Univ. of Mustansiriyah
College of Pharmacy
Branch of Clinical Laboratory Sciences

# Medical Parasitology

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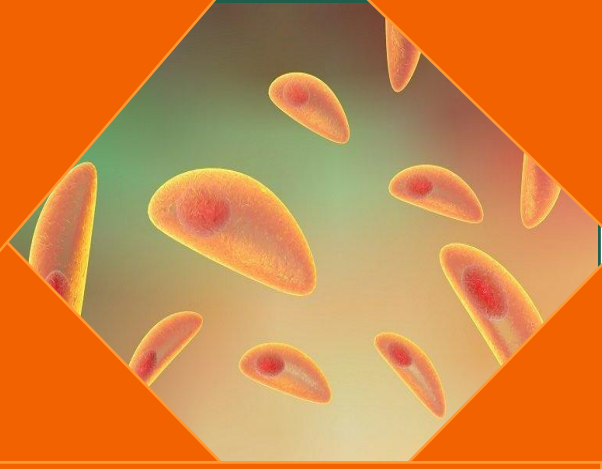


## Lec. 6 Sporozoa - Toxoplasmosis

### Toxoplasmosis

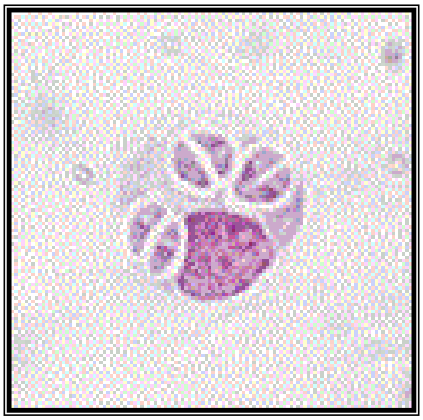
This disease is caused by a parasite called ***Toxoplasma gondii***. The parasite is found in a large number of mammals including man, and also found in the birds. Although the infection is cosmopolitan, surveys indicate that prevalence is highest in hot, humid climates and lowest in dry, cold climates. The principal means of acquiring the infection is either by ingestion of inadequately cooked meat (undercooked), primarily beef, pork, and lamb, or by the contact with feral or domestic cats. Any cat, no matter how well cared for, may carry and pass the infective stage of ***Toxoplasma***. Congenital toxoplasmosis is a very serious disease, and for this reason pregnant women should avoid contact with litter box filler used by cats. Flies and cockroaches have also been implicated as carriers of the infective stages from cat feces to food.

### Life cycle

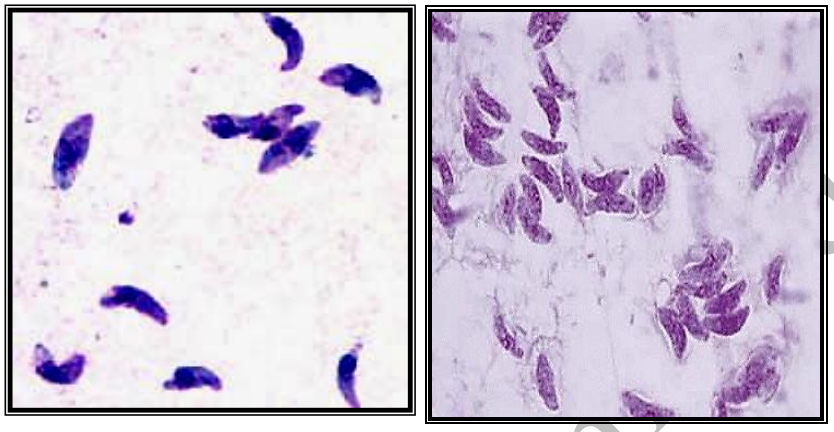
*Toxoplasma* parasite can attack a wide variety of tissue cells but seems to favor muscle, lymph nodes, and intestinal epithelium. Infection of intestinal epithelial cells occurs only in felines, probably the "normal" hosts, and this developmental pathway is termed the **enteric** or **enteroepithelial phase**. During this phase, the formation of oocysts containing sporozoite (the primary source of human infection) occurs. In other hosts, including many species of carnivores, insectivores and primates, there is only the **extraintestinal** or **tissue phase**.

