Update on the Diagnosis and Management of *Toxoplasma gondii* Infection in Cats

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Toxoplasma gondii is a coccidian that is one of the most prevalent parasites infecting warm-blooded vertebrates around the world.[1-3] Only cats complete the sexual phase in the gastrointestinal tract and pass environmentally resistant oocysts in feces. Sporozoites develop in oocysts after 1 to 5 days of exposure to oxygen and appropriate environmental temperature and humidity (Fig 1). Sporozoites can penetrate the intestinal tract of cats or intermediate hosts and disseminate in blood or lymph as tachyzoites during active infection. *Toxoplasma gondii* can penetrate most mammalian cells and will replicate asexually within infected cells until the cell is destroyed. If an appropriate immune response occurs, replication of tachyzoites is attenuated, and slowly dividing bradyzoites develop that persist within cysts in extra-intestinal tissues. Tissue cysts form readily in the central nervous system (CNS), muscles, and visceral organs. Live bradyzoites may persist in tissues for the life of the host.

Prevalence Rates

It is likely that most *Toxoplasma gondii*–infected cats are infected for life. Thus, serum antibodies are likely to correlate to current infection. *Toxoplasma gondii* seroprevalence rates vary by the lifestyle of the cat. In general, increasing prevalence correlates with increasing age from risk of exposure over time and with cats allowed outdoors because these cats are most likely to contract infected intermediate hosts. In a recent study of clinically ill cats, *T. gondii* antibodies were detected in 31.6% of the 12,628 cats tested.[4] In another study of feral cats in Florida, *T. gondii* antibodies were detected in 12.1%.[5] Although *T. gondii* infection is common in cats, the oocyst shedding period is generally <21 days. Thus, detection of *T. gondii* oocysts in feline feces is uncommon. For example, in 2 studies in the United States, *T. gondii* oocysts were detected in feces of <1% of cats.[6,7]

Pathophysiology

Infection of warm-blooded vertebrates occurs after ingestion of any of the 3 life stages (sporozoite, tachyzoites, bradyzoites) of *Toxoplasma gondii* or transplacentally. It is also possible that cats are infected lactationally.[8] Most cats are not coprophagic, and so most are infected by ingesting *T. gondii* bradyzoites during carnivorous feeding; oocysts are shed in feces from 3 to 21 days. Sporulated oocysts can survive in the environment for months to years and are resistant to most disinfectants. Results of a recent study confirm that the *T. gondii* oocyst shedding prepatent period is stage dependent (ingestion of bradyzoites has a shorter prepatent period than ingestion of sporozoites) and is not dose dependent.[9] In addition, transmission of *T. gondii* is most efficient when cats consume tissue cysts (carnivorism) and when intermediate hosts consume oocysts (fecal-oral transmission). *Toxoplasma gondii* infection of rodents changes the behavior of the prey species, making it less averse to cats, potentially increasing the likelihood that the definitive host (felid) will become infected and potentiate the sexual phase of the organism.[10]

Whether clinical toxoplasmosis occurs is dependent on both host and parasite effects. Some stains of *Toxoplasma gondii* appear to be more pathogenic than others, and some strains may have tissue affinities. For example, different strains of *T. gondii* appeared to be more likely to be associated with ocular disease in cats.[11] If a poor immune response is mounted after primary infection, overwhelming tachyzoites replication resulting in tissue necrosis is the major cause of disease.[1,2] This mechanism is also likely in cats with chronic toxoplasmosis that then become immune suppressed. One example is activation of *T. gondii* infection in cats after administration of immunosuppressive drugs like cyclosporine.[12,13] Other immune-suppressive diseases like feline immunodeficiency virus (FIV) can result in activation of toxoplasmosis.[14] The mechanisms for chronic clinical toxoplasmosis have not been fully determined.[1]

Clinical Abnormalities

The large majority of cats infected with *Toxoplasma gondii* never develop detectable clinical abnormalities. In general, the enteroepithelial cycle in the cat rarely leads to problems. Only 10% to 20% of experimentally inoculated cats develop self-limiting, small bowel diarrhea for 1 to 2 weeks after primary oral inoculation with *T. gondii* tissue cysts; this is presumed to be from the enteroepithelial replication of the organism. *Toxoplasma gondii* enteroepithelial stages were found in intestinal tissues from 2 cats with inflammatory bowel disease that had positive response to administration of

