Toxoplasmosis

Toxoplasma Infection

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Etiology
Toxoplasmosis is the result of infection by *Toxoplasma gondii*, an obligate intracellular protozoan parasite in the phylum Apicomplexa.

The major forms of the parasite are:
- Oocysts (containing sporozoites), which are shed in the feces.
- Tachyzoites, rapidly multiplying organisms found in the tissues.
- Bradyzoites, slowly multiplying organisms found in the tissues.
- Tissue cysts: walled structures, often found in the muscles and central nervous system (CNS), containing dormant *T. gondii* bradyzoites.

Geographic Distribution
Toxoplasmosis is found worldwide. Infections are particularly common in warm, humid climates and at lower altitudes.

Transmission and life cycle

Transmission
Carnivores and omnivores, including humans, can become infected when they eat raw or undercooked tissues containing tissue cysts or, occasionally, tachyzoites. Both herbivores and carnivores may ingest infective oocysts in food or water, inhale them in aerosols, or come into contact with contaminated soil. *T. gondii* can cross the placenta in some species, particularly sheep, goats, humans and small rodents. Transmission in transfused blood or transplanted organs is possible but rare. Flies and cockroaches can act as mechanical vectors.

Life cycle
*T. gondii* undergoes an asexual reproductive cycle in all species. The tissue cyst or oocyst wall is dissolved during digestion, releasing bradyzoites or sporozoites, which enter the lamina propria of the small intestine and begin to multiply as tachyzoites. The tachyzoites can disseminate to extraintestinal tissues within a few hours of infection, via the lymph and blood. They can enter nearly any cell and multiply; the host cell eventually ruptures and the released tachyzoites enter new cells. As host resistance develops, approximately 3 weeks after infection, the tachyzoites begin to disappear from the visceral tissues and form “resting” bradyzoites within tissue cysts. These cysts are found most often in the skeletal muscles, brain and myocardium. They generally do not cause a host reaction and can persist for life.

In Felidae, the definitive hosts, the parasites simultaneously undergo a sexual cycle of replication. After ingestion, some of the bradyzoites multiply within the epithelial cells of the small intestine. After numerous cycles of asexual reproduction, these bradyzoites initiate the sexual cycle (gametogony), which results in the formation of an unsporulated oocyst. The oocyst is excreted in the feces and sporulates in the environment. Sporulation takes approximately 1 to 5 days under ideal conditions, but may take up to several weeks. After sporulation, the oocyst contains two sporocysts, each with four sporozoites. Cats usually shed oocysts for one to two weeks.

Oocysts are highly resistant to environmental conditions and can remain infectious for as long 18 months in water or warm, moist soils. They do not survive well in arid, cool climates. Tissue cysts can remain infectious for weeks in body fluids at room temperature, and in meat for as long as the meat is edible and uncooked. Tachyzoites are more fragile and can survive in body fluids for up to a day and in whole blood for as long as 50 days at 4°C.

Reactivated infections
*T. gondii* tissue cysts are thought to rupture periodically, releasing bradyzoites. In immunocompetent hosts, immunity usually prevents the released parasites from multiplying; however, in immunosuppressed individuals, the bradyzoites can develop
into tachyzoites, causing clinical toxoplasmosis. In AIDS patients, toxoplasmosis is often a reactivated rather than a new infection. Many clinical infections in older cats are also thought to result from reactivated infections.

**Disinfection**

*T. gondii* oocysts are resistant to most disinfectants but can be inactivated by iodine, formalin and ammonia. They are also destroyed within 10 minutes by temperatures greater than 66°C (150°F), and can be killed with boiling water. Tachyzoites and tissue cysts are susceptible to most disinfectants, including 1% sodium hypochlorite and 70% ethanol. Tachyzoites are also inactivated at pH < 4.0. Freezing at −15°C for more than three days or −20°C for more than 2 days destroys a high percentage of the cysts.

