

## Parasitic Pathogens Affecting the CNS

### Medical Microbiology 201

Several protozoan and helminth parasites can affect the central nervous system. In some cases the parasite may have a tropism for the central nervous system (CNS) and this represents the primary affect of the pathogen. In many cases, though, the pathogen does not exhibit a specific tropism for the CNS and affects many other organs and tissues. However, the symptoms associated with the invasion of the CNS tend to be more pronounced.

#### Protozoan pathogens affecting the CNS

Among protozoa that affect the CNS (Table), the most notable is probably *Toxoplasma gondii*. Generally infections with *Toxoplasma* are quite benign and generally only cause problems in patients exhibiting an immunocompromised state (see below).

<b>Protozoa Affecting the Central Nervous System</b>	
<b>Protozoan</b>	<b>Disease</b>
<i>Toxoplasma gondii</i>	associated with congenital defects and AIDS
African trypanosomes	African sleeping sickness
<i>Plasmodium falciparum</i>	cerebral malaria
<i>Entamoeba histolytica</i>	rare invasion of the brain
Free-living ameba	rare cases

African trypanosomes initially are found in the blood and can cause a febrile illness. The parasites can also invade other tissues including the CNS. *Trypanosoma rhodesiense* causes a rapidly progressing disease in which the invasion of the CNS occurs over weeks. The more common *T. gambiense* will exhibit an acute blood stage lasting several weeks followed by a slow progression to a chronic disease (6-12 months). The chronic stage is initially characterized by invasion of the lymphatics. The parasites will later cross the blood brain barrier and invade the CNS. The resulting disease is described as a meningoencephalitis and is associated with various neurological impairments. If not treated, these nervous impairments tend to worsen until progressing to coma and death.

Malaria is also a disease primarily associated with the blood and febrile illness. *Plasmodium falciparum* can cause a more severe disease affecting the CNS known as cerebral malaria. Cerebral malaria is characterized by an impaired consciousness. The presenting symptoms are severe headache followed by drowsiness, confusion, and ultimately coma. Convulsions are also frequently associated with cerebral malaria. Erythrocytes infected with *P. falciparum* cytoadhere to endothelial cells of capillaries which results in their sequestration in tissues. This sequestration of the infected erythrocytes in the cerebral microvasculature is believed to contribute to the clinical manifestations associated with cerebral malaria. For example, the sequestered infected erythrocytes can block the capillaries leading to hypoxia. The actively metabolizing parasite can also deplete the local glucose levels and produce a lactic acidosis. In addition, proinflammatory cytokines, such as tumor necrosis factor- $\alpha$ , may also participate in the pathophysiology of cerebral malaria.

*Entamoeba histolytica* is normally an infection of the large intestines. However, the ameba can also become extra-intestinal and metastasize to other tissues with the liver being the most

commonly affect organ. On occasion the ameba and invade the CNS causing neurological manifestations. Extraintestinal amebiasis is a relentless and progressive disease which will result in death if untreated.

There are some free-living ameba, which are normally found in soil and water, that can cause disease (Table). This is a rare event in which the ameba gain access to the CNS and cause serious disease.

**Free-Living Ameba Capable of Causing Human Disease**

<b>Ameba</b>	<b>Niche</b>	<b>Disease</b>
<i>Naegleria fowleri</i>	fresh water	acute primary amebic meningoencephalitis (PAM)
<i>Acanthamoeba</i> species	soil and water	chronic granulomatous amebic encephalitis (GAE); skin or lung lesions; amebic keratitis
<i>Balamuthia mandrillaris</i>	soil	sub-acute or chronic GAE; skin or lung lesions

*Naegleria fowleri* produces a fulminant, and almost always fatal, acute meningoencephalitis in persons who were previously in excellent health. Almost all reported cases have been associated with swimming in warm or heated waters a few days prior to the onset of symptoms. The portal of entry appears to be the olfactory neuroepithelium in the nasal cavity. The trophozoites probably migrate along the olfactory nerves into the brain. The symptoms of PAM resemble bacterial meningoencephalitis and PAM is generally characterized by a sudden onset of headache and fever. Nausea, vomiting and other symptoms related to increase intracranial pressure may also be evident. There is a rapid progression from headache and fever to coma. Occasionally seizures are observed and death is the usual outcome.