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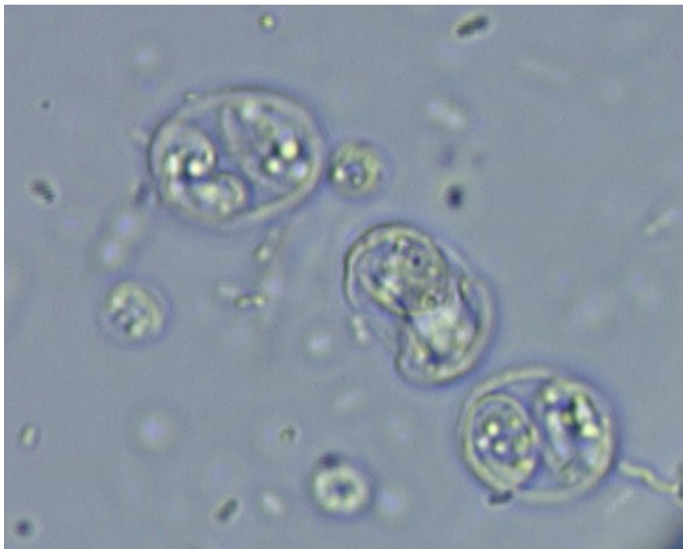

Figure 1. Sporulated oocysts of *Toxoplasma gondii*. The oocysts are 10 × 12 μm in diameter.

anti-*Toxoplasma* drugs.[15] Eosinophilic fibrosing gastritis was recently described in a *T. gondii*-infected cat.[16]

Fatal extraintestinal toxoplasmosis can develop from overwhelming intracellular replication of tachyzoites after primary infection; hepatic, pulmonary, CNS, and pancreatic tissues are commonly involved.[1-3,17-19] Kittens infected by the transplacental or transmammary routes develop the most severe signs of extraintestinal toxoplasmosis and generally die of pulmonary or hepatic disease. Common clinical findings in cats with disseminated toxoplasmosis include depression, anorexia, and fever followed by hypothermia, peritoneal effusion, icterus, and dyspnea. Disseminated toxoplasmosis has been documented in cats concurrently infected with feline leukemia, feline immunodeficiency, or feline infectious peritonitis viruses, as well as after cyclosporine administration for skin disease or after renal transplantation.[12,13,20]

Chronic toxoplasmosis occurs in some cats and should be on the differential diagnoses list for cats with anterior or posterior uveitis, cutaneous lesions, fever, muscle hyperesthesia, myocarditis with arrhythmias, weight loss, anorexia, seizures, ataxia, icterus, diarrhea, dypnea, or pancreatitis.[1-3,21-25] Toxoplasmosis appears to be a common infectious cause of uveitis in cats; anterior uveitis or posterior uveitis can occur and the manifestations can be either unilateral or bilateral (Fig 2).[1,26,27] Kittens infected transplacentally or lactationally commonly develop ocular disease.[11]

Laboratory and Radiographic Abnormalities

Cats with clinical toxoplasmosis can have a variety of clinicopathologic abnormalities, but none document the disease. The organism should be on the differential list for cats with nonregenerative anemia, neutrophilic leukocytosis, lymphocytosis, monocytosis, neutropenia, eosinophilia, proteinuria, bilirubinuria, as well as increases in serum protein and bilirubin concentrations, and creatinine kinase, alanine aminotransferase, alkaline phosphatase, and lipase activities.[1-3]

Pulmonary toxoplasmosis most commonly causes diffuse interstitial to alveolar patterns; pleural effusion has rarely been documented as well. Mass lesions may be detected on computed tomography or magnetic resonance imaging examinations. Cerebrospinal fluid (CSF) protein concentrations and cell counts are often higher than normal with the predominant white blood cells in CSF being small mononuclear cells. However, increased neutrophils also are commonly found in cats with acute central nervous system disease.

Diagnostic Tests

The antemortem definitive diagnosis of feline toxoplasmosis can be made if the organism is demonstrated; however, this is uncommon, particularly in association with sublethal disease. Bradyzoites or tachyzoites are rarely detected in tissues, effusions, bronchoalveolar lavage fluids, aqueous humor, or CSF.[21,24,25,28] *Toxoplasma gondii* oocysts are 10 × 12 μm oocysts and, when found in feces of cats with diarrhea, suggest toxoplasmosis. However, *Besnoitia* and *Hammondia* infections of cats produce morphologically similar oocysts. Recently, polymerase chain reaction (PCR) has been used to document *T. gondii* DNA in feces and can be used to differentiate *T. gondii* from other organisms.[29] *Toxoplasma gondii* DNA can be amplified from the blood of healthy cats, and so

