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Helminthiasis

Summary

Roundworms or nematodes:

- Separate sexes
- Adult in intestine lumen or larvae in tissue
- Some species have lung passage of larvae
- Transmission faecal-oral (directly or indirectly, e.g. via food), transcutaneous
- Filaria are part of the nematodes

Tapeworms or cestodes:

- Hermaphrodite adults in the intestine or larvae in the tissues
- Transmission faecal-oral or via food

Flukes or trematodes:

- Most are hermaphrodite, except blood flukes (= schistosomiasis)
- Are found in blood vessels, the intestine, biliary tract, lungs
- Transmission via food (distomatoses) or transcutaneous (schistosomes)
- First intermediate host is always a freshwater snail

Worms, Life cycles

All intestinal roundworms (nematodes) have a fairly complex cycle, but almost always without an intermediate host (Capillaria phillipinensis is an exception = mainly through the ingestion of raw fish). The lack of an intermediate host which can only live in a well-defined ecosystem, explains the cosmopolitan character of intestinal nematodes. All intestinal nematodes have separate sexes and lay eggs which can be found in faeces. Sometimes only the female survives in the intestine. In Strongyloides larvae hatch before they arrive in the outside world. The larvae of nematodes have several consecutive development stages.

Larval tissue nematodes: The larvae of some nematode species infect various human tissues.
These are accidental infections and do not represent the natural life cycle of the parasite. The larvae of canine and feline roundworms (Toxocara sp.) and also those of Gnathostoma may penetrate humans “by mistake” and cause visceral larva migrans. The larvae migrate through the liver, eyes, brain and so on, where they cause a granulomatous inflammatory reaction.

*Trichinella* larvae are found in the muscles and the heart.

- Filaria are a separate group. They are live-bearing (do not lay eggs) and generally their intermediate hosts are insects.

**All flukes** (trematodes) have a cycle with an obligatory intermediate host. The first intermediate host of these flatworms is always a freshwater snail. The larvae which comes from the snail then, depending on the species either infects a second intermediate host (fish, crab), encysts on certain plants or penetrates the final host directly through the skin. It is precisely the presence of the intermediate host which determines whether a particular fluke can be present or not in any given area. All food-borne trematode infections are zoonoses. Infestations by flukes are always via larval forms, never via eggs. Except for schistosomes all trematodes are hermaphrodite (no separate sexes).

**All tapeworms** (cestodes) are parasites which are found in the intestinal lumen as adults. They are hermaphrodites. Each animal has both testes and ovaries. They have a head (scolex) and body segments (proglottids). There is generally only one adult worm in the intestinal tract (Fr.: ver solitaire = tapeworm) but multiple infections do occur. The larval forms of these worms (hydatid, cysticercus) may be located in various organs.

**Worms, Transmission**

Several ways of infection are possible:

**Oral transmission**

- **Human faeces.** Faecal-oral transmission is important in several worm infections. Soiling by infected human faeces is responsible for infestation by *Ascaris, Enterobius, Trichuris*, cysticercus larvae (larval *T. solium*). Larvae from hookworms and *Strongyloides* may also be ingested orally.

- **Animal faeces.** Humans become infected with the eggs of *Toxocara* (visceral larva migrans) and *Echinococcus granulosus* (hydatid cysts) by eating products which have been contaminated by animal
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excreta.

**Infected meat.** Eating raw or insufficiently cooked meat which contains larvae, leads to infection by *Trichinella*, adult *Taenia* and *Gnathostoma*.

**Infected fish.** Eating raw or insufficiently cooked fish [Latin American ceviche, Japanese sushi and sashimi, Dutch maatjesharing (herring), Norwegian gravlax (salmon), Hawaiian lomi-lomi (raw salmon), Spanish boquerones (anchovies in vinegar)] may lead to infection with: (1) nematodes such as *Anisakis* or *Pseudoterranova* larvae, *Capillaria philippinensis*, *Gnathostoma*; (2) cestodes such as *Diphyllobothrium* (fish tapeworm) and *Diplogonoporus*; (3) trematodes such as *Metagonimus* and *Heterophyes* (small intestinal flukes), *Clonorchis* and *Opisthorchis* (liver flukes).

**Infected crabs and crayfish.** Eating larvally infested, raw or insufficiently cooked crabs may lead to paragonimiasis (lung fluke).

**Contaminated plants.** Infection with the giant intestinal fluke (*Fasciolopsis*) occurs via the consumption of several kinds of raw plants e.g. waternut and water chestnut on which larvae are encysted. *Fasciola hepatica* (liver fluke) is transmitted via contaminated water cress.

**Contaminated water.** Drinking water containing *Cyclops* (small crustaceans) infected with *Dracunculus* leads to Guinea worm infection.

### Skin Penetration

Larvae of *Strongyloides* and hookworm enter through the skin from the soil. They then penetrate deeper. The hookworm *Ancylostoma braziliense* also penetrates skin but cannot go deeper. It stays in the skin and give rise to cutaneous larva migrans. *Schistosoma* cercariae penetrate the skin when humans come into contact with infested water.

### Through a vector

Filaria are transmitted by the bite of various Diptera: mosquitoes and flies. *Dracunculus* has *Cyclops* as its vector a small crustacea.
Diagnosis

General

It is important to bear in mind that many worm infections may be diagnosed by simple examination of the faeces, sputum, urine, blood or skin. Helminths which produce a large numbers of eggs or larvae are naturally easier to identify than infections with only a few eggs or larvae. In the latter case it is helpful to enrich the volume of the parasitic material to be examined, by means of concentration techniques. In this way it is possible to make a diagnosis in many patients who have a low worm load.

The tests mentioned above cannot however produce a diagnosis in the following cases:

- Infection with immature parasites. In acute Katayama fever no eggs are found early in the disease.
- Infections with male worms. This is why it is important to know whether or not a parasite is hermaphrodite e.g. in infections with male *Ascaris lumbricoides*.
- Infections with adult worms which are located in an enclosed space such as the brain.
- Infections with larvae where the human is the intermediate host e.g. cysticercosis, echinococcosis and visceral larva migrans. Trichinellosis may also be included here.
- Infections with old or damaged worms e.g. after use of anthelmintics.
- Many patients with loasis do not have microfilariae in their blood

Microscopic recognition of worm eggs

Recognition of worm eggs requires training, practice and experience. Otherwise it is possible to interpret a certain microscopic structure wrongly for years (quality control is important).

Size. Since infections with *Ascaris lumbricoides* are so common the size of a fertilised egg (60 µm) can be used as a reference measure. If no special microscopic eyepiece is available to carry out measurements, the relative size of a structure can be compared to a fertilized *Ascaris* egg.

- Eggs much larger: *Fasciola hepatica*, *Fasciolopsis buski*, *S. mansoni*, *S. haematobium*
- Eggs somewhat larger: *Paragonimus*, *S. japonicum*, *Trichostrongylus orientalis*, *Hymenolepis diminuta*, *Ascaris* unfertilised egg
- Same dimensions: hookworms eggs, *Hymenolepis nana*, *Diphyllobothrium latum*
- Eggs somewhat smaller: *Trichuris*, *Enterobius*, *Taenia solium*, *T. saginata*
- Eggs much smaller: *Clonorchis*, *Metagonimus*, *Opisthorchis*.
Shape. Most eggs are symmetrical. The exceptions are those of Enterobius, Trichostrongylus orientalis, Dicrocoelium dendriticum and unfertilised Ascaris. The eggs of hermaphrodite trematodes often have an operculum this small structure is not always easy to see. Some other worms also have it (D. latum). Polar caps occur in Trichuris trichiura and Capillaria sp., giving them a lemon-like appearance. Some eggs, such as various schistosomes, have a spine. These may be large or small compared to the egg, and protrude either terminally or laterally.

Colour. Many eggs have a rather yellowish brown colour due to bile salts. Some are more or less colourless (hyaline), such as those of hookworms, T. orientalis, E. vermicularis and Ascaris (if there is no protein mantel on the egg).

Egg shell. This may be surrounded by a knobbly protein layer, as in Ascaris. In some worms the egg shell is thin, as in hookworms. In others it is thick, as in lung flukes.

Nematodes

Tissue nematodes

Trichinella sp

Summary

- Trichinellosis = Trichinosis
- Trichinella: adult worm in intestinal wall (not in the lumen), larvae in muscles and heart
- Transmission by eating infected meat, so there is never a free-living parasite
- Hypereosinophilia, fever, muscle pain, oedema chiefly peri-orbital
- Faeces negative for parasites (no eggs)
• Muscle biopsy positive for larvae
• Filaria are part of tissue nematodes

**Historical note**

In 1835 a 51-year-old Italian bricklayer died of tuberculosis in St Bartholomew’s Hospital, London. Jim Paget, a first-year student (later of “Paget’s disease” or osteitis deformans fame), was present during the autopsy and observed fine hard white inclusions in the diaphragm. Similar inclusions had been observed by doctors from time to time in the past but were attributed to commonplace muscle calcification, which quickly blunted the dissecting scalpel. Paget inspected the lesions with a hand lens and with a compound microscope in the British Museum. At the time there was only one such instrument in the entire Museum and it belonged to Robert Brown, of “Brownian motion” fame. Paget quickly recognised their worm-like structure and wrote of his discovery to his brother. After the word got out, surgeon Thomas Wormald took a second piece of the “sandy” diaphragm to Richard Owen, at that time assistant conservator of the Huntarian collection in the museum of the Royal College of Surgeons. He later become a major figure in comparative anatomy and paleontology, coining for example the name “Dinosauria”. He published the discovery of the parasite (“a microscopic entozoon”, but didn’t give the proper credit to Jim Paget. The name “*Trichina spiralis*” was suggested. This name *Trichina* had already been given to a fly, and the name was later changed to “*Trichinella*”. In 1846, the American Joseph Leidy found *Trichinella* larvae in the pork he had for dinner. He hypothesized that trichinosis is caused by consuming undercooked pork. In 1859 Rudolph Virchow carried out transmission experiments in which infected human muscle was fed to a healthy dog. After only 3 to 4 days adult *Trichinella* worms were found in the dog’s duodenum and jejunum. He also discovered that heating the meat for 10 minutes was enough to stop transmission. He started to spread the message that eating raw or lightly smoke-cured ham was dangerous. In Germany, where sausages were an important part of the daily diet, he provoked resistance from the German Veterinarian’s Society. At a public meeting when denounced by a veterinarian, he showed the public an infected piece of ham and challenged his opponent to dare to eat it. In front of the crowd the veterinarian wisely declined the offer. Virchow’s reputation grew quickly after this incident. When later challenged to a duel by Baron von Bismarck, he choose infected sausages as his weapon. The Baron declined to eat them after hearing what trichinosis was but the two men became friends later on. These days, Virchow is mainly remembered as the father of cell theory (“omnis cellula e cellula” or every living cell comes from another living cell).

PS. Robert Brown died in 1858, just before Charles Darwin received news from Alfred Russel
Wallace’s independent discovery of the role of natural selection in the evolution of animals and plants. It was Brown’s death that provided the vacant slot in the Linnean Society’s programme that allowed Darwin (spurred on by Wallace’s findings) to describe his theory (and Wallace’s) in public.