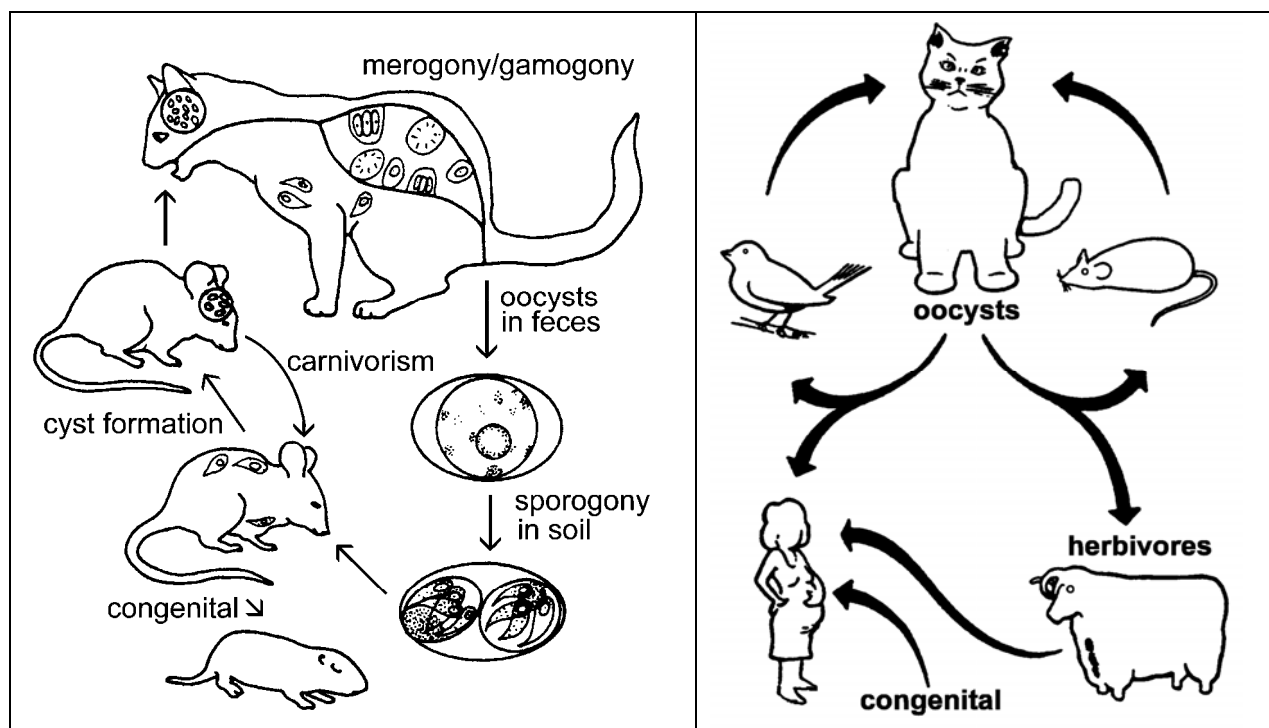
*Acanthamoeba* have been associated with infections of the CNS, skin, lungs and eyes. Infections of the CNS are generally associated with an immunocompromised state or diminished health. The portal of entry for *Acanthamoeba* is not known but believed to be either the respiratory tract via inhalation of cysts or through wounds in the skin that become contaminated by soil. Presumably the trophozoites disseminate by either a hematogenous route or a perivascular route in which the amebas crawl along the outside of the blood vessels. The onset of symptoms is often insidious and the clinical manifestations include subtle headache, personality changes and slight fever. GAE has a prolonged clinical course and can take weeks to months to progress to coma and death. Diagnosis is difficult and usually done at autopsy.

*Balamuthia mandrillaris* causes similar clinical manifestations as *Acanthamoeba*. However, in contrast to *Acanthamoeba*, *Balamuthia* can cause a subacute-to-chronic infection which is more rapidly progressing. In addition, *Balamuthia* appears more capable of infecting healthy individuals. A primary lesion in the respiratory tract or skin has been noted in many of the infections suggesting that the infection is acquired via inhalation or via breaks in the skin.

