Cytauxzoon felis is a protozoal organism that causes fatal illness in domestic cats. It is related to other Cytauxzoon spp of African ungulates and was first recognized in Missouri in 1976.1 Geographically limited primarily to the south central and southeastern United States (Figure 1), C. felis seems to infect only felidae and therefore poses no zoonotic or agricultural risk.2 Diagnosing cytauxzoonosis in cats is based on compatible clinical signs and identifying the organisms in tissue or blood. No form of therapy has been proven effective, and most ill cats die despite supportive and/or antimicrobial treatment.

C. felis is a protozoan organism belonging to the order Piroplasmida and the family Theileriidae. Like its relatives in the genus Theileria, C. felis exists in distinct erythrocytic and non-erythrocytic life phases. After infection, the organism undergoes an asexual reproductive phase referred to as schizogony. Schizonts of C. felis occur in mononuclear phagocytic cells, whereas the schizont phase of the genus Theileria occurs in lymphocytic cells.3 The infected macrophage cells occlude venules in the liver, spleen, lung, and lymph nodes1 (Figure 2). The schizont phase is most closely associated with clinical disease, and the degree of schizogony is reflected in the severity of illness.4 In domestic cats, the schizont burden is extensive, whereas it is usually small and brief in mildly affected species such as the bobcat.5 Fission of the schizonts results in formation of merozoites.6 Merozoites are released when the infected macrophage ruptures; these merozoites undergo endocytosis by erythrocytes. In erythrocytes, these forms are referred to as piroplasms. Although visualization of piroplasms on a peripheral blood smear is the most direct and simple way to diagnose infection, it is the schizont phase that leads to venous congestion, thrombotic disease, organ failure, and ultimately death.4,7,8 Piroplasms may persist for life after recovery from schizogony in both domestic and nondomestic cats without apparent clinical consequences for infected animals.5,10
PROPOSED LIFE CYCLE AND TRANSMISSION

Although its natural life cycle is not completely understood, *C. felis* is a tickborne disease.11 Bobcats are persistent carriers of this organism after infection and are the presumed reservoir for *C. felis.*2,12 Ticks presumably transmit the organism from one cat to another by feeding.11 The only tick that has been experimentally demonstrated to be a competent vector of *C. felis* is *Dermacentor variabilis,* although many other species of ticks may feed on wild or domestic cats.11,13 Although domestic cats generally succumb to infection and are considered terminal hosts, the eastern bobcat (*Lynx rufus rufus*) usually develops mild or subclinical infection.2,5,12 Excessive investigation has shown that nonfelidae species, including immunodeficient mice, cannot be infected.5 However, both clinical and nonclinical infection has been demonstrated or at least strongly suspected in several felidae, including a captive white tiger (*Panthera tigris*), Florida panthers (*Felis concolor coryi*), a Texas cougar (*Felis concolor*), and cheetahs (*Acinonyx jubatus*).14–17

Infection can be accomplished experimentally by inoculating schizont-containing tissue.16 However, inoculating erythrocytes that contain piroplasms only results in persistent erythroparasitemia without the clinical illness that results from the schizont phase of infection.11 It appears that the piroplasms must develop in their next life stage in an intermediate host, such as ticks, to produce the virulent schizont form. Therefore, transfusion from cats that have recovered to ones that are naive would not result in illness even if erythrocytes contain piroplasms.10,11 However, transfusion from recently infected cats during clinical illness or just before onset of illness can transmit infection because circulating monocytes can contain schizonts.7,15 Blood-donor cats should be in good health, kept free of ectoparasites, and ideally housed indoors to minimize this very small risk. Close contact between cats in the absence of tick vectors does not pose a risk of disease transmission.15 Although multiple cats within a household are commonly infected, this circumstance is more likely related to common exposure to infected tick populations than to direct cat-to-cat contact.