General

Geographical distribution of *Trichinella spiralis*

Map showing the areas endemic for the different subspecies of *Trichinella spiralis*: *Trichinella spiralis spiralis*, *Trichinella spiralis nativa*, *Trichinella spiralis nelsoni*. Copyright ITM

Trichinosis or trichinellosis is a zoonosis. It refers to infection with the larval and adult stages of a group of closely related nematodes which belong to the genus *Trichinella*. The infection is meat-borne. Typically pork is implicated. Other meat sources such as horses and wild game, certain birds and even reptiles increase in significance as more study results are becoming available. Carnivores and omnivores represent the most important reservoirs.
Trichinella species

There are 9 *Trichinella* species. All species can develop in mammals and some in birds or even reptiles. The parasites are widespread on all continents except Antarctica. *T. spiralis* occurs in temperate regions and infects mainly pigs. *T. nativa* occurs in the arctic and subarctic areas in terrestrial and marine carnivores (e.g. polar bear, walrus). These parasites are resistant to freezing which is important for meat storage. *T. britovi* occurs in temperate areas of the Palearctic region, as well as North and West Africa. *T. spiralis nelsoni* occurs in Africa and southern Europe with a reservoir in wild carnivores and wild pigs.
More than 100 species of mammals are susceptible to the infection. By and large pigs and horses seem to be responsible for the majority of human infections. Horses are considered herbivores, but 32% of horses tested ate meat when offered. The feeding of animal products to horses is a practice that occurs in several countries. Eating walrus meat plays a role in the arctic. On a global scale *T. spiralis* is responsible for the majority of human infections. Rats play an important part in the transmission in pig-raising areas. It is unclear if they form a true reservoir. The use of rat pesticides can actually augment transmission as poisoned rats are easy prey for pigs.
Gravid female worms embedded in the intestinal mucosa release newborn larvae. These larvae measure about 100 µm by 6 µm. These immature larvae are extracellularly exposed to the humoral immune system. The larvae migrate to the intestinal lymphatics, then enter blood vessels and subsequently penetrate striated muscle cells. Then something strange happens. After entering the muscle cell, the larvae are completely intracellular. This is unique. They will convert their host cell into a so-called nurse cell. Their metabolism is mainly anaerobic, which helps their survival after the death of the host. In the muscle cells, larvae can survive several decades. They are now called infective larvae and are visible with low magnification. Larvae do not mature or become encapsulated in heart muscle. When a new host ingests muscle tissues, the larvae are released in the stomach by digestion. In the duodenum they penetrate the villi and undergo 4 molts, developing into adults which measure about 1 mm (males) to 3 mm (females) with a thickness of about 30 µm. Males and females copulate and 6 to 7 days post-infection, the females start to produce new-born larvae. This continues for a few weeks according to the immune response of the host. Afterwards adults are expelled. It is extremely rare to find an adult worms in a human patient.

**Clinical aspects**

Light infections may be asymptomatic. About 70 live larvae are sufficient to provoke clinical disease. In more typical cases there is nausea, non-bloody diarrhoea, abdominal pain, vomiting and fever; a few days after eating infected meat. After 10 days the fever tends to increase. The patient is very ill, asthenic and debilitated, there are muscle pains and a typical peri-orbital oedema (differential diagnosis acute trypanosomiasis, angiodema, gnathostomiasis and nephrotic syndrome). This oedema is caused by invasion of the small muscles around the eye. In severe cases, oedema extends to arms and legs. Conjunctival and subungual haemorrhages may occur (due to vasculitis, not endocarditis). There may be signs of myocarditis, encephalitis, urticaria and asthma. A small number of persons may develop a maculopapular rash after the onset on muscular pain. There is often very significant eosinophilia. This lasts from several weeks to three months. A massive decrease in eosinophils in persons with severe trichinellosis predicts a severe outcome. Myositis causes an increase in the muscle enzymes (creatine phosphokinase, CK). Wandering newborn larvae can become trapped in small blood vessels leading to vasculitis and peri-vasculitis with diffuse or focal lesions in the central nervous system. Aspecific cortical and subcortical lesions (ischemia) can be identified on MRI, and much more rarely, white matter lesions (granulomatous reaction). Severe myalgia generally lasts for two to three weeks. Dyspnoea is relatively common and is primarily caused by invasion and inflammation of the diaphragm. After a few months the symptoms are reduced or disappear, although asthenia and chronic muscle pain can persist for up to 6 months. Mild infections are self-limiting but live larvae will persist in muscles for years.
Trichinella spiralis in a muscle biopsy. Copyright ITM

The clinical picture is of a patient with acute fever and myalgia, pronounced asthenia, possibly diarrhoea and a swollen face. Cardiopulmonary, neurological or renal complications may be fatal. The consumption of insufficiently cooked or raw meat can often be found in the patient’s history, and this is often game that the patient has hunted (e.g. wild boar) or raw meat eaten in Asian cuisine or the Arctic. Here it is important to consider the incubation period; one week for severe disease, two weeks for moderate disease, and three to four weeks for benign forms. Sometimes the infection can be traced to infected horsemeat. There is leukocytosis with eosinophilia, although eosinophilia can be absent in immunocompromised persons (renal graft, HIV, chronic myeloid leukaemia). Muscle biopsy should be performed (deltoid muscle or other). An infection is clinically patent in humans when the number of larvae per gram of muscle biopsy is around ten and severe when above hundred. In early
stages of infection, histology is more sensitive than trichinelloscopy. The larvae can be seen coiled inside myocytes. There are various serological techniques (e.g. ELISA, Western blotting) for identifying antibodies against Trichinella species. Serology is negative during the first days of the febrile phase (seroconversion during second to fifth week of infection). PCR can be performed in the International Trichinella Reference Centre (Instituto Superiore di Sanita, Rome, Italy). Remember that there will be no eggs in the faeces.

**Treatment**

For mild infection symptomatic treatment is often sufficient. In the early stage albendazole (800 mg/day) or mebendazole at high doses can eradicate adult worms in the intestine. Mebendazole is poorly absorbed. Albendazole 800 mg daily for 7-14 days may be used, in combination with high-dose prednisolone. With treatment the duration of the disease may be reduced to one or two weeks. Pyrantel is sometimes used during pregnancy, but its efficacy is disputed.

**Prevention**

- Meat should be well boiled or roasted through.
- Importance of meat inspection. The identification of *Trichinella* larvae in muscle samples is limited to post-mortem inspection of carcasses. Selection of muscles for sampling in meat inspection requires identification of predilection sites in a particular animal, but in low grade infection, distribution of the larvae is not homogeneous. In pigs infected with *T. spiralis*, predilection sites are the diaphragm crus, the tongue and the masseter. The diaphragm of a slaughtered animal is inspected (the piece of muscle of a certain minimum weight is flattened between two glass slides and examined using transillumination). This technique (trichinoscopy) is not so good for *Trichinella pseudospiralis* because it is not surrounded by a capsule and is easily missed. Pooled muscle samples can be inspected with a method which employs artificial enzymatic digestion to free and to look for the larvae.
- Pig food (which may include infected rats) should be boiled for 30 minutes.
- To store pork for 10 days at -25°C is generally impractical in developing countries. In the West meat is sometimes irradiated with high doses of gamma rays, which will kill any larvae.
Angiostrongylus cantonensis

Life cycle and transmission

In 1938, Angiostrongylus cantonensis was discovered in rat lungs by Chen in Canton, China. The first human case description dates from 1945. Recently, the taxonomical position of the worm as changed and A. cantonensis has been transferred to the genus Parastrongylus, but in this text we will continue to use the generic name Angiostrongylus. Infection with A. cantonensis is the most common aetiology of eosinophilic meningitis. Angiostrongyliasis occurs primarily in Southeast Asia, throughout the Pacific Basin, including Hawaii, Fiji, Indonesia, Philippines, Japan, mainland China, Taiwan and Papua New Guinea, but also in several Caribbean nations (Bahamas, Cuba, Puerto Rico, Dominican Republic and Jamaica). Occasionally small outbreaks occur.

Final hosts

A wide variety of rodents are final hosts, primarily in the genera Rattus and Bandicota. Eggs laid by the female worm hatch in branches of the pulmonary arteries. After hatching, first-stage larvae enter the alveoli, migrate up the trachea, are swallowed and reach the alimentary tract. Subsequently, they are excreted in the faeces of the animal. When a snail consumes these droppings, infection of the mollusk will ensue. Within about two weeks, infective third-stage larva will appear. When ingested by a rodent, these L3 larvae migrate to the brain via the blood circulation and develop into fourth-stage larvae and then young adults within the next 4 weeks. They migrate to the subarachnoid space, enter the venous plexus, and are carried to their final destination, the pulmonary arteries.

Humans and rats become infected through eating raw slugs or snails, soiled lettuce contaminated with mollusks, eating a carrier (“paratenic”) host, such as infected planarians, land crabs or freshwater shrimps. Certain freshwater as well as marine fish can become infected. Inside man, the neurotropic third-stage larvae pass from the intestinal tract to the meninges. They die 1-2 weeks after arriving in the human brain. Adult worms do not occur in humans.

Clinical aspects

Angiostrongyliasis (infection with A. cantonensis, the rat lungworm) has an incubation period of 2-35 days. Symptoms are due to migration of the larvae in the brain and the inflammatory reaction which occurs. The disease presents with acute moderate to severe headache (100%). Besides the headache, patients can complain of eyeball pain. Visual problems can occur, due to involvement of one or more
cranial nerves (diplopia, acute strabismus, gaze palsy) or due to migration of the larva into the eye, which can lead to retinal detachment and blindness. Nuchal rigidity occurs in about 66% of patients and Brudzinski’s sign is present in ± 66%. Facial nerve paralysis, transient ataxia, delirium, seizures, cognitive dysfunction, hyperesthesia in various dermatomes and paraesthesia of arms and legs, trunk or face may occur and some symptoms may persist for months, although chronic disease is rare. Vomiting and nausea are self-limited and stop after a few days. Fever occurs in less than 50% of patients. The disease tends to be more serious in children. The disease is self-limiting. Most symptoms disappear spontaneously within 4 weeks of onset (range 2-8 weeks). Mortality is less than 1%.

**Diagnosis**

Eosinophilia of peripheral blood or CSF is not always present on initial laboratory testing. Pleocytosis may be absent early in the course of infection. Larvae are rarely detected in the CSF. The CSF can be clear or cloudy, but does not contain blood (except in case of a traumatic tap). The absence of focal lesions on CT or MRI-scanning of the brain distinguishes *A. cantonensis* infections from most other helminthic infections of the brain. Immunodiagnosis (ELISA, Western Blot) is possible in some centers. There is a poor correlation between the serological results of serum and CSF. Since in most cases, larvae will not be recovered in the cerebrospinal fluid and an autopsy will not be performed (the infection is not lethal in general), the diagnosis will be a tentative one, relying on the history, positive serology and exclusion of other causes.

**Treatment**

Analgesics are usually needed. Steroids (e.g. prednisolone 60 mg/day x 2 weeks or dexamethasone) shorten the duration of the headache. When performing a spinal tap, the opening pressure is increased in about 60% of patients. Repeated spinal taps to reduce the intracranial pressure are sometimes performed. Antihelminthics are thought by some not to be effective and considered to worsen the symptoms, probably because of the inflammatory reaction to antigens released by dying worms. Some clinicians use mebendazole or albendazole, but controlled studies are lacking.

**Gnathostoma sp.**

Nematodes of the genus *Gnathostoma* belong to the *Gnathostomatidae*. At least 13 species have
been identified, with 5 recorded in humans. Various species may cause severe infections in humans: *G. spinigerum* (in several geographical areas), *G. doloresi, G. hispidum, G. nipponicum* (all 3 only in Japan), *G. binucleatum* (only in the Americas). Humans are infected by eating raw or undercooked shellfish, freshwater fish, frogs or chicken. The male worms are 10-25 mm long and the females’ measure 25-55 mm. The third-stage larvae, which are responsible for disease in humans, measure about 3 mm. The final host for *G. hispidum* is the pig. The usual final hosts for *G. spinigerum* are dogs and cats. The eggs reach the outside world in the faeces. If they are dropped into water they will hatch 10 days later. Freshwater copepods (*Cyclops*, belonging to water fleas) are the first intermediate hosts. Fish, amphibians and various mammals may become infected by eating the infected *Cyclops*. There is low host-specificity and humans can also become infected.