## Toxoplasmosis

*Toxoplasma gondii* is a coccidian parasite which infects humans as well as a wide variety of mammals and birds. It exhibits a predator-prey type life cycle and felines are the only definitive host. Toxoplasmosis is found throughout the world, except for extremely cold or dry climates, but tends to be more prevalent in tropical climates. Serologic studies have shown prevalence rates up to 70% by the age of 25 in some central American populations. In the United States an estimated 0.5-1% of the population becomes infected each year and prevalence ranges from 10-25% by the age of 25. Toxoplasmosis is most often a benign disease. Noted exceptions are in the cases where the infection was acquired congenitally or in immunocompromised individuals.

Life cycle and transmission. *Toxoplasma* has a complex life cycle consisting of intestinal and tissue phases. The intestinal phase of the infection occurs only in felines and exhibits a typical coccidian life cycle consisting of merogony and gamogony. Merogony is an asexual reproduction which occurs within the intestinal epithelial cells resulting in the production of merozoites. These merozoites are released from the intestinal epithelial cells and then reinvade other intestinal epithelial cells. As an alternative to this asexual reproduction, the parasite can undergo a sexual process known as gamogony resulting in the production of micro- and macro-gametes. The gametes will fuse and develop into oocysts which are excreted in the feces. These immature and non-infective oocysts undergo a process known as sporogony at ambient temperature resulting in the formation of sporozoites. This maturation to the infective oocyst generally takes 1-4 days. The sporulated oocysts remain infective for months in shaded moist soil.



Intermediate hosts, such as rodents and birds, become infected through the ingestion of sporulated oocysts. Sporozoites are released, penetrate the intestinal epithelium, and invade macrophages and other types of cells. These intracellular forms are called tachyzoites and cause the acute

stage of the infection. Tachyzoites replicate within the host cell by binary fission. The host cell will rupture and release the tachyzoites which will invade new host cells and repeat the replicative cycle. Infected macrophages will disseminate the tachyzoites throughout the host during this acute infection. As the host develops immunity the replication rate will slow and the infected host cells will become encapsulated (ie, form tissue cysts). These slowly replicating forms are called bradyzoites and represent a dormant or resting stage. Bradyzoites are viable, but metabolically quiescent. The bradyzoites are primarily found in brain and muscle tissue, whereas the tachyzoites tend to be in reticuloendothelial cells (eg., liver and spleen). The bradyzoite stage represents a chronic infection and probably persists for the life of the host.

The tissue phase of the infection can also be transmitted congenitally to offspring and to other intermediate hosts through carnivorousism. Ingestion of an infected animal will release the bradyzoites from the tissue cysts which then infect cells in the new host. The course of the infection is the same whether oocysts or tissue cysts are ingested. In other words, the parasites will go through an acute phase characterized by rapid replication of tachyzoites until the new host develops immunity. This will be followed by a chronic phase characterized by dormant tissue cysts containing bradyzoites. Ingestion of an infected intermediate host by the cat will initiate the intestinal stage of the life cycle involving merogony and gamogony in the intestinal epithelial cells. Cats can also support the tissue stage of the infection if they ingest oocysts.

In regards to human transmission, infections are primarily acquired through the ingestion of food of water contaminated with oocysts or the ingestion of undercooked meat infected with tissue cysts. Most infections in the United States and Europe among adults are probably acquired from undercooked meat. The especially high seropositive rate in France (up to 90%) is likely due to a cultural predilection for lightly cooked or raw meat. Mutton and pork are more common sources than beef. *Toxoplasma* can also be transmitted from mother to fetus, often with dire consequences (see below). Transmission of *Toxoplasma* as a result of organ transplants is also possible. Tissue cysts from a chronically infected organ donor reactivate when transplanted into a previously uninfected organ recipient. In addition, the immunosuppressive therapy can also reactivate a latent infection in the recipient. Transmission by transplantation is now rare, though, due to screening of donor and recipient before transplantations. Acquisition of tachyzoites from an acutely infected person via blood transfusion is also possible, but rare.