**Infections in Humans**

**Incubation Period**

In humans, the incubation period is 10 to 23 days after ingesting contaminated meat, and 5 to 20 days after exposure to infected cats.

**Clinical Signs**

In immunocompetent non-pregnant individuals, infection with *T. gondii* is usually asymptomatic. Approximately 10-20% of patients develop lymphadenitis or a mild, flu-like syndrome characterized by fever, malaise, myalgia, headache, sore throat, lymphadenopathy and rash. In some cases, the disease may mimic infectious mononucleosis. The symptoms usually resolve without treatment within weeks to months, although some cases may take up to a year. Severe symptoms, including myositis, myocarditis, pneumonitis and neurologic signs including facial paralysis, severe reflex alterations, hemiplegia and coma, are possible but rare. Ocular toxoplasmosis with uveitis, often unilateral, can be seen in adolescents and young adults; this syndrome is often the result of an asymptomatic congenital infection or the delayed result of a postnatal infection.

Infections acquired during (or, rarely, just before) pregnancy can lead to congenital toxoplasmosis of the infant. The symptoms are usually due to infection of the developing brain and/or retina. The incidence and severity of the disease vary with the stage of pregnancy; infections are least likely to cross the placenta during the first trimester but are most severe when they do. The spectrum of disease varies from severe congenital toxoplasmosis characterized by chorioretinitis, hydrocephalus, convulsions and intracerebral calcifications, to mild cases with only slightly diminished vision. Ocular disease is usually bilateral; the most common symptom is chorioretinitis but strabismus, nystagmus and microphthalmia may also be seen. Infants infected late in gestation may have a fever, rash, hepatomegaly, splenomegaly, pneumonia or a generalized infection. Many infected infants are asymptomatic at birth; however, most will develop learning and visual disabilities or even severe, life-threatening infections later in life, if left untreated. Abortions and stillbirths may also be seen, particularly when the infection occurs in the first trimester.

Toxoplasmosis is often severe in immunosuppressed patients. Neurologic disease is the most common sign, particularly in reactivated infections. Encephalitis, with symptoms of headache, disorientation, drowsiness, hemiparesis, reflex changes and convulsions, may lead to coma and death. Necrosis from multiplication of the parasite can cause multiple abscesses in nervous tissue, with the symptoms of a mass lesion. Chorioretinitis, myocarditis and pneumonitis also occur.

**Communicability**

Toxoplasmosis is not directly communicable from person to person except *in utero*. Approximately half of all untreated infections are thought to cross the placenta; infection of the fetus is particularly likely during the second and third trimesters. Rarely, *T. gondii* may be transferred in contaminated blood or organs during a transfusion or organ transplantation.

Toxoplasmosis is the most common work-related parasitic infection in laboratory workers. Infections can be acquired by accidental inoculation, splashing, inhalation or ingestion. The source of infection may be blood or blood products, semen, feces or tissues.

**Diagnostic Tests**

Toxoplasmosis can be diagnosed by direct observation of the parasites in tissues, including bronchoalveolar lavage material and lymph node biopsies. Immunohistochemical staining and electron microscopy are also used. PCR techniques can be helpful, particularly for detecting congenital infections *in utero*. *T. gondii* can also be isolated from muscle, brain, blood or other body fluids, using cell culture or mouse inoculation. Computed tomography techniques are sometimes helpful in cases of cerebral toxoplasmosis and ultrasound may be used in the fetus.

More often, infections are detected by serology. The IFA and ELISA tests are used most often in humans. Other serologic tests include the Sabin-Feldman dye test, indirect hemagglutination, latex agglutination, modified agglutination and complement fixation. A toxoplasmin skin test is sometimes used in epidemiologic studies. IgM-specific tests are performed when it is important to know the time of infection, e.g. in a pregnant woman. A negative IgM test strongly suggests that the infection was not recent, but a positive IgM test is difficult to interpret; *Toxoplasma*-specific IgM can be found for up to 18 months after the acute infection and false positives are common. Before treatment is started, the U.S. Centers for Disease Control and Prevention (CDC) recommends that all IgM positives be verified by a *Toxoplasma* reference laboratory such as CDC or the Toxoplasmosis Serology Lab, Palo Alto.
Medical Foundation, Palo Alto, CA. Rising titers can also be used to detect acute infections. Serology is unreliable for active CNS toxoplasmosis in immunocompromised patients, as antibody production may be delayed and/or low.