The incubation time can be as long as 10 years. The larvae cannot develop into adult worms in humans. They migrate through the body and in doing so may trigger itching, transient subcutaneous swelling with local erythema and possible discrete pain. These symptoms occur after an interval of days to weeks. The swellings are caused by local oedema, necrosis and haemorrhages within the migration path. If the larvae penetrate vital organs (e.g. the brain) the situation may become life-threatening. Gnathostomiasis is an important cause of eosinophilic meningitis and myelitis. Almost all cases of neurognathostomiasis are reported from Thailand and result from infection with *G. spinigerum*. Gnathostoma larvae typically enter the spinal cord along the nerve roots resulting in radiculomyelitis. The worm can ascend the spinal cord and reach the brain. This journey can take several years. Spinal cord disease result in radicular pain followed by ascending paralysis of legs or quadripareisis with bladder dysfunction and eosinophilic pleocytosis in the cerebrospinal fluid. Diagnosis can be confirmed via serology. Most often ELISA is performed, followed by Western Blot if positive; a positive 24-kD band is nearly 100% specific for gnathostomiasis. Mechanical / surgical extraction of the larva is possible in a minority of patients (11% in one series). No randomized trials of anthelminthic therapy have been conducted. The treatment is symptomatic and if possible / necessary also surgical. Albendazole 400 – 800 mg daily for 21 days is often used as an etiologic treatment. An alternative is two repeated doses of ivermectine. Corticosteroids have been used to treat cerebral and spinal oedema.

**Toxocara sp.**

Nematodes of the genus *Toxocara* belong to the Ascarididae. *Toxocara canis* and *T. cati* are parasites which can cause a **visceral larva migrans** syndrome (fever, hepatitis, pneumonitis, urticarial,
eosinophilia) with or without asthma. If they reach the retina, they may lead to chorioretinitis with blindness as a possible outcome. Infection occurs by swallowing an egg that has reached the outside world via the feces of a dog (*T. canis*) or a cat (*T. cati*). A *Toxocara* parasite may become adult and eggs may appear in the faeces of humans in exceptional circumstances (e.g. HIV infection AIDS). Definitive diagnosis is established via detection of larvae in a tissue biopsy, though symptoms rarely justify such an aggressive diagnostic approach. ELISA is useful for visceral larva migrans, but not for ocular larva migrans. Cross-reactivity with other parasite antigens is common. Treatment is based on steroids and albendazole or diethylcarbamazepine (DEC). Nevertheless the effect of the anthelmintic treatment on the extra-intestinal larvae is limited. Intra-ocular infection resulting from *Toxocara* larvae may lead to traction upon the retina resulting in retinal detachment. Vitreoretinal surgery has a good chance of leading to an improvement in vision in approximately 50% of cases.

LAST UPDATED BY ADMIN ON JUNE 24TH, 2022

**Filariasis**

**Summary**

Major filariasis

Lymphatic: *Wuchereria* (90%) and *Brugia* (10%)

- Lymphangitis + adenitis + superinfection
- Lymphatic obstruction with hydrocele, lymphoedema and elephantiasis
- Chyluria, intermittent fever and asthmatic syndrome.
- Microfilariae principally at night in blood
- Transmission via mosquitoes

Onchocerciasis: *Onchocerca volvulus*

- Skin nodules, pruritus, eye lesions, swollen lymph nodes, sometimes lymphoedema
- Microfilariae in skin samples (snip, scarification) and eye (anterior chamber)
- Transmission via simulids

Loiasis: *Loa loa*
• Calabar oedema, subconjunctival migration across the eye, subcutaneous migration
• Microfilariae in blood during the day
• Transmission via fly which bites during daylight

“Minor” filariasis

• Mansonellosis (M. perstans, streptocerca, ozzardi)
• Dirofilariasis (D. immitis, …)
• Dracunculiasis (D. medinensis)

Filariae are nematodes that live as adults in various human tissues. They do not lay eggs, but constantly produce enormous numbers of larvae (microfilariae) in humans. These are found in the skin or blood. Human-to-human transmission occurs via insects: the parasites are thus “arthropod-borne”. Animal reservoirs play no role of significance in most places, except in subperiodic Brugia malayi. Filariasis only exist in warm climates because of the high temperature necessary for the development of the worm in the vector.

There are several species of filariae, but 6 are commonly pathogenic:

• Wuchereria bancrofti
• Brugia malayi
• Brugia timori
• Loa loa
• Onchocerca volvulus
• (Mansonella streptocerca)

There are 2 filariae that are often well tolerated by humans: Mansonella perstans and Mansonella ozzardi. The reason for this tolerance is not known; however it should be recognised that not all people infected with these filariae are asymptomatic. Insufficient is known about these parasites.

Dirofilariasis is for the most part only of anecdotal importance and no microfilariae are found in humans.

Dracunculiasis is traditionally included among the filariasis, although there are marked clinical differences between this parasite and the other filariae.
Lymphatic filariasis

General

*Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori* cause lymphatic disorders. *Wuchereria bancrofti* is the most widespread of the human filariae in the world. The majority of infections occur in Asia, but this parasite also causes considerable problems in Africa and the north-west of South America. There is a periodic and a subperiodic form.

*B. malayi* occurs in Southeast Asia. There are two forms: a periodically transmitted form (without animal reservoir) and a subperiodic form (animal reservoir in monkeys). Consequently, subperiodic *B. malayi* infection is a zoonosis.

*Brugia timori* is limited to a few islands around Timor.

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<tr>
<th>Parasite</th>
<th>Rhythm</th>
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<th>Main vector</th>
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<td><em>W. bancrofti</em></td>
<td>Periodic</td>
<td>Humans</td>
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<td><em>W. bancrofti</em></td>
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<tr>
<td><em>B. malayi</em></td>
<td>Periodic</td>
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<td><em>B. malayi</em></td>
<td>Subperiodic</td>
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<tr>
<td><em>B. timori</em></td>
<td>Periodic</td>
<td>Humans</td>
<td>Anopheles</td>
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Transmission

It became clear that the parasites are transmitted via the bite of infected mosquitoes, primarily by the night-biting *Culex (quinquefasciatus)* and *Anopheles* mosquitoes. This biting behaviour is important as the numbers of microfilariae in the peripheral blood systematically fluctuate over a 24-hour period reaching their highest levels at night. There is a remarkable periodicity of the microfilariae. The density of parasites is greatest at the time when the chance of transmission is greatest (at night).

*Wuchereria bancrofti* becomes adult in human lymphatics and lymph nodes. The adult female worms are 0.2 mm wide and can be up to 10 cm long. The males are shorter (40 x 0.1 mm). *Brugia* adults are about half this size. They can survive for up to 20 years, but the average life time is 5 years. Approximately 8 months after infection *W. bancrofti* microfilariae appear in the circulation. For Brugia sp, this prepatent period is about 3 months.

**Historical note**

In 1866, the German doctor Otto Wucherer discovered numerous microfilariae in patients with haematuria and chyluria in Bahia, Brazil. In 1872 the Briton, Lewis, in Calcutta discovered that
patients with elephantiasis were infected with filariae. Bancroft was the first to discover the adult worm in an abscess and later in fluid which he tapped from a hydrocele during his surgical practice. He was one of the first to suggest that disease was transmitted by mosquitoes, although it was Patrick Manson (1844-1922) who reported the development of filarial embryos in the mosquito. Because microfilariae were periodically detectable in the blood, the Scottish doctor Patrick Manson suspected that night-biting mosquitoes might be responsible for transmission.

**Pathogenesis**

The adult worm induces an immunological reaction in humans. The basic lesion is a sterile inflammation around the worm; in and around the lymph nodes and lymph vessels. In the case of lymphangitis, there is often retrograde inflammation (centrifugal spread). This inflammation leads to obstruction of lymph vessels, resulting in temporary lymphostasis and lymphoedema. Following repeated attacks, irreversible damage to the lymphatics occurs with permanent “non-pitting” lymphoedema. Sometimes abscesses occur at the site of dead adult worms. There is also evidence that indicates adult worms can themselves directly attack the lymphatics (irrespective of the immunological response).

In humans with severe symptoms, low or no microfilaraemia is often found, whereas humans with high microfilaraemia often have no symptoms. The reasons for this apparent paradox is, that the resulting pathology is caused by the patient’s own immunological response to the adult worms. If the reaction is violent, few adult worms and microfilariae survive but considerable inflammation will occur with sequelae. During infection with the filariae the immunological response evolves. Down-regulation can occur and some patients do not produce any interferon-gamma after exposure to parasitic antigen. This is currently the subject of intense study. It is likely that this influence on the immune system explains the many asymptomatic patients in endemic areas. Both infected amicrofilaemic and microfilaraemic patients display lymphangiectasis on ultrasound or scintigraphy. The adult worms seem to induce multiplication of endothelial cells and dilatation of lymph vessels, even in the absence of inflammation. On the opposite side, when there is a violent immune reaction against the microfilariae, Weingarten syndrome appears (see below).

**Worm load**

There is no multiplication of adult parasites in humans so that the worm load and the degree of illness is proportional to the number of infective larvae transmitted by infected insects. The number of insect bites is directly proportional to the duration and intensity of exposure in a filariasis region. In most cases; severe disease is only seen in humans who have lived for a long time in an endemic area. The
patient’s individual immunological response has a significant role in the development of the various symptoms.

**Endosymbiont**

The intracellular *Wolbachia* endosymbiont is apparently an obligate parasite of these worms. These bacteria are related to *Rickettsiae*. Their presence appears to be favourable for the growth and fertility of the nematode. This has become a target for therapeutic intervention, after it was observed that *Wolbachia* is susceptible to tetracyclines.

**Clinical aspects**
Severe myxedema as complication of hyperthyroidism. This needs to be distinguished from lymphatic filariasis

The majority of infected people exhibit no or few obvious clinical signs even though they can have microfilariae in their peripheral blood. Although these people are asymptomatic or paucisymptomatic, almost all have subclinical disease with microscopic haematuria or proteinuria, dilated tortuous lymphatics and, in males, scrotal lymphangiectasia. Among the more obviously symptomatic the acute temporary signs and symptoms caused by inflammation should be distinguished from those resulting from chronic lymph tract obstruction.

**Signs of inflammation**

Adenolymphangitis: Acute pain and inflammation in one or more lymph nodes (groin, axilla, elbow, neck). This is associated with fever and general malaise. Retrograde lymphangitis often occurs after 4 to 8 hours. There is centrifugal redness, pain and heat over the course of the lymph vessels. Pyogenic lymphangitis proceeds centripetal, not centrifugal. In most cases, the symptoms last 3-4 days. Each episode results in several days of incapacity for work.

Inflammation of testis and spermatic cord: acute pain, swelling and fever. Repeated funiculitis (inflammation of the spermatic cord) results in thickening of this structure.

Filaria fever: Irregular fever often occurs without external lymph node inflammation, as a result of inflammation of the deeper lymphatics and lymph nodes. The fever may recur irregularly for months or years after the patient leaves an endemic region (observed in 20,000 American military personnel who fought in the South Pacific during the Second World War, an area endemic for *W. bancrofti*).