CLINICAL PRESENTATION

Feline cytauxzoonosis is most commonly reported in middle-aged cats, although it can occur at any age.8,10 Sex and breed predilections have not been identified.8 Outdoor cats are more likely to acquire this disease, presumably because of increased exposure to tick vectors.8,10 The greatest risk of infection seems to occur in the spring and early summer, presumably when the tick vectors are most active. Sixty-one of 81 (75%) cases evaluated at the University of Missouri Veterinary Medical Diagnostic Laboratory and Veterinary Medical Teaching Hospital over the past 5 years were seen from May through July.

The onset of clinical disease occurs 1 to 3 weeks after infection.4,18 Clinical signs are nonspecific and include anorexia, lethargy, dyspnea, icterus, and pallor.1,3,4,9,10,17 Physical examination usually demonstrates pyrexia (often marked), but hypothermia is common in moribund cats.1,8–10 Tachypnea and tachycardia are typical, with or without overt respiratory distress.4,9 Abdominal palpation often reveals splenomegaly and/or hepatomegaly.1,4,8 Altered mentation, vocalization, seizures, and coma may occur in the later stages of disease.18,20 The disease course is rapid, and most cats succumb within 1 week of initial clinical illness.7,8,21
DIAGNOSIS

Although historical and physical findings are nonspecific, a patient with acute onset of fever, pallor, icterus, and splenomegaly or hepatomegaly in an endemic region should immediately prompt clinicians to suspect cytauxzoonosis. The differential diagnosis might include *Mycoplasma haemofelis* infection (formerly *Haemobartonella felis*), cholangitis or cholangiohepatitis, immunemediated hemolytic anemia, retroviral disease sequelae, toxoplasmosis, and feline infectious peritonitis. Diagnostic testing should be directed toward both confirming the infection and eliminating diagnostic differentials from consideration. Of the routine imaging and initial laboratory tests, only examination of peripheral blood smears can confirm the diagnosis. Visualizing erythrocytic piroplasms is sufficient evidence to confirm infection. Piroplasms are most often shaped as 1 to 1.5 µm signet rings (Figure 3), but “safety pin” and tetrad forms are also observed, as are chains of organisms resembling cocci.9,17 Although piroplasms are a specific finding, they are not present in all infected cats, particularly early in the disease course.3,8–10 In fact, piroplasms may be absent in up to 50% of cases at the initial illness7 but may persist indefinitely in cats that have recovered from infection.10 Infected macrophages on the feathered edge of a peripheral blood smear may also be visualized and used to confirm the presence of *C. felis*8 (Figure 4).

Pancytopenia can often be found via a complete blood cell count, although thrombocytopenia and neutropenia can be inconsistent.8,9,22 Anemia is typically normocytic, normochromic, and nonregenerative because of the acute nature of the illness.22 Moderate to marked thrombocytopenia is believed to be related to consum-
tive processes, including disseminated intravascular
coagulation (DIC). Of seven experimentally infected
cats, only one developed a prolonged activated partial
thromboplastin time (aPTT). Coagulation studies
have been reported from relatively few clinical cases but
have often identified prolonged aPTT. In our clinical
experience, prolonged aPTT is common and often pro-
found. Erythrophagocytes has been identified occasi-
onally, with hemolysis occurring principally in the
extravascular compartment. Bone marrow crowded
with schizont-laden macrophages may lead to neutrope-
nia, but neutrophilia resulting from an inflammatory
response to infection may be identified alternatively.
Hyperbilirubinemia is very common as a result of
both intrahepatic infiltration of schizont-loaded
macrophages as well as hemolysis and liver enzymes
can often be increased. Prerenal azotemia, hyper-
glycemia, and electrolyte and acid–base disturbances
have been documented in many infected cats. Bilir-
ubinuria is common, but hemoglobinuria has not been
observed because hemolysis is largely extravascular.

