (weaning, neutering, descenting, vaccination, and shipment in a short period). These situations favor infection and can be seen in shelters, farms, and pet shops.

## **CLIENT EDUCATION**

- Ouarantine
- Improved hygiene
- · Avoid overcrowding.
- Reduce stress.

## SUGGESTED READINGS

Dominguez ER, et al: Abdominal radiographic and ultrasonographic findings in ferrets (*Mustela putorius furo*) with systemic coronavirus infection, Vet Rec 169:231, 2011.

Garner MM, et al: Clinicopathologic features of a systemic coronavirus—associated disease resembling feline infectious peritonitis in the domestic ferret (*Mustela putorius*), Vet Pathol 45:236–246, 2008.

Martínez J, et al: Identification of group 1 coronavirus antigen in multisystemic granulomatous lesions in ferrets (*Mustela putorius furo*), J Comp Pathol 138:54–58, 2008.

Perpiñán D, et al: Clinical aspects of systemic granulomatous inflammatory syndrome in ferrets (*Mustela putorius furo*), Vet Rec 162:180–184, 2008.

# CROSS-REFERENCES TO OTHER SECTIONS

Aleutian Disease Epizootic Catarrhal Enteritis Lymphoma Splenomegaly

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