**Signs of chronic obstruction**
Wuchereria bancrofti filariasis, elephantiasis of the genitals. Copyright ITM
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Wuchereria bancrofti filariasis, elephantiasis of the genitals. Copyright ITM

**Hydrocoele**: accumulation of fluid in the tunica vaginalis. Hydrocoele often occurs in orchitis (inflammation of the testis). This is very common in endemic regions. Microfilariae are often found in hydrocoele fluid. Large hydrocoele can be very inconvenient. Sexual incapacity associated with genital filariasis is a major concern for those infected. Shame, anxiety, sexual problems and social stigmatisation are widespread. In the differential, inguinal hernia is important. Besides the fact that it can be reducible or irreducible (even obstructed), it is not possible to feel above the upper edge of the swelling. A testis tumour, tuberculosis of the epidydimis and chronic lymphogranuloma venereum and chronic schistosomiasis also need to be ruled out.

**Lymphoedema and elephantiasis**: Chronic lymphostasis can lead to lymphoedema. The first sign is the loss of contour around the ankles. Later, a reversible pitting oedema appears. After this has turned into non-pitting oedema, the skin will thicken. Lymphoedema is most striking in the legs, scrotum, breasts and arms. The labia and penis are somewhat less frequently affected. If the lymphoedema persists for a long time, elephantiasis can occur. The skin is then markedly thickened and can become wart-like. The oedema is “non-pitting” because there is also a proliferation of connective tissue. The tissue is fibrotic and hard. Recurrent erysipelas (bacterial superinfection) causes the elephantiasis to increase still further. Entry points for bacteria are; fissures caused by athlete’s foot, traditional scarifications, insect bites and small scratch wounds. *Brugia* infections mostly cause elephantiasis confined to lower legs and lower arms.

**Lymph leakage**: The rupture of swollen lymphatics into the renal pelvis can cause chyluria (milk-like pale pink urine). This can have an insidious or sudden onset. The prevalence is low. It is often recurrent. The chyluria is often more pronounced in the morning and after a heavy fatty meal. This sort of fistula can follow a very chronic course. Rupture of lymphatics in the abdominal cavity or thorax results in chylous ascites and chylothorax (chyle = lymph). A protein-rich white fluid is obtained on aspiration. Lymph leakage into the area of the tunica vaginalis results in chylocoele. Clumping of lymph proteins in the ureters can cause obstruction. Long-term extensive chyluria results in hypoproteinaemia. The rupture of numerous small skin lymphatics in the scrotum can lead to a constantly wet, sticky scrotum which is particularly unpleasant.

**Tropical pulmonary eosinophilia, Weingarten’s syndrome.**

Tropical pulmonary eosinophilia is particularly common in India and Southeast Asia. In other geographical areas it seems to be rare. Pulmonary symptoms are predominant: cough, dyspnoea,
asthmatic syndrome. Chest X-rays consistently show patchy infiltrates, in contrast to Loeffler’s syndrome in which they are more fleeting. Microfilariae can be detected on lung biopsies. Sometimes the lymph nodes swell and splenomegaly occurs. The erythrocyte sedimentation rate increases and there is marked eosinophilia (usually >3000 cells/mm3). There are no microfilariae in the peripheral blood. Serological tests for filariae are strongly positive. This condition responds very well to therapy with DEC (in contrast to Loeffler’s syndrome). Usually 6 mg/kg/day x 21 days is given. Steroids can be given if other diagnoses (e.g. strongyloidosis) can be excluded. If not treated it can lead to pulmonary fibrosis. Tropical pulmonary eosinophilia needs to be differentiated from classic astma, tuberculosis, chronic strongyloidosis, schistosomiasis (does not occur in India), repeated *Ascaris* migrations and toxocariosis.

### Endomyocardial fibrosis

Chronic hypereosinophilia can cause cardiac lesions such as endomyocardial fibrosis or fibroplastic endocarditis. The contents of the eosinophilic granules (including major basic protein) are toxic to the endocardium and the adjacent myocardium. A restrictive cardiomyopathy develops.

**Clinical difference between W. bancrofti and Brugia infections.**

*Brugia* infections rarely lead to genital lesions or chyluria. The elephantiasis tends to be limited to below the knee. A filarial dance sign cannot be obtained on ultrasound.

### Diagnosis

Microfilariae should be searched for in blood: thin smear, thick smear, concentration method (Knott’s test, microfilter). Because of the periodicity, it is best to take the blood at night. A small dose of DEC can increase microfilaraemia during the day: the microfilariae are then expelled from the pulmonary vascular bed; it is optimal to sample 45 mins after administration of 100 mg of DEC (adult dose). This does not work for people who have a disturbed sleeping pattern. Do not use DEC in an onchocerciasis area (Mazotti reaction). Albendazole and ivermectin do not provoke a release of microfilariae into the peripheral blood. Microfilariae are sometimes detected in chylous urine, hydrocoele fluid and ascites fluid.

Indirect diagnosis can be made by serological detection of antibodies. Serological testing is of limited sensitivity and specificity.

Lymph node biopsies should be avoided as they obstruct lymph drainage still further.
Live adult *Wuchereria* worms can be detected by Doppler ultrasound of the scrotum. Dilated lymphatics are observed in which moving worms are found (“filarial dance sign”). This tool has however limited sensitivity; strangely enough adult *Brugia malayi* are almost never detected by ultrasound.

Circulating antigen of adult *W. bancrofti* can be detected with an antigen-capture ELISA but this is not practical in the field (although it is in a central laboratory). Several ICT tests have been developed which are very simple (like an ICT-test for malaria). There is no diurnal variation in the concentration of free circulating antigen so that nocturnal blood sampling is not necessary. It is a powerful test for studying the efficacy of chemotherapy. People who have no microfilariae in the blood but who do harbour live adult *W. bancrofti* test positive. People who recover no longer have circulating antigen in the blood. For population surveys, the previous standard parasitological techniques (nocturnal blood samples) were cumbersome, time-consuming, expensive and very intrusive. The use of rapid tests detecting circulating antigen has entered the clinical practice in endemic areas.

There is still no commercially available antigen test for detecting *Brugia* infections, which is a problem in *Brugia* endemic regions.

PCR tests have been developed that detect DNA of *W. bancrofti, Brugia malayi* and *B. timori*. They are used predominantly in epidemiological work and research settings.

**Differential diagnosis lymphedema:**

- Primary lymphedema: aplasia or hypoplasia lymphatics, tendency towards symmetrical lesions
- Lepromatous leprosy
- *Chlamydia trachomatis, LGV*
- Contact dermatitis with recurrent erysipelas
- Pretibial myxedema
- Chromomycosis
- Mycetoma
- Loiasis: Calabar swelling
- *Onchocerciasis*: hanging groin
- Kaposi sarcoma
- Lymphatic damage (surgery, radiation, burns, TB, malignancy)
- Podoconiosis
Podoconiosis

Podoconiosis (syn. lymphatic siderosilicosis or lymphoconiosis) is a chronic disorder characterised by the very slow onset of oedema, subsequent lymphoedema and later elephantiasis (mostly limited to below the knee). The disease is caused by immunological response to certain minerals (silicates, zirconium or beryllium-containing minerals). When walking barefoot on ground containing these minerals, dust particles can absorbed through the soles of the feet via small wounds. They are then transported via the lymphatics to the inguinal lymph nodes where they cause a local inflammatory reaction. Atrophy and fibrosis of the lymphatics occur subsequently (in contrast to bancroftiasis where dilatation occurs). The disorder occurs in well-defined areas (specific mineral composition of the soil!) in people who walk about barefoot, such as Ethiopia, Kenya, Rwanda, Uganda, West Africa and India. Whereas lymphatic filariases occur predominantly in lower-lying areas (vector biotope), podoconiosis is characteristic of higher-lying zones. This is not absolute. Other signs of bancroftiasis are absent (hydrocoele, eosinophilia, and nocturnal microfilaraemia). Confusion with mycetoma (“Madura foot”) or with classic Kaposi’s sarcoma is possible.

Treatment

General

Self-help groups in a community can play an important role. In an acute situation, pain relief, antipyretics and anti-inflammatories are indicated. In chronic lesions of the scrotum, surgery can be performed. Elephantiasis of the limbs is relatively treatment-resistant. Physical methods (lymph drainage by massage) should be continued for a long time and will not in any way alter the fibrotic component of the swelling. Permanent compressive bandages are not practical in a warm, moist environment. A firm, compressive dressing (elastic bandages) may be applied centripetally. These are then changed daily and relatively good results can be achieved in this way, particularly if elastic compressive stockings can be worn afterwards. Microsurgery with the creation of several lymphovenous anastomoses is difficult.

Hygiene and antibiotics

Good, enforced hygiene can dramatically reduce the number of complications. General cleanliness, washing with soap and disinfection of wounds are crucial. If bacterial superinfection is present, this should be treated appropriately. There is often a fungal infection between the toes (athlete’s foot),
which acts as a portal of entry for various bacteria. Simple hygiene is important and should be stressed:

- Washing the affected part of the body twice daily with soap and water
- Elevation of the affected limb at night
- Keeping nails clean
- Wearing shoes
- Disinfecting skin wounds rapidly and properly
- Systemic antibiotics for superinfection (erysipelas)
- Treating athlete’s foot
- Daily physical exercise to improve lymph drainage
- Physiotherapy
- Diethylcarbamazine or DEC

Diethylcarbamazine (= DEC)

Was introduced in 1947. In 1967 Frank Hawking, father of the famous physicist Stephen Hawking, published the results of a study in Brazil of the effect of enriching cooking salt with DEC on lymphatic filariasis. DEC (Notezine®, Hetrazan®, Banocide®) has a rapid, but indirect microfilaricidal effect on *Wuchereria* and *Brugia*. DEC somehow modifies the microfilariae so they can be destroyed by the immune cells. If it is taken for prolonged periods, there is also an incomplete macrofilaricidal effect. The dose conventionally given as monotherapy is 72 mg/kg (in total) over 10-14 days (e.g. 50 tablets of 100 mg), although often it will be stated that 3 divided doses after meals will be better. There is evidence to show that lower doses for shorter periods are as effective (e.g. single dose of 6 mg/kg). DEC in monotherapy has an efficacy of ± 90% (against microfilariae). Pregnancy is a contraindication for the administration of DEC. This medication is fairly well tolerated, but systemic reactions can occur, caused by the massive and sudden death of microfilariae. Recent studies suggest that these reactions are due to the abrupt release of *Wolbachia* in the human tissues (substantial increase in Wolbachia DNA by pCR). Symptoms may include malaise, pruritus, urticaria, fever, headache, vomiting and asthmatic crisis (cf. Mazzotti reaction in onchocerciasis and the Jarish-Herxheimer reaction in spirochaetosis). This usually happens in the first 48 hours. For mild reactions antihistamines can be used, in severe reactions steroids are indicated. Local tissue reactions can also occur around dead macrofilariae (lymphangitis, abscess, funiculitis). Those local reactions can occur up to several weeks after therapy. Most microfilaraemic patients have a transient increase of haematuria and/or proteinuria after starting DEC. Because of these potential side effects, treatment is started with a low dose and increased progressively. It sometimes needs to be repeated. The microfilariae are not killed immediately by DEC, but their phagocytosis is facilitated. The indirect
effect of DEC means that microfilariae can remain alive in cavities (e.g. hydrocoele). This can give rise to confusion, but otherwise is not important as microfilariae are not pathogenic. If the adult worms are not killed, microfilariae reappear in the blood 3-6 months later.

Ivermectin (Mectizan®, Stromectol®)

This drug became available in 1984 for the treatment of onchoderciasis. It is also active as a microfilaricide against *W. bancrofti*. It has the enormous advantage that it can be given in one oral dose and has few side effects. It is not macrofilaricidal, even if repeated at high doses. It is useful in the control of bancroftiasis (suppressing microfilaraemia stops transmission to the vectors) but probably not in helping individual patients. The combination of single dose DEC with single dose ivermectin is much more effective (99% of decrease of microfilariae load at least for 12 months) than each medication alone.