Newborn infants are tested with IgM- and IgA-capture ELISAs. Samples from infants are all tested by the Toxoplasma Serology Laboratory in Palo Alto, CA.

Treatment
Antibiotics may be used in pregnant women, immunocompromised patients with organ involvement, congenitally infected infants or individuals with ocular disease. Treatment of acute infections during pregnancy reduces the risk of infection in the fetus by approximately 50%. Healthy non-pregnant individuals may not be treated, as the infection is self-limiting and typically mild. Antibiotics cannot destroy tissue cysts and may not be able to eradicate actively dividing parasites.

Prevention
The risk of infection can be reduced by proper food preparation. Meats should be cooked to a temperature sufficient to kill *T. gondii*; the internal temperature of beef, lamb and veal steaks or roasts should reach at least 145°F (63°C), and pork, ground meat and wild game should be cooked to 160°F (71°C). Whole poultry should reach a temperature of 180°F (82°C) in the thigh. Freezing, salting, pickling and smoking do not reliably destroy *T. gondii*. Fruits and vegetables should be peeled or washed thoroughly to remove oocysts.

Good hygiene is important in preventing infections. Kitchen items should be washed with hot soapy water after they have contacted raw meats, raw seafood or unwashed fruits and vegetables. Hands should be washed after contact with raw meat, soil or sand and before eating or touching the face. Pregnant women and others at risk should wear gloves when gardening and during other soil or sand contact.

To help prevent transmission of *T. gondii* to humans, cats should be fed only commercial pet food or well-cooked meats. Indoor cats are less likely to transmit toxoplasmosis than outdoor cats. Litter boxes should be cleaned daily to reduce the risk of oocyst sporulation, and rinsed with boiling water. Pregnant women should avoid cleaning the litter box; if this is unavoidable, they should use gloves then wash their hands.

Human vaccines are not available.

Morbidity and Mortality
*T. gondii* infection is one of the most common infections in humans; in worldwide serological surveys, 3-80% of healthy adults have been exposed to this parasite. Infection is asymptomatic in 80-90% of non-pregnant, immunocompetent individuals, and usually causes mild disease in the remainder. Most cases are sporadic but small epidemics may occur, usually associated with contaminated food or water. Immunity appears to be lifelong unless the individual becomes immunosuppressed.

Congenital toxoplasmosis is not nationally reportable in the U.S. Regional studies in the 1970s (Alabama and New York) reported disease rates of approximately 10 per 10,000 live births, while a more recent study, conducted from 1986-1992 in New England, reported 1 case per 10,000 live births. Other sources suggest a rate of 1 per 4,000 live births. Infections are more likely to cross the placenta during the second and third trimesters, but are most severe if the fetus is infected in the first trimester. In one study, 13% of congenitally infected infants became infected during the first trimester and 80% had severe disease, while 29% became infected during the second trimester and 30% of these infants had severe disease. Half of the infants were infected during the third trimester and 70-90% had subclinical infections.

Severe, life-threatening infections are also seen in immunocompromised persons. In one study, Toxoplasma encephalitis occurred in 25% of AIDS patients and was fatal in 84%.