Clinical features. Toxoplasmosis in adults and children past the neonatal stage is usually benign and approximately 80% of infected persons are asymptomatic. Acquisition of the infection via either oocysts or tissue cysts results in an acute infection in which tachyzoites are disseminated throughout the body via the lymphatics and hematogenously. This acute stage will persist for several weeks as immunity develops. Antibody production requires 1-2 weeks and cellular immunity occurs 2-4 weeks post-infection. Both humoral and cellular immunity are important, but the cellular response appears critical for the conversion from acute (ie, tachyzoites) to chronic (ie, bradyzoites) infection. When symptoms do occur they are generally mild and typically described as mononucleosis-like (i.e., chills, fever, headache, myalgia, fatigue and swollen lymph nodes). A chronic lymphadenopathy without fever persisting or recurring for up to a year has also been noted as a symptom of toxoplasmosis. Rarely do immunocompetent individuals exhibit severe symptoms and the acute infection almost always progresses to the chronic stage. This latent chronic-stage infection probably persists for the life of the patient without producing any progressive pathology.

Congenital (ie, transplacental) infections are more likely to be symptomatic and can be severe. Congenital transmission can only occur during an acute infection (ie, tachyzoites) acquired during pregnancy. Mothers with a chronic infection acquired before the pregnancy are not at a risk for transmitting *Toxoplasma*. One-third of mothers acquiring the infection during pregnancy will pass the infection to fetus. Severity of disease varies with age of fetus and is more severe early in pregnancy. However, transmission is more frequent later in pregnancy. Congenital infection can result in: spontaneous abortion, premature birth, or full-term birth with or without overt symptoms. Typical disease manifestations include: retinochoroiditis, psychomotor disturbances, intracerebral calcification, hydrocephaly, and microcephaly. Ocular symptoms due to retinochoroiditis are particularly common. Twenty percent will exhibit symptoms at birth and 82% will develop symptoms by adolescence.

<b>Outcomes of Congenital Transmission</b>	
5-10%	death
8-10%	severe brain and eye damage
10-13%	moderate-severe visual impairments
58-72%	asymptomatic at birth with some developing retino-choroiditis or mental impairments later

Toxoplasmosis has been long noted as an opportunistic infection in regards to reactivation of latent infections due to immunosuppression associated with organ transplants and certain cancer treatments. During the 1980's toxoplasmic encephalitis emerged as a common complication associated with AIDS. Early symptoms of toxoplasmic encephalitis can include headache, fever, lethargy, and altered mental status with progression to focal neurological deficits and convulsions. The disease is almost always due to a reactivation of a latent infection. In other words, the tissue cysts rupture and the release bradyzoites which transform into tachyzoites. The focal lesions are caused by the destruction of host cells in the immediate vicinity of the reactivated tissue cyst. This reactivated infection tends to remain confined to the CNS and does not spread to other organs. Other forms of the reactivated disease, especially retinochoroiditis, pneumonitis, myocarditis and myositis, may occasionally occur in conjunction with immunosuppression.

Diagnosis, treatment and prevention. Diagnosis of toxoplasmosis is rarely made through the detection or recovery of organisms, but relies heavily on serological procedures. Parasites can be detected in biopsied specimens, buffy coat cells, or cerebral spinal fluid. These materials can also be used to inoculated mice or tissue culture cells. However, detecting tachyzoites from these materials is difficult.. Therefore, serologic tests are recommended for diagnosis.

The serologic diagnosis of *Toxoplasma* is also complex because of the prevalence of sero-positive individuals. High antibody titers by themselves are not definitive evidence of an acute infection. Congenital infections are similarly difficult to diagnose serologically because maternal IgG crosses the placenta and persists for several months. Acute infections are characterized by high IgM titers and/or a significant increase in total antibody titer in a sample taken two weeks later. The serology may also correlate with the acute stage symptoms in some individuals. Lack of IgM and lack of changes in the total antibody titers in serial samples is more consistent with the chronic stage of the infection. Imaging techniques, such as computed tomography (CT) scanning and magnetic resonance imaging (MRI), are useful in the diagnosis of toxoplasmic encephalitis. Most of the patients have multiple ring and/or nodular enhancing lesions with edema. The detection of these lesions combined with serology or symptoms can be used to diagnose toxoplasmic encephalitis.