Additional diagnostic tests may be considered in ill
cats. Imaging techniques do not contribute directly in
diagnosing \textit{C. felis} infection, but splenomegaly and
hepatomegaly would be expected. For cats in which
piroplasms have not been identified, samples fromfine-
needle aspiration of the lymph nodes, spleen, or liver may
provide evidence of infection. These organs are typically
heavily infiltrated with schizont-loaded macrophages, and
infected cells may be readily identifiable by cytologic
examination (Figure 4). Although polymerase chain
reaction testing can be used in a research setting to con-
firm the presence of \textit{C. felis} DNA, such testing is not
commercially available. Likewise, serologic testing for
antibodies to \textit{C. felis} is neither available nor practical
because of the acute nature of the disease process.

\section*{TREATMENT}

Because there are no proven effective therapies for
this infection, preventing the disease should be the goal
of veterinarians and owners. Transmission occurs via a
bite from an infected tick, so indoor cats are less likely
to be infected than are cats that go outdoors. Ectopara-
site control is the ideal for all cats. Our preference for
tick prevention is topical spray or spot-on fipronil.

Although \textit{C. felis} infection has been traditionally
viewed as uniformly fatal, there have been recent reports
of cats that survive, including those treated with
supportive care alone and in combination with antimicro-
bial therapy. Regardless of antimicrobial treatment,
supportive care is crucial for these gravely ill cats.

There are no proven therapies with efficacy
against \textit{C. felis} infection.
plication of cytauxzoonosis, heparin therapy (100 to 150 U/kg SC q8h) has been recommended prophylactically. If used to treat established DIC, the dose should be titrated to effect based on measured increases in partial thromboplastin time and should be accompanied by transfusion of fresh or fresh-frozen plasma. Although antimicrobials designed to combat bacterial infections are not useful in eradicating C. felis infection, most reports of cats that survive describe adjunctive use of such drugs. A variety of antibiotics have been used empirically, including sodium ampicillin, enrofloxacin, and doxycycline.

Definitive treatment options involve antiprotozoals. Thus far, prospective studies have failed to demonstrate efficacy for such therapy. The antiprotozoal hydroxynaphthoquinolones parvaquone and buparvaquone are the drugs of choice for Theileria infection of African cattle. Despite the close relationship of C. felis to Theileria spp, these drugs have demonstrated a complete lack of efficacy in treating cytauxzoonosis in trials to date.

Recent publications have described using imidocarb dipropionate (Imizol, Schering-Plough Animal Health) or diminazene aceturate (Ganaseg, Novartis Animal Health [not available in the United States]) to treat cytauxzoonosis. These aromatic diamidine compounds are used to treat various protozoal agents, including Babesia spp and African trypanosomiasis. Imidocarb is readily available in the United States. If imidocarb is used, atropine pretreatment should be administered to minimize adverse cholinergic effects. In a single anecdotal report, five of six cats treated with diminazene aceturate (two doses at 2 mg/kg IM 3 to 7 days apart) and one cat treated with imidocarb dipropionate (two doses at 2 mg/kg IM 7 days apart) survived infection. All cats received simultaneous aggressive supportive care.

Although encouraging, anecdotal reports do not provide proof of treatment efficacy. Survival may have been related to supportive care or C. felis strain variation rather than to antiprotozoal drug therapy. In fact, in a recent report of 18 cats that survived infection with C. felis, only a single cat received treatment with an antiprotozoal (i.e., imidocarb dipropionate). This same report also mentioned unpublished work that suggested that imidocarb lacks efficacy in treating experimentally induced cytauxzoonosis. In addition, the first published case report of a naturally infected domestic cat that survived did not involve administering an antiprotozoal.

UNANSWERED QUESTIONS

A better understanding of why some domestic cats survive infection may enhance our ability to prevent or treat this infectious disease. Innate resistance may occur in some cats, perhaps as a result of limited schizogony. In rare instances, domestic cats have been identified with chronic erythroparasitemia but no known history of clinical illness, similar to the bobcat reservoir. The possibility that these parasitized cats were infected with a morphologically similar but distinct organism was discounted based on nucleotide sequencing of specific gene segments from the organism as well as through antibody detection. The existence of a less virulent strain of C. felis seems to be a more likely explanation for at least some of the survivors, particularly because many of the 18 cats that survived as documented by Meinkoth et al were from a single geographically limited area.