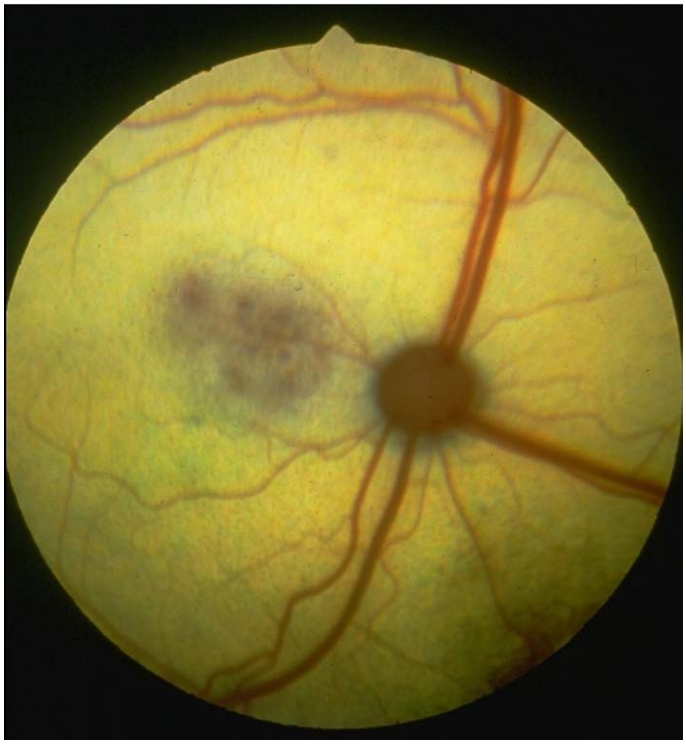

Figure 2. *Toxoplasma gondii*–associated chorioretinitis in an experimentally inoculated cat.

positive PCR results do not correlate to clinical disease.[30] Thus, PCR assays are used most frequently with tissues to document that the organisms seen were *T. gondii* or with aqueous humor or CSF (www.dlab.colostate.edu). Results of serum antigen assays or immune complex assays have also been assessed but are generally only used in research because results do not correlate with clinical illness.[31-33]

Detection of *Toxoplasma gondii* antibodies in serum is used most frequently in the diagnosis of clinical toxoplasmosis. A multitude of different techniques have been assessed including enzyme-linked immunosorbent assay (ELISA), immunofluorescent antibody, western blot immunoassay, and a variety of agglutination tests.[33-39] A latex agglutination assay and an indirect hemagglutination assay are available commercially. These assays can be used with serum from multiple species and theoretically detect all classes of immunoglobulin directed against *T. gondii*. However, these assays rarely detect antibody in feline serum samples positive only for immunoglobulin (Ig) M.[36] ELISA, immunofluorescent antibody, and western blot immunoassay have been adapted to detect IgM, IgG, and IgA antibody responses by using heavy chain specific secondary antibodies.[34,39,40] *Toxoplasma gondii*–specific serum IgA antibody responses are similar to IgG antibody responses, and this antibody class is usually only measured in research studies. Several commercial laboratories in the United States offer *T. gondii* IgM and IgG testing by ELISA (www.dlab.colostate.edu). The following are common findings concerning *T. gondii* IgM and IgG antibody test results.

Toxoplasma gondii IgM Antibody Titers

- Using ELISA, approximately 80% of healthy, experimentally infected cats have detectable *Toxoplasma gondii*–specific IgM in serum within 2 to 4 weeks after inoculation with *T. gondii*; these titers generally are negative within 16 weeks after infection.[34]
- As described in some healthy women, persistent IgM titers (> 16 weeks) have been documented commonly in cats coinfected with FIV and in cats with ocular toxoplasmosis.[26,41] Because of these findings and the finding that some cats never have a detectable IgM response, IgM titers cannot accurately be used to predict when a cat shed oocysts. If a clinician is concerned that an individual cat is shedding *Toxoplasma gondii* oocysts, a fecal flotation should be performed.
- In one study of cats with clinical toxoplasmosis, *Toxoplasma gondii* IgM titers were detected in the serum of 93.3% of the cats, whereas *T. gondii* IgG titers were detected in 60% of the cats. Thus, IgM antibodies have a higher positive predictive value than IgG for clinical feline toxoplasmosis.[33,42]
- Some cats with chronic *Toxoplasma gondii* infections that have gone from IgM positive to IgM negative can have IgM titers detected again after repeat inoculation with *T. gondii*, primary inoculation with the Petaluma isolate of FIV, and administration of glucocorticoids without detection of clinical signs of toxoplasmosis.[33,43] Thus, presence of IgM antibodies in feline serum does not always prove clinical toxoplasmosis in cats.