Infections in Animals

<table>
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<th>Species Affected</th>
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<td>Members of the Felidae, including domestic cats, are the definitive host. Most mammals and birds can serve as intermediate hosts. Among domestic animals, infections are most common in cats, sheep, goats and swine. Lower infection rates are seen in dogs and horses. Cattle seem to be relatively resistant to infection. Titors are generally low and transient, and parasites have rarely been isolated from this species.</td>
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Infection Period
The incubation period for naturally acquired, acute disease appears to be unpublished; however, it is probably similar to the 5-23 day incubation period in humans. Experimentally infected kittens develop diarrhea 5-6 days after infection. Reactivation can occur years after the initial infection. In cats, the prepatent period (from infection to the shedding of oocysts) is usually 3 to 21 days. The prepatent period is much shorter when infection is by tissue cysts than oocysts.

Clinical Signs
Most infections in animals are asymptomatic. Clinical toxoplasmosis is seen most often in sheep and goats. Occasional cases are also seen in young or immunosuppressed animals of other species.

Sheep and goats
Toxoplasmosis in adult sheep and goats is usually asymptomatic; however, infections acquired during pregnancy can cause abortions, stillbirths, or mummification or resorption of the fetus. Congenitally
infected lambs may be incoordinated, weak and unable to nurse, and have a high mortality rate. Fever and dyspnea may also be seen in generalized infections. Lambs infected late in gestation may be born infected but asymptomatic. Abortions and diseased lambs or kids do not recur during subsequent pregnancies.

**Cats**

Most infected cats are asymptomatic, but generalized acute (2 to 3 days), subacute (2 to 3 weeks) and chronic (months to years) infections have been reported, particularly in young or immunocompromised animals. Some cases have been associated with feline immunodeficiency virus (FIV) infection. The early symptoms include lethargy, persistent fever despite treatment with some antibiotics, and anorexia. Dyspnea and other signs of pneumonia are seen in many cats, but coughing and pleural effusion are uncommon. Infections with severe respiratory signs are often fatal, even with treatment. In some cats, toxoplasmosis may be characterized by hepatitis or pancreatitis, or mimic the symptoms of a systemic disease such as panleukopenia. Central nervous system (CNS) signs, particularly common in older cats, vary with the site of the lesion and may include convulsions, restless, somnolence, head pressing, teeth grinding, personality changes, hyperesthesia, atypical vocalizations, incoordination, trembling, opisthotonos or circling. Spinal cord signs, including paralysis and depressed reflexes, have also been reported. Enteric signs are common in experimental infections but uncommon in natural disease. Diarrhea is the most common symptom; on rare occasions, it may be associated with a palpable granuloma in the intestine. Severe enteric infections can occur in kittens, in association with viral respiratory illness or other disease. Abortion, metritis and the birth of premature, weak or deformed kittens can occur but seem to be rare.

Ocular signs are common and may include generalized retinitis or irregular reddish, dark or pale retinal foci; in some cases, the retina is partially or completely detached. The retinal vessels may be congested, and hemorrhages and exudates may cloud the vitreous humor. The iris, ciliary body and aqueous humor can also be involved, but the conjunctiva and nictitating membranes are rarely affected. Chronic low-grade infections may cause glaucoma, corneal opacity and panophthalmitis.

**Dogs**

Most infected dogs are asymptomatic; clinical toxoplasmosis is most common in puppies or in immunosuppressed older dogs. Many cases are seen in dogs with canine distemper, ehrlichiosis or other diseases. The symptoms vary with the affected organ(s). Toxoplasma encephalitis can be associated with either focal or multifocal neurological signs; the symptoms may include hyperexcitability, depression, seizures, head tilt, intention tremor, paresis and paralysis. Infected dogs may also develop myositis-polyradiculoneuritis, characterized by bilateral rigidity of the pelvic limbs, with progressive paresis and a synchronous pelvic limb hopping gait. In this syndrome, the pelvic limb muscles are rigid and non-painful on palpation and slowly become atrophic. The most severe cases are usually seen in dogs less than 6 months old. Acute hepatitis, which is often fatal, may be associated with icterus, abdominal effusion, lethargy, fever, vomiting, diarrhea and signs of CNS or ocular involvement. Interstitial pneumonia, myocarditis, lymphadenopathy, tonsillitis, diarrhea and vomiting have also been reported. Ocular signs may include retinitis, uveitis and iridocyclitis. Some cases attributed to *T. gondii* before 1988 may have been caused by the related parasite *Neospora caninum.*