Five stages occur in the life cycle of ***Toxoplasma gondii***. Although all the five stages occur in cats, only two stages found in man, other mammals and in birds; these two stages are:

1. The intracellular trophozoites or proliferative form (**tachyzoites**), which usually seen during the acute infection. They may found in various sites in the body of the host.

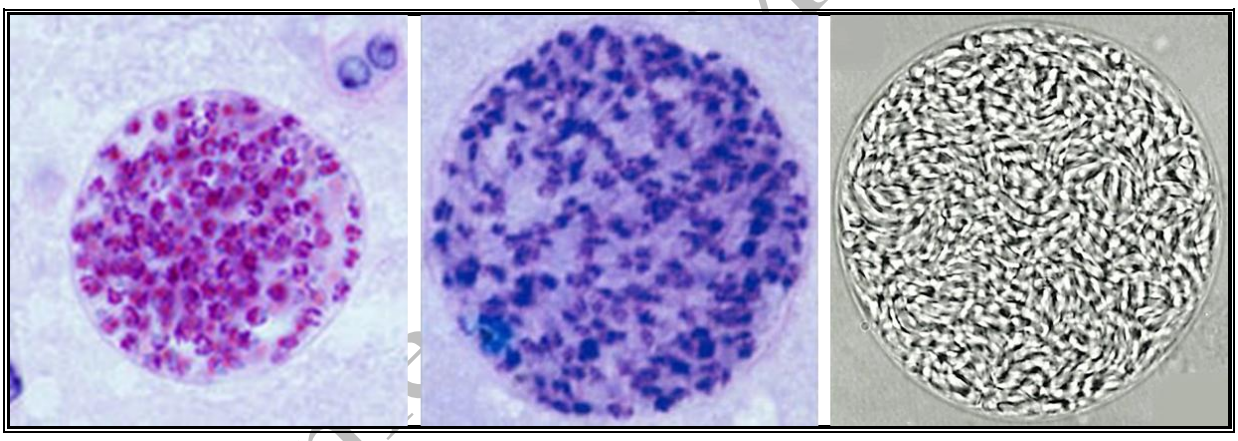


***Toxoplasma gondii*, Trophozoites (tachyzoites) in the host tissue.**



***Toxoplasma gondii*, tachyzoites**

2. The encysted form (**bradyzoite**) that is found during chronic or latent infection.



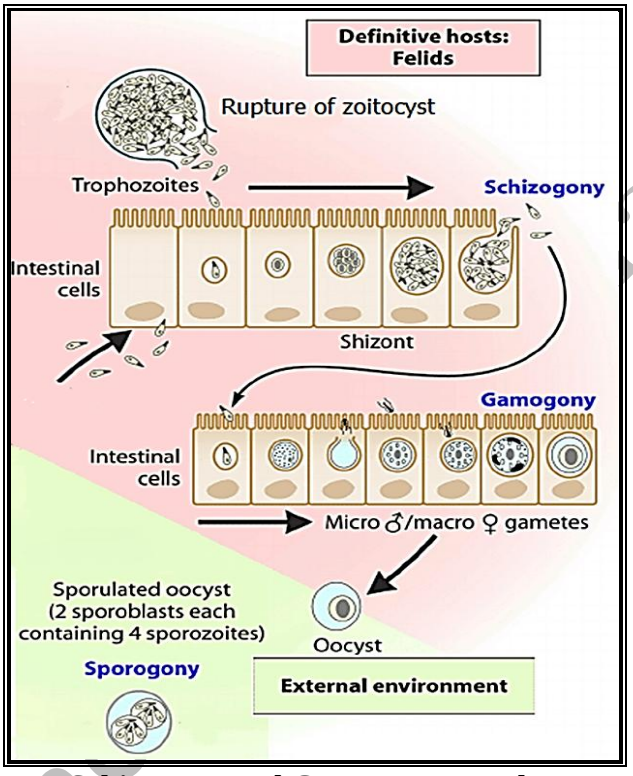
***Toxoplasma gondii*, bradyzoites (or zoitocysts)**

The trophozoites are crescent-shaped, 4-8µm in length and 2-3µm in width with one end more pointed than the other. The cysts that occur in chronic infection are formed when the parasite multiplies and produce a wall within the host cell. Reproduction is by endodyogeny.