Most patients are started on a combination therapy of pyrimethamine (Daraprim®) and sulfadiazine. Clindamycin (Cleocin®) can be substituted for the sulfadiazine in patient not tolerating sulfa drugs. Spiramycin is recommended for prophylactic use during pregnancy. The exact treatment strategy depends on the patient's situation (Table). Symptomatic patients, including those with active retinochoroiditis, should be treated until manifestations have subsided and there is evidence of acquired immunity. Similarly, asymptomatic children under the age of five should be treated for 3-6 weeks to avoid later occurrences of retinochoroiditis. Immunocompromised patients must be treated and therapy should continue for 4-6 weeks after cessation of symptoms. This should then be followed by prophylaxis for as long as the immunosuppression lasts. AIDS patients should also be supplemented with folic acid (Leucovorin®). Corticosteroids to suppress inflammation are co-administered to patients with ocular toxoplasmosis.

**Treatment Strategies for Toxoplasmosis**

<b>Condition</b>	<b>Duration</b>	<b>Comments</b>
symptomatic disease	until symptoms subside and evidence of immunity	
active retinochoroiditis	until symptoms subside and evidence of immunity	+ corticosteroid (anti-inflammatory)
asymptomatic children (<5 years)	3-6 weeks	prevents retinochoroiditis
immuno-compromised	4-6 weeks after symptoms subside + continued prophylaxis	+ folic acid in AIDS

The prognosis for acute toxoplasmosis in immunocompetent adults is excellent. Acute infections in the fetus or young children may be followed by repeated attacks of retinochoroiditis. Treatment does appear to reduce the frequency of these attacks. If begun early enough, treatment of immunosuppressed patients usually results in improvements, but recrudescences are common.

Control measures for toxoplasmosis focus on avoiding the two major sources of infection: raw meat and material contaminated with cat feces. Cooking meat thoroughly (at least 150°F) and washing hands after handling raw meat will prevent infection with tissue cysts. Activities to reduce infective oocysts include: cleaning the cat litter box within 24 hours, covering sand boxes, and controlling strays. Always keeping cats indoors will reduce the chances of the cat becoming infected. Prevention is especially important during pregnancy when the consequences of infection are most severe.

## Cysticercosis

Many helminthes migrate throughout the body and therefore also invade the brain where they will often result in neurological symptoms. Most of these helminthes are found predominantly in other organs (Table). The exception is *Taenia solium*, or the pork tape worm, in which 60-90% of infected individuals will exhibit an involvement of the CNS. It is the greatest cause of acquire epilepsy worldwide. The disease is referred to as either cysticercosis or neurocysticercosis depending on whether the CNS is involved.