**Swine**

Outbreaks of toxoplasmosis, with generalized infections, abortions, stillbirths and neonatal mortality, are occasionally reported in swine. Fever and interstitial pneumonia, with dyspnea and coughing, may be seen in young animals. Weakness, cachexia, incoordination, trembling and diarrhea have also been reported. In pigs, *T. gondii* can also cause myocarditis, hepatic necrosis, meningoencephalomyelitis, chorioretinitis, lymphadenopathy and myositis.

**Other species**

Fever, encephalitis, ataxia and retinal degeneration have been reported in horses. Cattle rarely have symptoms but fever, respiratory distress, nasal discharge and conjunctival hyperemia have been described in experimentally infected calves. Symptomatic infections, some fatal, can be seen in rabbits, guinea pigs and other small mammals. Infected rodents may abort repeatedly. Some species of marsupials and New World monkeys are highly susceptible to toxoplasmosis. Infections in birds are common but rarely symptomatic.

**Communicability**

Toxoplasmosis is communicable only in Felidae. Experimentally infected cats, 6-months older and older, usually shed oocysts only when they are first infected, and are resistant to reinfection. Nursing or recently weaned kittens can shed oocysts a second time before becoming resistant. Naturally infected cats may also be able to re-shed cysts if they are reinfected or immunosuppressed, but this appears to be uncommon. Shedding usually lasts for two weeks or less, but a few cats can shed oocysts for up to a month.

**Diagnostic Tests**

Toxoplasmosis is often diagnosed by serology. Serologic tests used in animals include enzyme-linked immunosorbent assays (ELISAs), an indirect fluorescent antibody (IFA) test, complement fixation, the Sabin-Feldman dye test, direct and indirect hemagglutination, latex agglutination and modified agglutination tests. IgG
Toxoplasmosis

and IgM titers may be used to differentiate recent from older infections. Rising titers, taken 3 to 4 weeks apart during the acute and convalescent stages, can also indicate a recent infection.

In cats, active infections can also be diagnosed by fecal flotation for oocysts. *Toxoplasma* oocysts, which are ovoid and 10-12 μm in diameter, are morphologically indistinguishable from *Hammondia, Isospora* and *Besnoitia*.

In all species, tachyzoites or bradyzoites may be found in the aqueous humor in ocular disease, CSF in neurologic disease, and in impression smears, biopsies or post-mortem samples from a variety of other tissues. Well-preserved organisms in impression smears are crescent-shaped and stain well with any Romanowsky stain; degenerating organisms, which often occur in lesions, are usually oval, with poorly-staining cytoplasm. In thin sections, tachyzoites are oval to round and stain similarly to host cells. Tissue cysts are usually spherical, with silver-positive walls; the bradyzoites stain strongly with periodic acid Schiff stain. The tissue forms of *Toxoplasma* are similar to *Neospora caninum* and *Sarcocystis* species; these organisms can be distinguished by tissue immunocytochemistry, ultrastructural studies or polymerase chain reaction (PCR) assays. *T. gondii* may also be isolated in cell cultures or by mouse inoculation.

**Treatment**

Antibiotics and supportive therapy are used to treat clinical disease. Antibiotics do not destroy the bradyzoites, and do not eliminate infections.

**Prevention**

Preventative measures may help to reduce congenital disease in sheep. If possible, cats should be kept away from pastures and barns where pregnant sheep and goats are kept. After an abortion, the placenta and abortion products should be removed, and the area cleaned and disinfected. A modified live vaccine is also available for sheep in Europe and New Zealand.

To prevent cats from becoming infected and serving as sources of infection for humans, they should not be fed raw or undercooked meat. Indoor cats are less likely to become infected, due to reduced exposure to rodents.