Members of the cat family (Felidae) are the only known definitive hosts for the sexual stages of *Toxoplasma gondii* and thus are the main reservoirs of infection. Cats become infected with *Toxoplasma gondii* by carnivorism. After tissue cysts (**bradyzoites**) or **oocysts** are ingested by the cat, viable organisms are released and invade the epithelial cells of the small intestine where they undergo an asexual followed by a sexual cycle and then form oocysts, which are excreted.

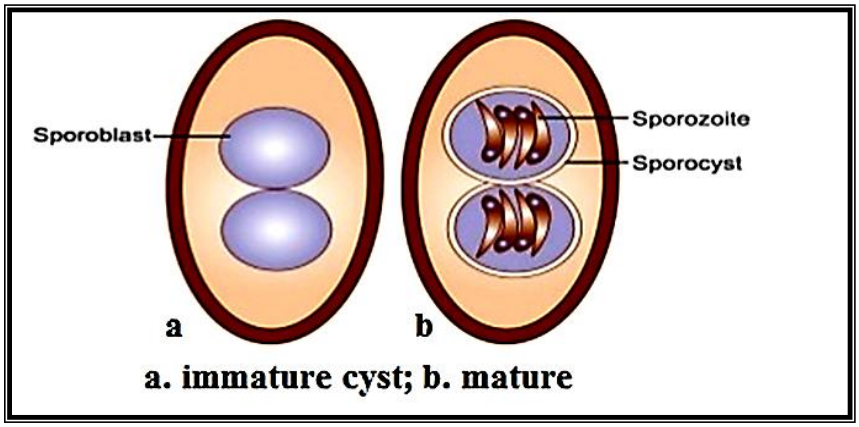
The asexual multiplication of the schizont stage (**schizogony**) occurs inside the epithelial cells of the cat intestine where it is producing a large number of merozoites which invade the intestinal epithelium again.

The sexual cycle (**gametogony**) also occurs in the cat's intestine where the micro and macrogametocytes produces; the union of the two types produce a zygote which develops to oocyst exit with the feces of the cat. This oocyst requires many days to transform to infective.

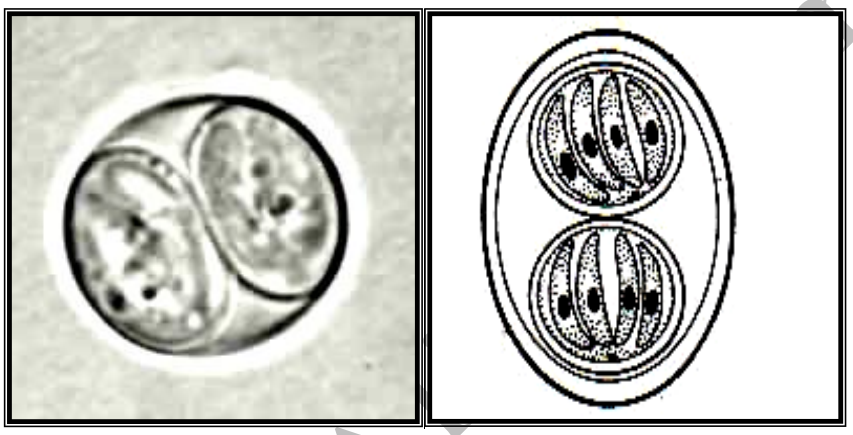



**Schizogony and Gametogony cycles.**

During the primary infection of the cats, for a period of 1-2 weeks, the cat sheds unsporulated oocysts that measure approximately 10 by 12µm. Sporulation at room temperature 20 to 22˚C requires 3-4 days; during this time the zygote divides into two sporocysts, each with a sporoblast. Four sporozoites are formed within each of these sporocysts. The ripe, infective oocyst thus contains two sporocysts each with four sporozoites arranged into two groups.