Toxoplasma gondii IgG titers

- *Toxoplasma gondii*–specific IgG can be detected by ELISA in serum in the majority of healthy experimentally inoculated cats within 3 to 4 weeks after infection.[33,34]
- By the time IgG antibodies are detected in feline sera, the oocyst shedding period has usually been completed. Thus, IgG seropositive cats are of minimal public health risk.
- *Toxoplasma gondii* IgG antibody titers can be detected for at least 6 years after infection in experimentally inoculated cats; because the organism probably persists in tissues for life, IgG antibodies probably do as well.[38]
- Single, high IgG titers do not necessarily suggest recent or active *Toxoplasma gondii* infection; healthy cats commonly have titers >10,000 six years after experimental induction of toxoplasmosis.[38]
- Some cats with low *Toxoplasma gondii* antibody titers can become seronegative based on the cutoff value used in an individual assay, even though *T. gondii* is still within tissues. Based on an approximate 10% interassay variation in the ELISA technique, some cats with low positive IgG titers (1:64) can be positive for IgG antibodies on one analysis and negative on a subsequent analysis or vice versa.
- The demonstration of an increasing *Toxoplasma gondii* IgG titer can document recent or active infection, but in experimentally infected cats, the time span from the first detectable positive IgG titer to the maximal IgG titer is approximately 2 to 3 weeks. Thus, some cats with clinical toxoplasmosis will have reached their maximal IgG titer by the time they are evaluated serologically.
- Rising *Toxoplasma gondii* IgG antibody titers occur in healthy infected cats as well as cats with clinical toxoplasmosis, and so when assessed alone do not prove clinical toxoplasmosis.
- In humans and cats with reactivation of chronic toxoplasmosis from immune suppression, IgG titers only rarely increase.
- For the reasons discussed above, antibody test results alone cannot be used to make a diagnosis of toxoplasmosis. However, the following combination can be used to make a presumptive antemortem diagnosis:
  - Demonstration of antibodies in serum, which suggests infection by *Toxoplasma gondii*

- Demonstration of an IgM titer >1:64 or a 4-fold or greater increase in IgG titer, which suggests recent or active infection.
- Clinical signs of disease referable to toxoplasmosis.
- Exclusion of other common causes of the clinical syndrome.
- Positive response to appropriate treatment.

Because the organism cannot be cleared from the body, most cats will be antibody-positive for life, so there is little reason to repeat serum antibody titers after the clinical disease has resolved or to administer drugs with *Toxoplasma gondii* activity to cats without clinical signs of toxoplasmosis.

The combination of aqueous humor or CSF *Toxoplasma gondii*–specific antibody detection and organism DNA detection by PCR is the most accurate way to diagnose ocular or CNS toxoplasmosis (www.dlab.colostate.edu).[26,27,44] Although *T. gondii*–specific IgA, IgG, and organism DNA can be detected in aqueous humor and CSF of both normal and clinically ill cats, *T. gondii*–specific IgM has only been detected in the aqueous humor or CSF of clinically ill cats and so may be the best indicator of clinical disease.

Treatment

Cats with suspected clinical toxoplasmosis should be administered supportive care as needed. Clindamycin hydrochloride administered (10 to 12 mg/kg, orally [PO], every 12 hours) for 4 weeks or a trimethoprim-sulfonamide combination administered (15 mg/kg, PO, every 12 hours) for 4 weeks has been used most frequently by the author for the treatment of clinical feline toxoplasmosis (Table 1).[1,42] One of the drugs should be prescribed for 1 week because most clinical signs of toxoplasmosis will begin to resolve within that time period. If a positive response is recognized, treatment should be continued for 4 weeks if possible. If there is a poor response to therapy after the first 7 days, an alternate drug should be considered. Recurrence of clinical signs may be more common in cats treated for less than 4 weeks (MR Lappin, unpublished data).