Albendazole

Albendazole has a very limited macrofilaricidal effect. It has been shown however that the combination of single doses of ivermectin with albendazole suppresses microfilaraemia by 99% for at least 15 months. This combination is more effective than each medication used separately. This combination also has the great advantage of eliminating diverse intestinal worms and of treating scabies (ivermectin).

Tetracyclines

Tetracyclines are active against the endosymbiotic *Wolbachia*, and their eradication results in long-term sterility and eventual death of macrofilariae. This has become a new therapeutic point of attack, and this is the first effective macrofilaricidal treatment (although indirect and slow). Initial clinical studies showed a favourable effect of a 8-week course of tetracycline on the clinical symptoms and the number of adult worms as reflected by the decrease/suppression of worms detected by ultrasound, decrease/suppression of circulating antigen load. In addition, a much lower rate of adverse reaction was observed when compared to the classic DEC treatment. Subsequent studies showed that a 4-week course of doxycycline has a similar efficacy as a 8-week course, but treatments of shorter duration do not seem to provide the same clinical benefit (although a microfilaricidal effect was also observed). Nowadays, a 4 to 6-week course of doxycycline (200 mg/day) is the first-line treatment for the patient diagnosed with acute or chronic lymphatic filariasis.

Of note, azithromycin does not deplete the *Wolbachia*, so that there is still no therapeutic option for
children and pregnant women. A 2 to 4-week course of rifampicin (but not a 1-week course) has substantial anti-Wolbachia activity, but its therapeutic implications need to be further studied.

Combination therapy

Combination therapy (albendazole 400 mg + ivermectin 200µg/kg) or (albendazole 400 mg + DEC 6 mg/kg) is largely used in mass drug administration at present to stop transmission. The second regimen is not used in countries where onchocerciasis occurs (risk of Mazotti reaction with acute blindness).

For the individual symptomatic patient, some experts recommend to combine a 6-week course of doxycycline with 14 days DEC, although the clinical superiority of this combination over doxycycline monotherapy has not been demonstrated so far.

**Prevention**

At the end of the 20th Century, it was estimated that about 120 million people were infected and about 43 million were symptomatic. In May 1997, the WHO adopted a resolution to eliminate lymphatic filariasis as a public health problem. The programme “Global Programme to Eliminate Lymphatic Filariasis” or “Global Lymphatic Filariasis Initiative” was launched in the year 2000. It is based on two approaches:

- annual single dose, two-drug treatment allowing suppression of microfilaraemia for a year and which can be given as mass treatment for 5-6 successive years [albendazole + ivermectin in onchocerciasis areas; albendazole + DEC in other areas],
- simple diagnostic tests that can be performed by a finger prick at any time of the day.

An alternative used in some countries (China, Taiwan) is DEC 0,3% medicated salt x 12 months. It is hoped to eradicate lymphatic filariasis by about 2020. Good financial backing has been provided but this still needs to be extended. Technical training, logistics and management support should be organised. Continuous monitoring and evaluation should constitute an integral part of the programme.

Of note, a recent small study in Papua New Guinea suggests that a triple-drug therapy (DEC + albendazole + ivermectin) would suppress the microfilaraemia for up to 2 years (and should be considered in heavily infected patients). This requires confirmation in larger trials.
The focus of disease control has been mass drug administration programs as described above. Vector control with insecticide-treated bed nets is useful where Anopheles (night biting mosquito) transmit the parasite. Repellents as personal protection tools prevent on an individual level. Currently, no vaccine exists.

Onchocerciasis

Introduction

Onchocerciasis (syn. onchocercosis) is a disease resulting from infection by the nematode *Onchocerca volvulus*. The principal characteristics of the condition are pruritic dermatitis, subcutaneous nodules and ocular lesions. It is also known as “river blindness” because the blackfly vector breeds near fast-flowing streams and rivers.

Distribution
Map of onchocerciasis endemic area in Latin America. Adapted from publication of ‘Programa para la Elimination de la Oncocercosis en las American – OEPA’, with special thanks to Dr Juan Martin Moreira.
The disease occurs principally in large parts of Africa, especially West and Central Africa (including both Congos and Angola), but also in Sudan, Ethiopia, the north of Uganda and even Tanzania. About 99% of the cases are now limited to Africa, the remaining being observed in a few foci in Latin America (disease about to be eliminated there).

**Vector**

The infective larvae are transmitted by *Simulium* mosquitoes (“blackflies”). They reproduce in rocky rivers with fast stream and can cover large distances. The fact that the insects are good fliers makes vector control difficult. Sometimes there are only a few ecologically very suitable places, where thousands of eggs are then laid. This can lead to the sudden simultaneous appearance of massive numbers of adult insects when the environmental conditions are right.

Only female insects suck blood (from humans as well as animals). This happens during the day in the open at well-defined times. The bite is painful.
Life cycle

There is no significant animal reservoir. *Onchocerca volvulus* microfilariae are more tissue parasites than blood parasites.

The more insect bites someone suffers over the course of the years, the greater the worm load. After a bite from an infected insect, the infective larvae develop in humans to become adult worms (macrofilariae) that live subcutaneously. The prepatent period (time between infection and detection of microfilariae) is 3 to 15 months.

The macrofilariae lie coiled subcutaneously in nodules and can live for up to 15 years. These nodules are predominantly located on the scalp and upper body in people living in Central and South America but occur more on the pelvis and legs in Africans. This has to do with the biting habits of the vector. *Simulium damnosum* (Africa) tends to bite on the lower half of the body (98% of bites below the belt) and *Simulium ochraceum* (America) preferably bite on the upper part of the body. A female lays on average 1600 microfilariae per day. The microfilariae concentrate in the skin, eyes and lymph nodes. When the microfilariae die they cause a local inflammatory reaction.
Life cycle of *Onchocerca volvulus*.

Intracellular bacteria can be detected by electron microscopy in adult *Onchocerca volvulus* and also in the microfilariae. The bacteria belong to the genus *Wolbachia* of the Rickettsiales.
(Alphaproteobacteria) and are closely related to *Ehrlichia*, *Cowdria* and *Anaplasma*. The *Wolbachia* bacteria are transmitted transovarially, have a preference for oocytes and the lateral tissues (“lateral chords”) in the macrofilariae and have a development cycle that resembles that of the *Chlamydiae*. As for *Wuchereria* and *Brugia* filariae, they have also become a new point of attack for therapy. It was possible to render the macrofilariae in onchocercomata bacteria-free by means of a 6-week treatment with doxycycline. At the same time parasitic embryogenesis was totally impaired. *Wolbachia* bacteria are also susceptible to rifampicin and this might become an option (like for lymphatic filariasis) for children less than 8 years and pregnant women. How far these findings are relevant for clinical practice has not been fully elucidated. Wolbachia-antigen released in the circulation contributes to the discomfort which is seen soon after administration of classic anti-filarial medication, but these symptoms do not seem to occur with tetracyclines.

**Clinical aspects**

**Skin abnormalities**

Pruritus occurs locally or systemically. There are scratch lesions often with bacterial superinfection. The chronic itching has given rise to the terms “gale filarienne” and “craw craw”. If untreated the dermatitis assumes the form of a pruritic papular dermatitis, progressing to a chronic rough, coarse, papular dermatitis, often with postinflammatory hyperpigmentation, followed by lichenification, atrophy and finally patchy depigmentation (leopard skin).

Pea- to plum-sized subcutaneous nodules are found predominantly over bony protuberances such as the hip, pelvis, ribs, shoulder blades and skull. These need to be distinguished from cysticerci.

Though not always found (in Africa in only 30 to 60% of positive people), enlargement of the inguinal nodes is sometimes also present, resulting in what is known as “hanging groin”. Onchocerciasis causes localized elephantiasis (lymphoedema) in a number of cases.

**Ocular lesions**

Ocular lesions only occur after many years of severe infection and are therefore usually not present before the age of 30. They are more frequent in savanna regions than in the rainforest.

In onchocerciasis patients with heavy infections, microfilariae can be seen in the anterior chamber with a slit lamp. When microfilariae die, opaque fine 0.5 mm wide corneal lesions occur: keratitis punctata. This is corneal inflammation with small spots on the cornea accompanied by redness of the
conjunctiva. Sclerosing keratitis occurs later (hazy cornea with pannus formation) as well as iritis and uveitis, resulting in blindness (river blindness!). More rarely, there is involvement of the posterior part of the eye: chorioretinitis and optic nerve atrophy. Ocular lesions can be exacerbated by DEC therapy *(which is therefore formally contra-indicated)* but not by ivermectin.

There seems to exist an epidemiological link between onchocercosis and epilepsy, but more study on this subject is needed to confirm a causal relationship.

**The world’s leading causes of blindness are:**

- cataract (clouding of the lens),
- trachoma (eye infection with the bacterium Chlamydia trachomatis),
- glaucoma (increased intra-ocular pressure with damage to the optic nerve),
- xerophthalmia (secondary to vitamin A deficiency with initial night blindness, followed by dry eyes and corneal softening),
- onchocerciasis,
- diabetes,
- leprosy,
- maculopathy and
- trauma.

**Diagnosis**

**Detection of microfilariae in a skin snip**

Various techniques may be used for detecting microfilariae in the skin. A skin snip is often used. A needle is used to raise the skin and a fine piece is shaved off with a razor blade. A standardised punch biopsy is also possible. The piece of tissue is placed in physiological saline. The specimen is then examined 15 minutes to 3 hours later to see whether or not microfilariae have emerged. In early infections (first 15 months) not enough microfilaria are present in the skin to be detected with a skin snip.

**Detection of microfilariae in skin fluid.**

This is done by means of scarification with a sterile razor blade. Preferably several sites are examined
(often 4 sites are chosen). The fluid obtained can be collected on a glass slide and stained with Giemsa to allow identification.

**Detection of microfilariae at other sites**

Occasionally *O. volvulus* microfilariae are found in the blood and in the urine.

**Nodulectomy**

This is both diagnostic and curative if all the nodules are resected. However the palpable skin nodules are often outnumbered by deeper lying subcutaneous nodules. The macrofilariae are found in the nodule.

**Slitlamp examination**

This is a non-invasive test, but requires considerable experience. It is best to get the patient to lay his/her head on his/her knees for at least 2 minutes before the examination to allow more microfilariae to come into the anterior eye chamber.

**Mazzotti test**

If the diagnosis is doubtful, the patient may be given 50 mg DEC orally. If microfilariae are present, a severe itching reaction will occur within 2 hours. This is caused by an allergic reaction to the proteins released after the rapid breakdown of microfilariae. Because this is very unpleasant, this test should be used only when strictly necessary. An alternative tool, a patch with DEC, is better used (if available) because it causes a localised reaction on the skin.

**Serology**

Serology cannot distinguish between the various species of filariae. The antigen used is usually extracted from a different worm: Litosomoides sigmodontis. It is useless for patient care in endemic settings.

**Treatment**
**Ivermectin (Mectizan®, Stromectol®)**

Ivermectin is a fast-acting, safe and effective microfilaricide. Ivermectin has a broad spectrum and is active against various worms and arthropods (ectoparasites). In onchocerciasis, it is active against the free microfilariae and those that are still in the uterus of the female.

It can be given in a single oral dose (4 tablets of 3 mg for an adult; 200 microg./kg in children). It must be given repeatedly. The ideal frequency of administration (once a year or more frequently) still remains to be determined. Ivermectin does not penetrate the aqueous humour. Consequently it does not cause intra-ocular inflammatory reactions that might exacerbate ocular lesions. It was initially thought that pregnancy constituted a contra-indication to treatment with ivermectin but no increase in the incidence of abnormalities has been observed in neonates when the product has accidentally been taken by the mothers during pregnancy. In areas of Loa loa a slight risk of neurological side-effects of ivermectin exists (see below). In 1987 the manufacturer of ivermectin (Merck Company) announced that the company would make the medication freely available to combat onchocerciasis.