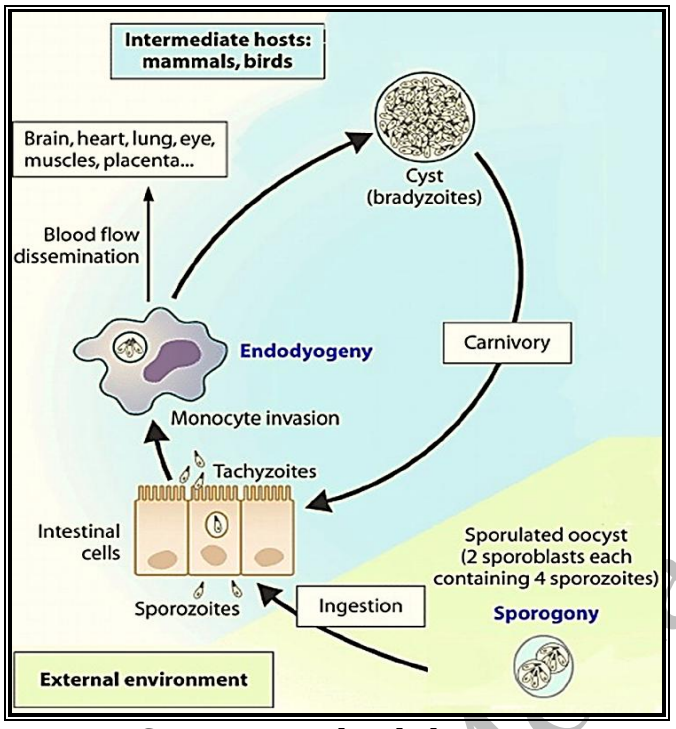

***Toxoplasma gondii*, unsporulated and sporulated oocyst structure.**



***Toxoplasma gondii*, magnified sporulated oocyst.**

These oocysts could stay infective for at least one year in the environment and are remarkably resistant to the disinfectants, freezing and drying, but are killed by heating to 70˚C for 10 minutes.

When these oocysts are ingested by other mammals, birds, or it could contaminate the human foods, an acute infection will occur. The sporozoites will be free because of the digestive juice action of the stomach and the intestine. They will reach to different sites in the body throughout the blood. It enters the brain, striated muscle, cardiac muscle, the liver, the spleen and the lung. The parasite will multiply there by endodyogeny and produce trophozoites crescent in shape (**tachyzoites**). These tachyzoites localize there and develop then into tissue cyst **bradyzoites**. In the human host these cysts most common in the skeletal muscle, myocardium, brain and eyes; they may remain throughout the life of the host. The cysts usually ranged in size from 5-50µm in diameter. They are usually spherical in the brain but more elongated in cardiac and skeletal muscles.




**Sporogony and endodyogeny**

The trophozoites that present in the animal muscles or inside the cysts containing the trophozoites considered the main source to the carnivores' infection, while the oocysts discharged with the cat feces infects the herbivores. Humans can become infected by any of several routes:

1. Eating undercooked meat of animals harboring **tissue cysts**.
2. Consuming food or water contaminated with cat feces or by contaminated environmental samples containing **sporulated oocyst** (such as fecal-contaminated soil or changing the litter box of a pet cat).
3. Blood transfusion or organ transplantation.
4. The human fetus could be infected through congenital infection (transplacentally) from the mother.
5. Accidental inoculation of **tachyzoites**.