Azithromycin (10.0 mg/kg, PO, every 24 hours) has been used successfully in a limited number of cats, but the optimal duration of therapy is unknown. Pyrimethamine combined with sulfa drugs is effective for the treatment of human toxoplasmosis but commonly results in toxicity in cats. Ponazuril has been used experimentally in *Toxoplasma gondii*–infected rodents and should be studied for the treatment of feline toxoplasmosis.[45,46] Currently, an optimal treatment regimen for the use of this drug is unknown. Cats with systemic clinical signs of toxoplasmosis, such as fever or muscle pain combined with uveitis, should be treated with anti-*Toxoplasma* drugs in combination with topical, oral, or parenteral corticosteroids to avoid secondary lens luxations and glaucoma. *Toxoplasma gondii*–seropositive cats with uveitis that are otherwise normal can be treated with topical glucocorticoids alone unless the uveitis is recurrent or persistent. In these situations, administration of a drug with anti–*T. gondii* activity may be beneficial.

Table 1. Drugs Used to Treat Clinical Toxoplasmosis in Cats

Drug	Dose (mg/kg)	Frequency (hours)	Route	Duration (weeks)
Azithromycin	10	q 24	PO	4
Clindamycin	10 to 12	q 12	PO	4
Trimethoprim-sulfa	15	q 12	PO	4

Prognosis

There is no evidence to suggest that any drug can totally clear the body of the organism, so recurrences are common and infected cats will always be seropositive. The prognosis is poor for cats with hepatic, CNS, or pulmonary disease caused by tachyzoites replication, particularly in cats that are immunocompromised by antiinflammatory drugs or retrovirus coinfection. Lens luxations and glaucoma can result in the need for enucleation. Cats with CNS clinical signs of disease may not normalize completely after therapy.

Prevention

To avoid exposure to *Toxoplasma gondii*, cats should not be allowed to hunt or be fed undercooked meats. Care should be taken to control transport hosts like cockroaches, which have been shown to carry *T. gondii* oocysts.

Zoonotic Considerations

Primary *Toxoplasma gondii* infection in immunocompetent individuals results in self-limiting fever, malaise, and lymphadenopathy, which may be not recognized or is misdiagnosed. Primary infection of mothers by *T. gondii* during gestation can lead to clinical toxoplasmosis in the fetus; stillbirth, CNS disease, and ocular disease are common clinical manifestations. As T-helper cell counts decline, approximately 10% of people with AIDS develop toxoplasmic encephalitis from activation of bradyzoites in tissue cysts.

People most commonly acquire toxoplasmosis by ingesting sporulated oocysts or tissue cysts, or transplacentally. To prevent toxoplasmosis, avoid eating undercooked meats or ingesting sporulated oocysts. In a recent study of 6282 meat samples from 698 retail meat stores, *Toxoplasma gondii* was detected by bioassay in cats in none of the beef or chicken samples tested and only in a small number of pork samples.[47] Although exposure to cats is epidemiologically associated with acquiring toxoplasmosis in some studies, touching individual cats is probably not a common way to acquire toxoplasmosis for the following reasons.[1-3,48-52]

- Cats generally only shed oocysts for days to several weeks after primary inoculation.

- Repeat oocyst shedding is rare, even in cats receiving glucocorticoids, cyclosporine, or in those infected with FIV or feline leukemia virus.
- Cats with toxoplasmosis inoculated with tissue cysts 16 months after primary inoculation did not shed oocysts.
- Cats are very fastidious and usually do not allow feces to remain on their skin for time periods long enough to lead to oocyst sporulation; the organism was not isolated from the fur of cats shedding millions of oocysts 7 days previously.

However, because some cats will repeat oocyst shedding when exposed a second time, feces should always be handled carefully. If a fecal sample from a cat is shown to contain oocysts measuring 10×12 μm, it should be assumed that the organism is *Toxoplasma gondii*. The feces should be collected daily until the oocyst shedding period is complete; administration of clindamycin (20 mg/kg, daily) blocked *T. gondii* oocyst shedding in cats when administered before infection and may shorten the oocyst shedding period if started after infection is documented.[1,53]

Because humans are not commonly infected with *Toxoplasma gondii* from contact with individual cats, testing healthy cats for toxoplasmosis is not recommended. Fecal examination is an adequate procedure to determine when cats are actively shedding oocysts but cannot predict when a cat has shed oocysts in the past. There is no serologic assay that accurately predicts when a cat shed *T. gondii* oocysts in the past, and most cats that are shedding oocysts are seronegative. Most seropositive cats have completed the oocyst shedding period and are unlikely to repeat shedding; most seronegative cats would shed the organism if infected. If owners are concerned that they may have toxoplasmosis, they should see their physician for testing.

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