**Moxidectin**

A promising new drug moxidectin, has been shown to have significant macrofilaricidal activity in animal studies and could be capable to interrupt transmission within six annual rounds of treatment. This drug might replace Ivermectin in the future.

**Tetracyclines**

Tetracyclines such as doxycycline and vibramycin can kill *Wolbachia* endosymbionts of macrofilariae. According to initial findings, the subsequent suppression of embryogenesis by ivermectin lasts much longer (at least 18 months) and results eventually to the death of the adult worms (macrofilaricidal effect). A four-week course of doxycycline is very effective in killing macrofilariae and is increasingly used in non-endemic settings to avoid repeated annual treatment with ivermectin for many years. In endemic countries however annual administration of ivermectin is still preferred for its fast effect on microfilariae (the pathogenic form in onchocerciasis) and its simplicity of use (mass drug administration of a 4-week doxycycline treatment is unfeasible).

**Nodulectomy**

This involves the removal of superficial nodules and is (was) popular in Central America.
Prevention

In 1968, the WHO decided to start a large scale onchocerciasis control programme (OCP). The emphasis of the programme is on vector control in areas where the disease is often associated with blindness (savanna-type onchocerciasis). Initially it involved 7 West African countries (Benin, Burkina Faso, Ivory Coast, Ghana, Mali, Niger and Togo).

After a few years of preparation, the vector control programme started in 1974. In 1978, and subsequently in 1986, the programme was extended to the west and south (including Guinea, Guinea-Bissau, Senegal and Sierra Leone) to a total of 11 countries. It covers an area of 1,235,000 km² with 50,000 km of river. Initially 30,000,000 people lived there. In view of the fact that an adult female worm lives on average 11 years, it was estimated that a minimum of 14 years of insect control would be necessary to eradicate the human reservoir of onchocerciasis. Later, after a successful (but costly) period of intensive vector control, activities focused on regular administration of ivermectin (after 1987 and the free access to this drug) through vertical programs and subsequently primary care settings in order to decrease both morbidity and transmission. At present interruption of transmission has been achieved in large areas and onchocerciasis no longer constitutes a public health problem there.

Loiasis

Introduction
Loa loa is a nematode that is solely present in the rainforest area of Central and West Africa. Adult Loa loa worms are 3 to 7 cm long and 0.5 mm wide. They live 4 to 17 years. The microfilariae appear 6 to 12 months after infection. They measure 230 to 300 µm by 7 µm.

The microfilariae are found in the blood and exhibit periodicity with the highest density occurring around midday. The adult filaria do not contain a bacterial endosymbiont, as opposed to Onchocerca volvulus and Wuchereria/Brugyia filaria where Wolbachia is endosymbiotic.
Transmission occurs via the bite of female Chrysops flies. They are insects with beautiful and often yellowish-gold iridescent eyes when they are alive (chrysos = gold). Chrysops flies belong to the Tabanidae, which suck blood of mammals and are active during the day. There is no animal reservoir.

**Clinical aspects**

The adult worms migrate through the subcutaneous tissues. This migration or the intermittent discharge of large quantities of microfilariae causes transient local oedema: Calabar swellings (Calabar is a place in Nigeria close to the border with Cameroon). There is also local redness and itching. Generalized itching is also described.

When the worm passes under the conjunctiva, it can be observed and removed (Loa loa is for this reason known as the eyeworm). There is no intra-ocular invasion and there is no risk of blindness. The adult worm migrates through the loose-meshed subconjunctival connective tissue. This migration can thus be observed macroscopically, in contrast to the migration of microfilariae of *Onchocerca volvulus*.

The subcutaneous passage of the worms can sometimes be perceived as an itchy and rapidly moving linear swelling. Dead worms can calcify and thus be radiologically visible (e.g. in the hands and wrists). In general, loiasis is accompanied by hypereosinophilia. This increases the risk for endomyocardial fibrosis.

**Diagnosis**

Serology is aspecific, useless and not performed in endemic areas.

Clinically: Calabar swellings and worm passage across the eye may be considered as pathognomonic for the disease and sufficient to establish a diagnosis in the absence of *Loa loa* microfilariae in the blood.
Dead and calcified adult Loa loa filaria, visible on a radiograph of the hands. Copyright ITM

Detection of microfilariae in peripheral blood (during the day) is obtained via a thin blood smear, thick smear or preferably via a concentration technique (Knott or nucleopore filter).
The number of *Loa loa* microfilaria in the peripheral blood can be very high. The higher the number, the higher the risk of neurological complications, especially when drug treatment is started. In order to diminish the risk apheresis can be performed.

### Treatment

Treatment of loiasis is based on administration of DEC for 3 weeks. The dose of DEC should be gradually build up over the course of 4 days, up to 400 mg/day. DEC is both micro- and macrofilaricidal against *Loa loa* although often several treatments are sometimes necessary.

Before starting with DEC, simultaneous onchocerciasis should be excluded in view of the risk of extremely unpleasant/severe Mazzotti reactions in the patient.

Ivermectin causes a marked but transient reduction in microfilaraemia. One week after administration on average 10% of the original microfilaraemia still persist.

With high microfilaraemia (>2000/ml; especially if >50,000/ml) there is an increased risk of neurological complications (headache, confusion, gait disorders, hypertension, incontinence, encephalopathy, coma) when DEC is administered. In such cases it is advised to associate prednisone 1 mg/kg for 4 days. Hospitalization for 4 days is advised since most side effects of starting treatment occur in this time frame. In very high microfilaraemia, even the administration of ivermectin (sometimes used to decrease the microfilariae load before DEC treatment) may be risky. In such a situation apheresis may be necessary although it requires complicated and expensive apparatus and specialised personnel (out of reach of most endemic settings). In low-resource settings, a 3-week course of albendazole can be used instead of apheresis in order to reduce microfilaraemias.

Removal of the adult worms during their migration beneath the conjunctiva (local anaesthesia with cocaine or tetracaine) is possible. But if this is not done, the worm creeps on spontaneously and leaves the eye. While extracting the worm from the eye care has to be taken not to rupture the worm, as this leads to a severe inflammatory reaction.

### Prevention

DEC 5 mg/kg, 3 days per month can –rarely– be used as prevention in an endemic region. DEC 300 mg per week (dose for adults) is also effective. Vector control is problematical as the breeding sites are very diffuse and widespread and the insects bite out of doors.
“Minor” filariasis

- Mansonellosis (M. perstans, streptocerca, ozzardi)
- Dirofilariosis (D. immitis,...)
- Dracunculiasis (D. medinensis)

Mansonella perstans

*Mansonella perstans* (formerly *Dipetalonema perstans*) is a nematode transmitted by *Culicoides* insects. These midges have an aggressive and very annoying biting behaviour principally at dusk but also to a lesser extent at night and during the day. They bite predominantly on hands, arms and head. They often fly in swarms around the face. In view of their large numbers, they can form a very severe plague. Control is difficult.
Midges. Culicoides sp. Vectors of Mansonella filaria. Copyright ITM
The infection is widely distributed in Africa but is more localised in Central and South America. *M. perstans* does not occur in Asia.

The adult worms live in body cavities (peritoneum, pleura and pericardium) and in perirenal fat. Most patients infected with *Mansonella perstans* are asymptomatic. A number of different symptoms and allergic reactions are sometimes ascribed to this parasite, but the disease spectrum has not yet been fully established.

The diagnosis is established by detecting the typical small microfilariae in the peripheral blood.

If asymptomatic, no treatment is necessary. A 6-week course of doxycycline with 200 mg/day resulted in a 97% cure-rate at 12 months in a study in Mali. Ivermectin, albendazole and DEC are inactive.
Mansonella streptocerca

*Mansonella streptocerca*

Above: Map showing areas endemic for Mansonella streptocerca filariosis. Copyright ITM

Streptocercosis is caused by *Mansonella streptocerca* (formerly *Dipetalonema streptocerca*). This nematode is confined to Central and West Africa. The parasite is transmitted by *Culicoides* midges. It
may be a zoonosis as morphologically identical parasites are found in chimpanzees. Adult worms live in the skin. Live worms’ cause no lesions but a local inflammatory reaction occurs when they die, with papules and possibly subsequent fibrosis. There are no eye lesions. Differentiation from onchocerciasis is necessary.

Many infected people are asymptomatic. The most frequent symptom is chronic pruritus. The skin is thickened and there are papules. Hypopigmented patches can occur which must be distinguished from leprosy, endemic treponematosis and onchocerciasis. Lymph nodes can be enlarged.

The microfilariae are found in the skin. Detection is as for onchocerciasis (skin snip, scarification with collection of dermal fluid). In the event of doubt or suspicion of leprosy, a biopsy is useful. DEC causes a Mazzotti reaction as in onchocerciasis.

DEC is micro- and macrofilaricidal for *Mansonella streptocerca*. Ivermectin is highly active against this parasite.

**Table: Overview of characteristics of microfilariae**

<table>
<thead>
<tr>
<th>Species</th>
<th>Location</th>
<th>Sheath</th>
<th>Period</th>
<th>Length</th>
<th>Tail nucleus</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Loa loa</em></td>
<td>blood</td>
<td>+</td>
<td>Day</td>
<td>275 µm</td>
<td>+ terminal</td>
</tr>
<tr>
<td><em>W. bancrofti</em></td>
<td>blood</td>
<td>+</td>
<td>Night (periodic strain)</td>
<td>260 µm</td>
<td>-</td>
</tr>
<tr>
<td><em>Brugia malayi</em></td>
<td>blood</td>
<td>+</td>
<td>Night (periodic strain)</td>
<td>220 µm</td>
<td>+ isolated</td>
</tr>
<tr>
<td><em>Brugia timori</em></td>
<td>blood</td>
<td>+</td>
<td>Night</td>
<td>290 µm</td>
<td>+ isolated</td>
</tr>
<tr>
<td><em>M. ozzardi</em></td>
<td>blood</td>
<td>-</td>
<td>-</td>
<td>200 µm</td>
<td>-</td>
</tr>
<tr>
<td><em>M. perstans</em></td>
<td>blood</td>
<td>-</td>
<td>-</td>
<td>&lt;200 µm</td>
<td>+ double row</td>
</tr>
<tr>
<td><em>M. streptocerca</em></td>
<td>skin</td>
<td>-</td>
<td>-</td>
<td>210 µm</td>
<td>+ and hook</td>
</tr>
<tr>
<td><em>O. volvulus</em></td>
<td>skin</td>
<td>-</td>
<td>-</td>
<td>250 µm</td>
<td>-</td>
</tr>
</tbody>
</table>
Dirofilariasis

Occasionally humans can be infected by species of filariae which normally have other vertebrates as the final host. The most well-known belong to the genus *Dirofilaria*.

*Dirofilaria immitis* is a worm that parasitises dogs and cats (so-called heart-worm). The adult worms are 10-30 cm long and are sometimes found in hundreds in the dog’s right heart chamber and/or pulmonary artery. The microfilariae are found in the dog’s blood and are transmitted via the bite of infected *Aedes* mosquitoes. Man is an accidental host in which further development of the parasite is not possible. Consequently there are no microfilariae in humans. The immature worms die in the branches of the human pulmonary artery which can cause coin lesions in the lung. These are asymptomatic round nodules, 2-3 cm in diameter, which are sometimes found by chance on a chest X-ray (coin lesion). As differential diagnosis with tumour is difficult, the diagnosis is often established on the basis of a lung biopsy. No treatment is necessary.