It is still unclear which tick species are capable of transmitting infection. Certainly, D. variabilis ticks are capable vectors for disease transmission. However, numerous other tick species are also likely to feed on wild or domestic cats. Furthermore, we have identified C. felis DNA in not only D. variabilis but also Amblyomma americanum ticks that were collected from regions in which the infection is endemic. No published studies have evaluated the ability of A. americanum or other tick species that feed on cats to serve as competent vectors for transmission.

CONCLUSION

Despite the devastating nature of C. felis infection in domestic cats, the current understanding of feline cytauxzoonosis is incomplete. Presumptive diagnosis in endemic regions is often based on nonspecific but compatible historical and physical findings. Definitive diagnosis relies on identifying the organism on either peripheral blood smears or tissue aspirates. Prospective controlled studies should be conducted before a particular treatment can be

**Using tick preventative is the best approach to prevent C. felis infection.**
endorsed. This is particularly true when the treatment itself carries significant expense or risk of adverse effects. For now, preventing infection in endemic regions must be emphasized. Although no vaccine is available, stringent measures to prevent tick attachment should provide a large measure of protection for at-risk cats.

REFERENCES


ARTICLE #5 CE TEST

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1. Which species is believed to be the definitive host of C. felis?
   a. bobcat  
   b. coyote  
   c. domestic dog  
   d. fox  
   e. domestic cat

2. Clinical diagnosis of C. felis infection should be based on
   a. positive results from polymerase chain reaction testing.  
   b. a fourfold increase in antibody titer.  
   c. identification of piroplasms in erythrocytes.  
   d. identification of schizonts in mononuclear cells.  
   e. identification of either piroplasms or schizonts.

3. Prominent clinical findings in cats infected with C. felis would not include
   a. pyrexia.  
   b. icterus.  
   c. uveitis.  
   d. paller.  
   e. splenomegaly.

4. Which statement regarding piroplasms of C. felis is incorrect?
   a. Piroplasms are not always identifiable at the onset of clinical illness with cytauxzoonosis.  
   b. Cats that have recovered from infection may continue to have low numbers of identifiable piroplasms indefinitely.
c. The severity of clinical illness is well correlated with the number or piroplasms in circulating blood cells.
d. Piroplasms are simply merozoites that have been taken up by erythrocytes via endocytosis.
e. Signet ring, “safety pin,” and tetrad forms as well as chains of organisms resembling cocci are all possible morphologies for piroplasms.

5. Prospective studies have documented the efficacy of __________ in treating C. felis infection.
   a. imidocarb dipropionate  d. enrofloxacin
   b. diminazene aceturate  e. none of the above
   c. parvaquone

6. Which statement regarding disease transmission is correct?
   a. Close contact with cats infected with C. felis poses a zoonotic risk to immunosuppressed humans.
   b. D. variabilis is a proven competent vector for transmission of C. felis to cats.
   c. Mutual grooming and mating can spread C. felis infection between domestic cats.
   d. Immunosuppressed mice can be infected and used as a model to study C. felis in cats.
   e. Transfusion of piroplasm-containing erythrocytes induces clinical illness in recipient cats.

7. Which laboratory change would not be expected in a cat with cytauxzoonosis?
   a. normocytic anemia  d. thrombocytopenia
   b. hemoglobinuria  e. elevated liver enzymes
   c. bilirubinemia

8. C. felis infection in domestic cats has not been reported in
   b. Oklahoma.  e. Arkansas.
   c. Georgia.

9. Cytauxzoonosis is best prevented by
   a. routine serologic screening for early infection.
   b. careful screening of all potential blood donors.
   c. strict isolation and quarantine of infected cats.
   d. population control of feral cats that might serve as disease reservoirs.
   e. preventing tick attachment.

10. Which complication is most likely to be associated with feline cytauxzoonosis?
    a. acute renal failure
    b. severe gastrointestinal ulceration
    c. disseminated intravascular coagulation
    d. peripheral neuropathy
    e. rhabdomyolysis