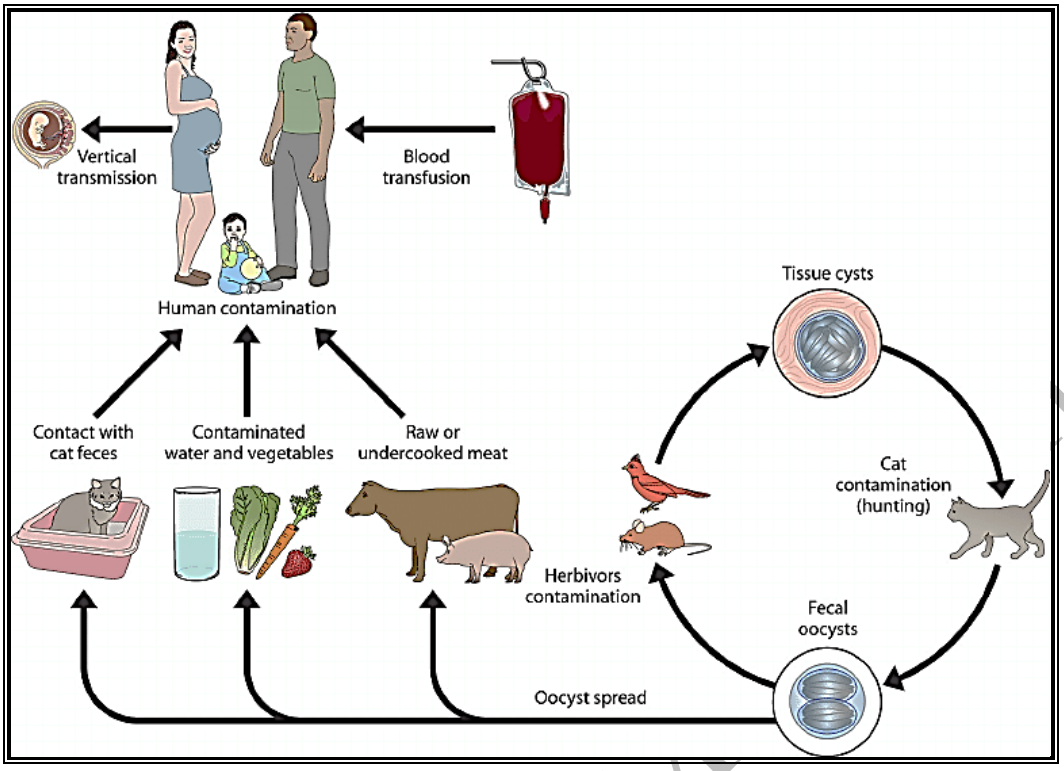
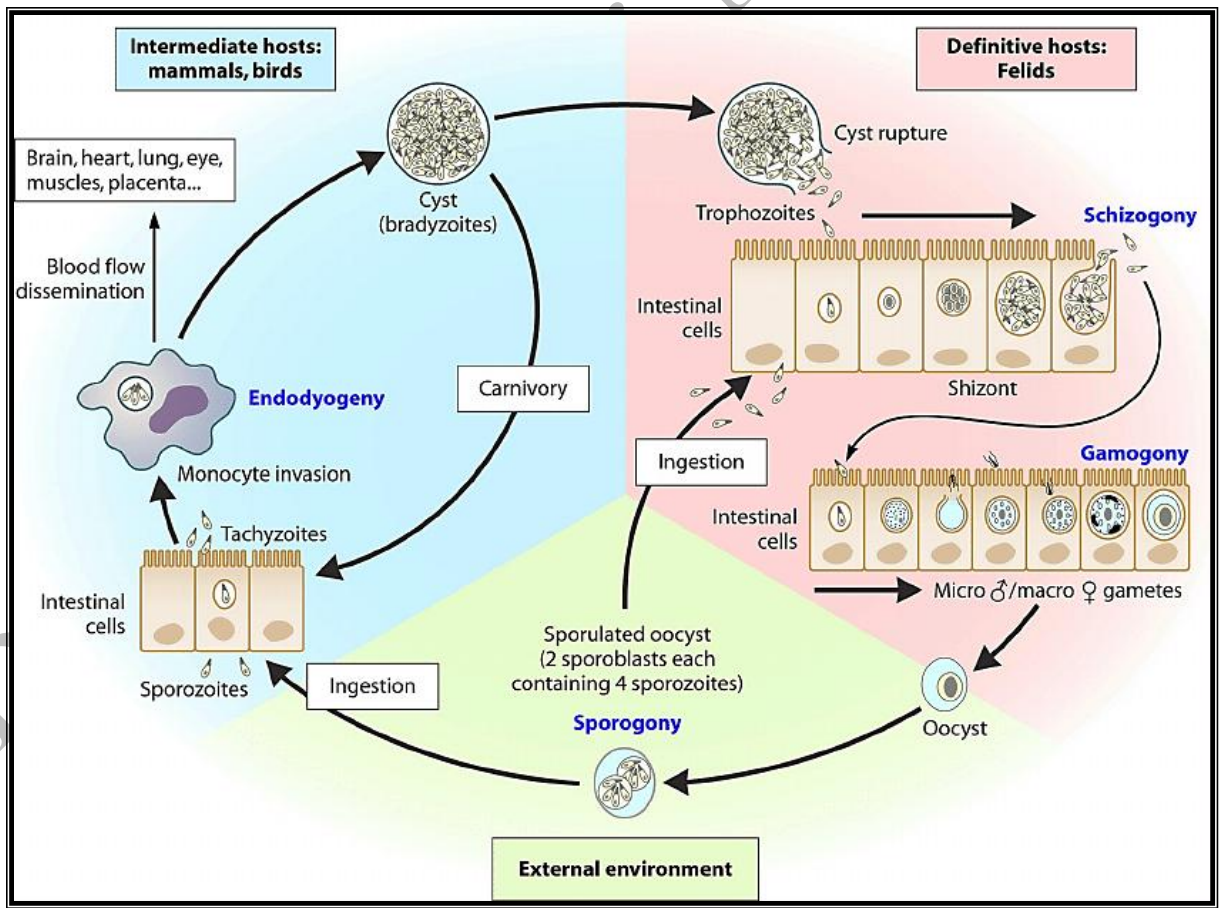