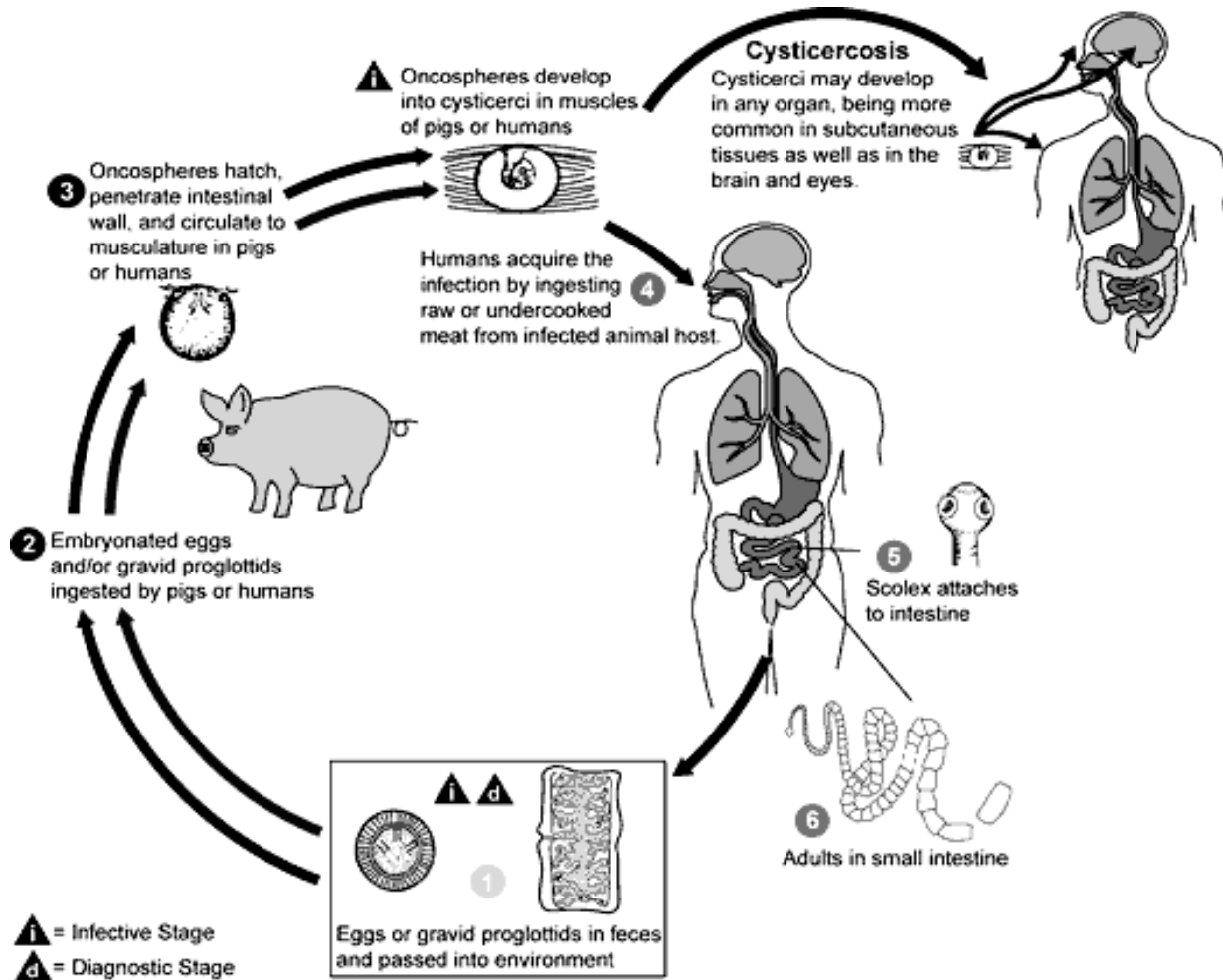
Helminthes Affecting the CNS		
Disease	Agent	Predominant Tissues
Cysticercosis	<i>Taenia solium</i> (pork tape Worm)	muscle and brain
Hydatid Disease	<i>Echinococcus</i> species	liver (75%) and lungs (15%)
Schistosomiasis	<i>Schistosoma</i> species	liver and bladder
Paragonimiasis	<i>Paragonimus</i>	lung
eosinophilic meningitis	<i>Angiostrongylus cantonensis</i> (rat lung worm)	lung
	<i>Gnathostoma spinigerum</i>	various organs

*Tanium solium* exhibits a worldwide distribution. It is especially common in Mexico, Central and South America, south-east Asia, China, elsewhere in Asia, and elsewhere where pig and pork products are consumed. More recently, cysticercosis has become an important parasitic disease in the United States, particularly in California and other states with a large immigrant population from Mexico and Central America. It is estimated that 1000 new cases of neurocysticercosis will be diagnosed each year in the United States. The increasing prevalence in this country has been attributed to the migration of large numbers of rural immigrants from developing countries to the United States. In addition, improvements in neuroimaging methods have led to better diagnosis.

Life cycle. The life cycle of *T. solium* involves the pig as the intermediate host and the human as the only definitive host. The definitive host, by definition, is the organism in which the sexually mature parasite (i.e., tapeworm) develops. Humans become infected by ingesting undercooked or raw pork infected with the cyticercus stage. The cysticercus is comprised of a fluid-filled bladder and an inverted scolex (i.e., head). Cysticerci are released in the stomach and the scolex everts and attaches to the mucosa of the small intestine. Attachment is mediated by suckers and a row of hooks on the scolex. Over the next 3-4 months the tapeworm will grow to its full length of several meters through the production of proglottids. Proglottids are segmental units which will extend down the small intestine with the more mature proglottids being further from the scolex. The most terminal proglottids are most mature and contain infectious embryonated eggs. These egg-laden proglottids detach and are passed in the feces.