Other *Dirofilaria* (*Nochtiella*) species (*D. repens, D. tenuis*) are sometimes found subcutaneously in a nodule in humans. These nodules can migrate which is clearly different from nodules caused by cysticercosis. *Dirofilaria repens* causes swelling in the subcutaneous tissues in general around the eye, although various other locations are possible including spermatic cord and omentum. Treatment consists of surgical removal. It should be noted that these filariae produce no microfilariae in humans. The diagnosis is usually curative (resection biopsy).

Intestinal Nematodes

Summary

- *Ascaris*: common, lung passage, sometimes intestinal or biliary obstruction
- *Trichuris*: common, symptoms only in severe infection (diarrhoea, anal prolapse)
- *Enterobius*: common, anal itch, exogenous auto-infection
- Hookworms: common, lung passage, anaemia if worms are numerous
- *Strongyloides*: common, chronic, larva currens, lung passage, endogenous re-infection, fatal hyperinfection
- *Capillaria philippinensis*: rare, diarrhoea, endogenous re-infection, sometimes fatal
The first five species are currently aggregated under the term “soil-transmitted helminthiasis” (STH). More than a billion people are infected with at least one species.

**Ascaris lumbricoides**

**Summary**

- A very common parasite, 15 to 40 cm long – jejunum (small intestine)
- Lung passage may cause transient asthma-like symptoms
- Generally atypical symptoms, or asymptomatic
- Sometimes obstruction of hollow organs (intestine, pancreas and biliary tract) causing severe complications

**Life cycle**
Cosmopolitan but much more common in the tropics. The eggs pass on to the ground via the faeces. Fertilized eggs require 10 to 40 days in the outside world to mature before they become infectious. Direct self-infection is thus ruled out. Once they are mature the eggs are taken up once more (faecal-oral transmission) via contaminated food, drink (fluids), dirty fingernails or hands. In the intestine small larvae emerge from the eggs and these bore through the intestinal wall. In this way they reach the blood (portal vein system). They are carried with the blood, through the liver to the lungs. Lung passage occurs 3 to 14 days after ingestion. In the lungs the larvae make their way to the bronchial lumen and ascent via the respiratory branches into the throat. They are subsequently swallowed and in this way they again reach the intestine. They grow into adult worms in the jejunum. They do not damage the intestinal wall. Adult worms do not multiply in the human host; the number of adult worms in an infected individual depends on the degree of exposure to infectious eggs over time. Egg laying begins two months after infection when both female and male worms are present in the intestine. Each female worm produces approximately 200,000 fertilized eggs per day. The adult worm
survives on average for 1 year. The creatures reach 15 to 40 cm, making them the largest nematode parasitizing humans. There is no animal reservoir. Occasionally infections with *Ascaris suum* occur (parasite of pigs); this worm resembles *Ascaris lumbricoides* very closely and some think the parasites are identical.

**Epidemiology**

This is the most common worm infection in humans. It has a cosmopolitan distribution. Children are most often infected. The eggs are very resistant, which makes it possible in certain circumstances for them to survive for a long time in the outside world (years). The number of eggs which can be found in the soil is a measure of the hygiene standard and degree of sanitation of an area (faecal pollution of the ground).

**Clinical aspects**

The vast majority are asymptomatic. Any illness caused by worms depends to an important extent on the number of parasites. The total worm load is only increased by repeated exposure (exceptions are *Strongyloides stercoralis* and *Capillaria filippinensis* which can multiply inside the human body). Some people have various forms of intestinal discomfort or allergic symptoms. Serious complications are rare. Nevertheless, in view of the large number of infected persons, the morbidity and mortality should not be disregarded.

**Lung passage symptoms**

The larvae undergo lung passage. This produces rarely symptoms of mild to severe cough, dyspnoea, thoracic pain and sometimes fever. The clinical picture is similar to asthma or pneumonia. On chest X-ray migratory infiltrates are rarely observed. Eosinophilia is present. This whole phenomenon is called “Loeffler’s syndrome”. The sputum contains many eosinophils, Charcot-Leyden crystals and sometimes also larvae. The symptoms last for some days or max. 2 weeks. Most of the time this goes unrecognized.

**Obstruction of, or migration in, hollow organs**

- When numerous adult worms are present they may form a tangle and cause mechanical intestinal obstruction manifested by a bloated abdomen, increased peristalsis with clangor, colicky pain, vomiting (bile, faecaloid) and dilated intestinal lumen on an abdominal X-ray.
- Migration into the biliary tract may lead to biliary obstruction (cholestasis) with possibly infection
(e.g. cholangitis, liver abscess, pancreatitis).

- Sometimes there is migration to the appendix with inflammation (appendicitis).
- Sometimes an adult *Ascaris* is present in vomitus.
- Occasionally an adult can penetrate the lacrimal duct.
- Recent surgical intestinal sutures can be breached by an invasive adult *Ascaris*, leading to bowel perforation and peritonitis. Pre-operative deworming is advised in endemic areas.
- Infection with *Ascaris lumbricoides* also plays a role in the development of pigbel (clostridial necrotizing enteritis, an often fatal type of food poisoning caused by a β-toxin of *Clostridium perfringens*; see chapter on diarrhoea).

**Malnutrition**

*Ascaris* itself does not cause malnutrition. In borderline malnutrition the presence of numerous worms can have a negative effect, however. It is also important to know that many patients suffer from anorexia. On a population level the mass treatment (deworming) has a positive influence on the cognitive development in children.

**Diagnosis**

Since an adult female lays up to 200,000 eggs per day, as a rule no concentration technique is necessary to detect eggs in the faeces. If infection is solely with one or more male worms then no eggs will be detected. Stool concentration methods for detection of *Ascaris* eggs (rarely needed in endemic areas) include Kato-Katz and FLOTAC techniques like for other intestinal worms. Charcot-Leyden crystals, which consist of lysophospholipase, an eosinophil-derived enzyme, may be seen by microscopic stool examination.

During lung passage there is significant eosinophilia. After lung passage there is no longer appreciable eosinophilia. Sputum analysis may demonstrate eosinophils and Charcot-Leyden crystals.

X-ray of the intestine with barium contrast may show one or more adult worms. The worm forms a long, thin dark area. Sometimes a central longitudinal radio-opaque line can be seen; this is the intestinal tract of the worm. Such a line is absent in tapeworms.

An ultrasound of the pancreas (Wirsung duct) or of the biliary tract and gallbladder may show an ectopic migrating adult *Ascaris*. 
**Treatment**

Mebendazole (Vermox®): 100 mg BD x 3 days, effective, broad spectrum (or 500 mg single dose)

Albendazole, 400 mg single dose effective, broad spectrum

Ivermectine: similar efficacy (single dose 200 µg/kg) as single dose albendazole

(Flubendazole (Fluvermal®): 100 mg BD x 3 days, effective, narrow spectrum; Piperazine (Adiver®): narrow spectrum; Pyrantel pamoate/ oxantel (Antiminth®, Combantrin®) can be used in pregnancy; Levamisole; Tribendimine; Nitazoxanide)

Pulmonary manifestations can be treated with bronchodilators or if severe with systemic corticosteroids if *Strongyloides stercoralis* infection is ruled out.

**Drug resistance**

Benzimidazole drugs bind to nematode β-tubulin and inhibit parasite microtubule polymerisation. Drug resistance against front-line antihelmintics is widespread in nematodes of livestock due to frequent treatment of animals. Therefore, the effectiveness of drugs must be closely monitored in regions where mass antihelmintic chemotherapy is administered.

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**Trichuris trichiura**

**Summary**

- Adult worms measure approximately 4 cm (sometimes seen in stool) - colon
- Faeco-oral transmission via eggs.
- Generally asymptomatic
- In severe infections diarrhoea and sometimes anal prolapse
- Role in bacterial dysentery or invasive amebiasis?
Life cycle

Trichuris trichiura egg

Trichuris trichiura egg with its typical polar caps, suggesting a lemon-shape. Copyright ITM
Trichuris suis, related to Trichuris trichiura, a nematode which frequently infects humans. Copyright ITM

*Trichuris trichiura* is a cosmopolitan nematode, but is rare in subarctic areas. This is an ancient parasite and this is demonstrated in that it also occurs outside the tropics is that eggs were found in Ötzi the iceman, a bronze-age mummy discovered in the Italian Alps, and in coprolites (fossilized faeces) in prehistoric salt mines in Austria.

The eggs are eliminated with the faeces. Infection is via the oral route, after obligatory maturation in the outside world. Eggs embryonate in the external environment for 10-30 days, depending upon temperature: slower when colder; no development above 37°C. It is possible that in nature (as opposed to the lab) much longer periods are possible. Many eggs remain viable in the soil for longer than a year; depending upon local humidity. In Bangladesh, a study of 2400 houseflies discovered
that 47% of the insects were carrying eggs (flies acting as mechanical transport vectors).

The embryonated eggs hatch after ingestion. It is likely that the hatching worm dissolved the polar caps with enzymes. The fate of the larvae after hatching the first 5-10 days is controversial. No studies have been done on humans. Serial necropsy of dogs infected with T. vulpis suggest that larvae first penetrate the mucosal duodenal epithelium, re-emerge into the lumen 8-10 days later and settle in the caecum. However, this data is questioned and it is unclear if this can be generalized to human infections. More study is required to answer some basic questions.

Larvae will undergo four molts. Egg laying begins about 2 months after infection. Experimental infection in human volunteers showed a somewhat longer prepatent period of 120-130 days. It is estimated that 5-22% of ingested embryonated eggs develop to patency. A female worm measures 3-5 cm and sheds between 3000-20,000 eggs per day. Since the uterus of a female worm contains approximately 60,000 eggs at any one time, this implies that between 5 and 30% of the eggs have to be replaced on a daily basis. The adult worm has a thin whip-like head with which it buries itself in the mucosa of the large intestine especially the caecum. The worm survives for 1-4 years on average, although extremes of 20 years are known.

**Clinical aspects**

Most infected humans remain asymptomatic. Only in severe infections (> 1000 worms; >10,000 eggs per gram of faeces) do symptoms occur: these include diarrhoea (dysentery type), malnutrition or anaemia. In undernourished children with chronic diarrhoea and tenesmus there is sometimes prolapse of the rectum, in which the worms can be seen on the prolapsed mucosa.

**Diagnosis**

Diagnosis is based on faecal examination. No concentration technique is necessary for clinically relevant infections. The Kato-Katz technique can be used to quantify egg numbers. Sometimes the worms can be seen on the rectal mucosa (rectoscopy or during anal prolapse). Normally there is no eosinophilia (since there is no larval migration).

**Treatment**

- Mebendazole 100 mg BD x 3 days, or 500 mg single dose (but less active: 65-70%)
- Albendazole 400 mg BD x 3 days (for cure rate above 90%)
- Ivermectine is also less active
- The combination treatment albendazole plus oxantel pamoate showed higher cure rates and higher
egg reduction rates than mebendazole or albendazole alone.
- The new tribendimidine drug has limited activity

Hookworms

Summary

- Blood-sucking worms 1 cm long (but never seen in the stool); in the jejunum
- Transmission by larvae: transcutaneous and oral
- Brief local itch after skin penetration, lung passage (but very rarely noticed)
- Generally asymptomatic
- In severe infection iron deficiency anaemia

Life cycle

There are two important hookworms: *Necator americanus* and *Ancylostoma duodenale*. [L. necator = murderer; Gr. ancylo = hook, stoma = mouth]. There are a few zoonotic hookworms which are of much less clinical importance and seldom cause infections in humans (e.g. *Ancylostoma ceylanicum*, *A. caninum*, *A. malayanum*, *Cyclodontostomum purvisi*). The adult worms are found in the small intestine. It is estimated that the life span of adult worms is 5 to 15 years. *Necator* lives longer than *Ancylostoma*. The adults measure approximately 1 cm. A few weeks or months after infection eggs can be found in the faeces. Once the eggs arrive in the outside world with the faeces, they take one week to mature to infectious larvae. At first they are rod-shaped = rhabditiform, later thread-shaped = filariform. They may survive for weeks or months (at an optimal temperature and humidity for as much as 2 years). A soil with neutral pH is optimal for their development, as is shade and a sufficiently high temperature (23°C to 30°C is ideal). If the faeces mix with urine the eggs die. Frost, direct sunlight and a soil saturated with salt or water are unfavourable conditions.