**Diagram for the routes of infection of *Toxoplasma gondii***




**Scheme for the life cycle of *Toxoplasma gondii***

## Symptomatology and pathology (Clinical Features)

Acquired infection with *Toxoplasma* in immunocompetent persons is generally an asymptomatic infection. However, 10% to 20% of patients with acute infection may develop cervical lymphadenopathy and/or a flu-like illness. The clinical course is usually benign and self-limited; symptoms usually resolve within a few weeks to months.

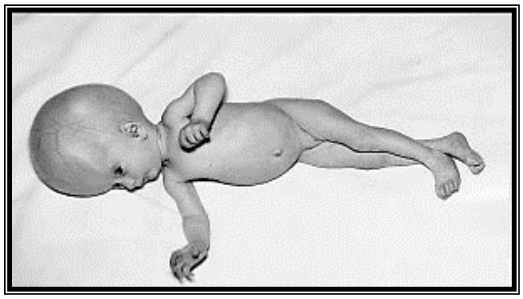
Toxoplasmosis may be classified as **acute**, **subacute**, **chronic**, or congenital. **Acute toxoplasmosis** in humans is characterized by parasitic invasion of the mesenteric lymph nodes and liver parenchyma. The most common symptom is painful, swollen lymph glands in the cervical and subclavicular regions, frequently accompanied by fever, headache, anemia, muscle pain and sometimes pulmonary complications. The tachyzoites proliferate in many tissues and tend to kill host cells rapidly. When cells from sites such as the retina or brain are involved, serious lesions often develop.

**Subacute toxoplasmosis** is merely a prolongation of the acute stage. Normally, the duration of the chronic stage is limited by the host's immunological system. However, if immunity develops slowly, the course of clinical toxoplasmosis can be extended. During this period, tachyzoites continue to destroy cells, producing extensive lesions in the lung, heart, liver, brain and eyes. Damage is usually greater to the central nervous system than to non-nerve tissues because of lower immunocompetence in the former.