Pigs become infected by ingesting food or water contaminated with eggs or proglottids. The embryonated eggs hatch after passing through the stomach of the pig and the embryo known as the oncosphere is released. Oncospheres penetrate the mucosa of the stomach or small intestine and are spread hematogenously to the muscles and other tissues of the pig. Once in the tissues the oncosphere develops into a cysticercus in 9-14 weeks.

Humans can also become infected by ingesting material contaminated with *T. solium* eggs. Therefore, cysticercosis is not acquired by eating infected pork as is commonly thought, but from *T. solium* eggs passed by humans infected with the adult tapeworm. Alternately, persons infected with the adult tapeworm may become autoinfected by reverse peristalsis as the eggs or proglottids regurgitate into the stomach and are thus stimulated to hatch. Just as in the pig, the oncospheres penetrate the intestinal mucosa and are hematogenously transported to the muscles, subcutaneous tissues, eyes, or CNS of humans.



Clinical disease and pathology. Ingestion of undercooked pork infected with cysticerci leads to taeniasis. The majority of patients are free of symptoms. Abdominal pain, distension, diarrhea and nausea have been attributed to tapeworm infections. However, there are no controlled data that clearly demonstrate an association between these symptoms and the tapeworm.

Cysticercosis is infection with the larval stage of the parasite which is acquired through the ingestion of eggs. The oncospheres cross the gut epithelium and are carried by the blood stream to various tissues and organs. Cysticerci may be present in large numbers in any tissue or organ of the body. Common sites include the brain, subcutaneous tissues, and eyes. Cysticerci

reach their final size of approximately one cm in 2-3 months and may live as long as five years. Outside of the central nervous system and eyes, cysticercosis does not result in major pathology. Subcutaneous infections present as small painless nodules that are most commonly observed in the arms and chest. The nodules may become swollen, tender and inflamed after a few months or years and then gradually disappear.

Invasion of the central nervous system (i.e., neurocysticercosis) is an important cause of human morbidity, and occasional mortality. Although this parasite is generally well tolerated while it is alive, its death triggers inflammation and edema. The clinical presentation of neurocysticercosis is varied and depends on the stage, number, size and locations of the cysticerci with the CNS and the immune response against the parasite. Epileptic seizures are the commonest manifestation of neurocysticercosis. Seizures occur in 50-80% of patient with brain cysts. Neurocysticercosis can also present with intracranial hypertension or hydrocephalus. These syndromes are related to a blockage of the circulation of cerebrospinal fluid (CSF). Occasionally a cyst will grow larger than the usual 1-2 cm and will mimic a tumor.

Diagnosis, treatment and prevention. The onset of seizures in healthy persons from endemic areas is suggestive of neurocysticercosis. Imaging techniques such as CT scans and MRI are useful for the identification of cysticerci within in the brain. The cysticerci may also be associated with edema and inflammation. Serological tests can also be used to detect *T. solium* antibodies in the serum or CSF. However, there are problems with sensitivities and cross-reactions with other parasitic worms. Accurate diagnosis depends on a combination of clinical, epidemiologic, radiographic and immunological information.

Extraneural cysticercosis is a benign condition and does not require specific treatment. Praziquantel (50 mg/ kg body weight, daily for 15 days) or albendazole (15 mg/kg body weight, daily for 30 days) are the recommended drugs for neurocysticercosis. Since the death of the parasite can elicit the symptoms, anti-inflammatory drugs, such as dexamethasone or prednisone, can be co-administered. Antiepileptic drugs such as phenytoin and carbamazepine may help prevent the seizures. Previously, surgical excision of the cysts was the standard treatment.

Improved personal hygiene is a key element in the prevention of cysticercosis in that this represents a typical fecal-oral type of transmission. In addition, thoroughly cooking pork will prevent taeniasis and the risk of auto-infection as well as minimizing transmission to other persons. Control measures to lower the incidence of disease include better disposal of human feces to prevent the infection of pigs. Agricultural inspection of pork may also lower the incidence. A vaccine for pigs is also being currently developed.

Mark F. Wiser, Ph.D.  
Department of Tropical Medicine  
wiser@tulane.edu  
<http://www.tulane.edu/~wiser/T2.html>