**Morbidity and Mortality**

Asymptomatic *T. gondii* infections are common in animals. Among domestic animals, the prevalence of infection is highest in cats, sheep, goats and swine, and low in cattle. Antibodies have been found in 15-58% of the cats in the U.S. and 25-100% worldwide. Infections are particularly common in strays and less prevalent in pets.

Clinical toxoplasmosis is rare and usually occurs sporadically, with the exception of congenital disease in sheep and goats and infrequent outbreaks in swine. Most symptomatic infections are seen in concurrently infected, immunosuppressed or young animals. Among immunocompetent animals, severe disease and deaths are most likely to occur in very young animals. In one study, the mortality rate was 21% in experimentally infected kittens weighing less than 1 kg, 4% in kittens from 1-1.5 kg, and 0% in cats over 1.5 kg. Mortality rates up to 100% have been seen in week-old kittens. Perinatal mortality rates in infected lambs, kids and piglets can be as high as 50%. Acute liver failure is often fatal in small animals.

Abortions can recur in some species but not in others. Sheep and goats usually abort only during the initial infection. Mice, rats, guinea pigs and hamsters can infect their progeny repeatedly without reinfection from outside sources.

**Post Mortem Lesions**

Toxoplasmosis lesions are related to parasite migration through the tissues and organs, with accompanying necrosis.

**Sheep and goats**

In *Toxoplasma* abortions of sheep and goats, 1-3 mm gray-white necrotic foci are found on the cotyledons of the placenta. The intercotyledonary region is usually normal or slightly edematous.

In infected animals, multiple granulomas may be found in the lungs, and the liver, spleen and kidneys may contain areas of necrosis. Hydrothorax, ascites and intestinal ulceration have also been observed. The central nervous system may contain hemorrhages, edema, ventricular dilatation and areas of inflammation.

**Cats**

In cats, the lesions may include pulmonary edema and small pale foci of consolidation, often with red centers, in the lungs. The liver may be enlarged, with small red or yellow foci or a mottled appearance; hepatitis may be accompanied by jaundice and other lesions. The spleen is sometimes enlarged, with pale or hemorrhagic foci, and may be covered in fibrin. The lymph nodes, particularly in the thorax and abdomen, are variably enlarged and reddened. Hemorrhages and focal pallor in the myocardium, pericardial effusion and edema have been reported in cases with cardiac involvement. Extensive involvement of the pancreas may appear as an abdominal mass. The adrenal glands may contain necrotic foci of varying size; in some cases, the medulla is replaced by fibrotic tissue. Intestinal lesions are uncommon but granulomas, usually associated with areas of chronic enteritis, are occasionally seen. Hemorrhages, necrosis, ulcers and desquamation of the mucosa have been noted in the stomach. CNS lesions are usually limited to microscopic abnormalities, but visible areas of necrosis are occasionally found. Ocular lesions of the retina, choroid and other structures may also be observed. Mural hemorrhages of the urinary bladder and kidney involvement are uncommon. Esophagitis and skin nodules are rare.
Swine
In pigs, post-mortem lesions may include pneumonia, hydrothorax, ascites, intestinal ulceration, and lymphadenopathy. The liver, spleen and kidneys may contain areas of necrosis, and multiple granulomatous lesions may be found in the brain.

Birds
In birds, necrotic foci may be seen in the liver, lymph nodes, lungs and spleen during acute infections.

Internet Resources

Centers for Disease Control and Prevention (CDC)
http://www.cdc.gov/ncidod/dpd/parasites/toxoplasmosis/default.htm

Material Safety Data Sheets – Canadian Laboratory Center for Disease Control
http://www.hc-sc.gc.ca/phys-lph/depds/msds-fss/index.html#menu

Medical Microbiology
http://www.ncbi.nlm.nih.gov/books/NBK7627/

The Merck Manual
http://www.merck.com/pubs/mmanual/

The Merck Veterinary Manual
http://www.merckvetmanual.com/mvm/index.jsp

References


* Link defunct as of 2012