Toxoplasmosis becomes **chronic** when immunity in the host becomes sufficient to suppress tachyzoite proliferation, accompanied by the formation of **zoitocysts** (the tissue cysts that contain the bradyzoites). The zoitocysts may remain intact for years, producing no clinical symptoms. However, a zoitocyst wall may occasionally rupture, releasing the bradyzoites. Most of which are destroyed by host responses, although some may penetrate cells and form new zoitocysts. The death of bradyzoites elicits a hypersensitive response. In the brain, nodules of glial cells gradually form at the sites of such reactions. In cases in which there are sufficient numbers of such nodules, the victim may develop symptoms of chronic encephalitis, sometimes accompanied by spastic paralysis. This is especially true in AIDS (acquired immune deficiency syndrome) patients, in whom *Toxoplasma* can cause severe brain damage. The presence and rupture of pseudocysts in the retina and choroid can lead to blindness. Chronic toxoplasmosis can also cause myocarditis, leading to permanent heart damage and pneumonia.

**Congenital toxoplasmosis** results from fetal transplacental infection. Such infection may result in stillbirth or a number of severe birth defects. Approximately 12% of infected infants

born alive die shortly after birth, and fewer than 20% of those surviving are normal by age 4. Abnormalities occur in the central nervous system, eyes and viscera with symptoms such as jaundice, microcephaly and hydrocephaly appearing at birth or shortly thereafter.



**hydrocephaly**

The incidence and severity of congenital toxoplasmosis vary with the trimester during which infection was acquired. Because treatment of the mother may reduce the incidence of congenital infection and reduce sequelae in the infant, prompt and accurate diagnosis is important.

At birth or shortly thereafter, the infants commonly have evidence of retinochoroiditis, cerebral calcification and occasionally hydrocephalus. Many infants with subclinical infection at birth will subsequently develop signs or symptoms of congenital toxoplasmosis. The most common form of toxoplasmosis acquired postnatally is manifested by lymphadenitis, fever, headache, splenomegaly, myocarditis, meningeoencephalitis and a typical pneumonia. Death often occurs in such cases and abortion for pregnant women.

It has been established that the following affect the level of pathology:

1. The age of the host, with older hosts being more resistant to the disease.
2. The virulence of the strain of *T. gondii* involved.
3. The natural susceptibility of the host.
4. The degree of acquired immunity of the host.

## Host immune response

Toxoplasmosis is considered an opportunistic disease. During the acute stage, IL-12 from activated macrophages along with TNF-α induces the natural killer (NK) cells to produce IFN-γ. The IFN-γ and TNF-α in turn activate anti-*Toxoplasma* activity in macrophages. $CD4^+$ and $CD8^+$ T cells are not involved in the innate immunity response.

During the chronic stage, acquired immunity to *T. gondii* exhibits inflammatory characteristics associated with Th1 type responses. In this instance, $CD8^+$ T cells and IFN-γ play major roles.

## Diagnosis

Diagnosis is usually achieved by serological tests using killed antigens, although tissue cysts may be observed in stained biopsy specimens. Diagnosis of congenital infections can be achieved by detecting the *T. gondii* DNA the in amniotic fluid using molecular methods such as the PCR. The diagnosis of toxoplasmosis may be documented by:

1. Serologic testing is the routine method of diagnosis, ex ELISA, IgG and IgM antibodies detection which is most commonly used today.

Newborn infants suspected of congenital toxoplasmosis should be tested by both an IgM and an IgA capture. Detection of *Toxoplasma*-specific IgA antibodies is more sensitive than IgM detection in congenitally infected babies.

2. Observation of the parasites in patient specimens, such as bronchoalveolar lavage material from immunocompromised patients, or lymph node biopsy.

3. Detection of parasite genetic material by the PCR, especially in detecting the congenital infections in the uterus.

## Treatment

Symptoms will usually go away within a few weeks. Treatment may be recommended for pregnant women, persons who have weakened immune systems, or persons with ocular disease or severe illness.

**Adult dosage:** Pyrimethamine 25-100 mg/day for 3-4 weeks plus Sulfadiazine 1-1.5g/four times a day for 3-4 weeks

**Pediatric dosage:** Pyrimethamine 2 mg/kg/day, then 1 mg/kg/day (max. dose 25 mg/day for 4 weeks) plus Sulfadiazine 100-200 mg/kg/day for 3-4 weeks

**Spiramycin**