Infection occurs via the mouth (*A. duodenale*) or via the skin (*A. duodenale* and *N. americanus*). If they enter through the skin, the young parasites have to pass through the lungs. A new dimension in the epidemiology of hookworm disease emerged when it was found that insufficiently cooked meat from paratenic hosts (= an intermediate host in which no development of the parasite occurs) such as pigs, cattle, rabbits and sheep can be responsible for transmission. The adult hookworms bore a hole in the mucosa of the duodenum and the small intestine and suck blood. They adhere with hooked
teeth in their mouth (Ancylostoma) or with two buccal cutting plates (Necator). A. duodenale sucks 5 to 10 times more blood than N. americanus (approximately 30 µl per day for Necator and 260 µl for Ancylostoma). Blood loss is caused primarily by parasite release of anticlotting agents -anticoagulant peptides that inhibit activated factor X and factor VIIa/tissue factor complex and that inhibit platelet activation- which causes continuous blood loss in the stool and only secondly due to actual blood consumption by the worm.

Clinical aspects
At the site where the hookworms penetrate, the skin may rarely develop a rash and itch (called “ground itch”). This is short-lived and rarely noticed. Lung passage also rarely produces symptoms, but may be accompanied by Loeffler’s syndrome. There are few intestinal symptoms. When infection with A. duodenale occurs by the oral route, the early migrations of third-stage larvae cause a syndrome known as Wakana disease, which is characterized by nausea, vomiting, pharyngeal irritation, cough, dyspnoea and hoarseness. Significant infections (>1000 worms) may result in pronounced anaemia. The haemoglobin level may sometimes be very low. Children and pregnant women in whom the iron supplies are already low, are particularly affected. Hypoproteinaemia may also occur and results in oedema and anasarca. Protein deficiency also has consequences for the production of immunoglobulins. Some patients exhibit geophagia. In history, certain regions in the USA were famed for their “quality” clay and people would cover great distances to eat this iron-containing soil.

Differential diagnosis:
Differentiation from Strongyloides larvae is based chiefly on the difference in morphology of the “head” end. The mouth is elongated in ancylostomes and shorter in Strongyloides. Sometimes, if intestinal transit has been swift eggs of Strongyloides stercoralis may be found in the faeces. These too should be differentiated from hookworm eggs.

Diagnosis
The eggs are found in fresh faeces. In an old stool (>24 hours) the eggs will have hatched and rhabditiform larvae can be seen (Gr. rhabdos = rod). There is mild eosinophilia. Since an adult hookworm lays approximately 25,000 eggs per day, as a very rough estimate 100 eggs per gram of faeces corresponds to 1 adult worm. The Kato-Katz concentration technique can be used to estimate the number of eggs per gram of faeces. The eggs of N. americanus and A. duodenale are morphologically indistinguishable.
Eggs of *Oesophagostomum* are morphologically identical to those of hookworms. Identification of the latter parasite can only be made by coproculture (identification of the typical stage 3 larvae).

**Treatment**

- Mebendazole 2 x 100 mg/day for 3 days. Also give iron supplementation and folic acid in anemia.
- Albendazole may be used in treatment (400 mg single dose) and is generally effective.
- Pyrantel 10 mg/kg for 3 days or levamisole 2.5mg/kg once or twice (less used nowadays)
- *Necator* and *Ancylostoma duodenale* are less sensitive to ivermectin (cure rate around 30%).
- Tribendimidine has a promising activity on hookworms

**Prevention**

Mass chemotherapy together with health education and sanitary provisions are strategies which are often used for morbidity control. The most heavily infected individuals are the chief target group. There are however increasing concerns about long-term sustainability. Wearing footwear only partly prevents infection because oral infection is also important for *Ancylostoma duodenale*. Children are the main victims as they rarely wear shoes and their whole skin is a portal of entry.

**Cutaneous larva migrans**

Some larvae from animal hookworms may penetrate human skin, but do not migrate deeper to the underlying tissues and organs. Their cycle thus reaches a dead end in the skin. Examples are the hookworms of dogs and cats (*Ancylostoma braziliense*, *Ancylostoma caninum*) and animal *Strongyloides* species. The migration of these larvae causes very itchy red lines on the skin which slowly move about (i.e. creeping eruption). A single oral administration of 12 mg of ivermectin (or albendazole 400 mg x 5 days) is effective.

**Strongyloides stercoralis**

**Summary**

- Infection with small worms 3 mm long (never seen in the stool) – small intestine
- Transmission by larvae is transcutaneous or oral
- Importance of endogenous re-infection and multiplication, which lead to very long-term infections
• Hypereosinophilia, larva currens with itch, chronic lung problems
• Hyperinfection in immunosuppression with steroids, HTLV-1

Life cycle

The adult female worm is found in the mucosa of the small intestine. Males cannot penetrate the intestinal mucosa and perish. Reproduction is asexual via parthenogenesis (=development of an embryo from an unfertilized egg cell). The females lay eggs after 2-3 weeks, from which larvae are quickly produced. Initially the larvae are described as rhabditiform. These quickly develop into filariform (infectious) larvae. These larvae may:

• either penetrate back into the intestinal mucosa (*Strongyloides* is one of the rare worms which can multiply in the human body).
• or pass to the perianal skin and from there again penetrate the body (auto re-infection). In auto re-infection there is always another lung passage. In this way an infection with *Strongyloides* may persist for a very long time (more than 30 years).
• or pass to the outside world with the faeces. From there after molting, they may go in either of two directions. The larvae either again penetrate the skin of a human (sometimes even via the mouth) or they develop to adult worms in the outside world. They may then via sexual reproduction in their turn lay eggs, from which new larvae develop. The worm can thus survive without a host.

Clinical aspects

Mild infection is generally asymptomatic. In severe infections there may be intestinal discomfort or diarrhoea. During lung passage symptoms may occur depending on the number of larvae. Auto re-infection via the skin may give sometimes rise to significant itching, chiefly peri-anal. Migration of the larvae in the skin leads to itching red swollen lines (on the rump, arms, face, etc.). These lines may occur anywhere and progress swiftly (up to 10 cm per hour). The swelling is the result of an urticarial reaction to the migrating larva (the larva itself is only 0.2 mm long). These lesion disappear spontaneously a few hours later, to reappear once more at a different site and this rather typical symptom is called “larva currens” (observed at some moment in about 20% of infected individuals).
Strongyloides stercoralis, larva currens. Such recurrent migrating linear urticarial stripes are pathognomonic for infection with this parasite. Copyright ITM

Immune suppression (especially HTLV-1 infection), achlorhydria (low gastric acid secretion), haematological malignancies including lymphoma, nephropathy, transplant patient taking immunosuppression (cyclosporine, tacrolimus), cytotoxic medication but especially the long-term use of systemic corticoids, all increase the risk of hyperinfection. In such cases there is extensive multiplication with spread of the larvae to all organs (including the brain) due to a dysfunction of the Th-2 helper cells. Symptoms include purpura-like skin lesions (initially often peri-umbilical), severe diarrhoea, pulmonary symptoms (dyspnoea, bronchospasms, bloody sputum) and meningoencephalitis. Hyperinfection with *Strongyloides stercoralis* may be accompanied by bacterial septicaemia (with usually Gram-negative bacteria). Mixed infection may occur. This probably depends on mechanical damage to the colon wall; adhesion of intestinal bacteria to the outside of migrating larvae and excretion of bacteria from the intestinal system of the parasite. Hyperinfection has a high mortality (75%). In chronic and persistent infection an underlying infection with HTLV-1 or use of
glucocorticoids should be considered. There have been fewer hyperinfections in AIDS patients than one would expect at first sight.

**Diagnosis**

The eggs hatch very rapidly in the intestine and are often not found in a faecal specimen. Larvae are found in the faeces. Often the numbers are not so high and specific concentration techniques, e.g. the Baermann method or modified agar plate method need to be used. In general, the diagnosis of *S. stercoralis* infection is difficult in the tropics as well as in travellers. Larvae can also be detected via duodenal intubation. Differentiation from hookworm larvae is necessary. Eosinophilia is almost always present, except when immune suppression exists. A history of larva currens is suggestive of strongyloidiasis and is enough to start treatment even if no larvae are found in the faeces. In hyperinfection larvae may be found in the sputum or in broncho-alveolar lavage fluid. The sputum must be regarded as infectious. If this sputum is cultured on blood agar, bacterial colonies can be seen which form a curvilinear pattern, reminiscent of a pearl necklace. This follows the migration of a larva on the agar plate, with translocation of the bacteria.

PCR on a stool sample is the most sensitive test, but is not widely available.

An ELISA test detecting IgG to filariform larvae in serum, can be used in immunocompetent hosts. However ELISA results can be falsely negative in immunocompromised hosts and in acute infection (as seen in travellers) during the window period. Cross-reactivity may occur in the presence of other helminth infections. As a whole serology is widely used in travel medicine to diagnose (past) exposure to *Strongyloides* but is almost nowhere available in the tropics.

**Treatment**

- Thiabendazole was used in the past, but had many side effects. Albendazole (400 mg twice daily for 3 to 7 days) is moderately effective. Mebendazole is not active.
- Ivermectin PO (200 µg/kg single dose) is easy to use and effective and at present is the first line treatment. Some experts recommend a second course after 1-2 weeks (an RCT is ongoing to answer this question). If immunosuppression is present, the cure rate with ivermectin is lower, certainly if cortisone has been taken. In such cases, successive courses of treatment should be administered. It should be mentioned that there are parenteral ivermectin formulations for veterinary use. They are not (as yet) registered for use in humans, but anecdotal case reports mention success with them.
- In hyperinfection it is important not to forget to use antibiotics, in view of the risk of severe
Enterobius vermicularis

Summary

- Cosmopolitan distribution
- Humans are the reservoir of this 1 cm long worm
- Ileocaecal region? Anal region: anal itch

Life cycle

This parasite is cosmopolitan. There is no intermediate host. Infection is via ingestion of eggs e.g. by eating food touched by contaminated hands or by handling contaminated clothes or bed linens. Eggs accumulate in the ileo-caecal region. After copulation the males die. The females migrate via the colon to the anus and lay their eggs chiefly at night as they creep over the peri-anal skin. This explains the nightly itching. Self-infection occurs by transferring infective eggs to the mouth with hands that have scratched the perianal area. Retro-infection or the migration of newly hatched larvae from the anal skin back into the rectum, may also occur. In rare cases there is vaginal itch because the females can also hide there. Sometimes the parasites are found in the appendix. The eggs must be sought not only in the faeces, but also on the peri-anal skin (using Scotch tape or other transparent sticky tape). In women the eggs may be found in the urine due to contamination. Apart from the itch there are few problems. There is a possible association between infection with Enterobius and infection with the possibly pathogenic amoeboflagellate, Dientamoeba fragilis. A hypothesis is that Enterobius vermicularis serves as a vector for D. fragilis, as D. fragilis DNA has been detected within surface-sterilized eggs of E. vermicularis.

Treatment

- Mebendazole 100 mg (Vermox®), to be repeated after 1 and 2 weeks. Albendazole is also effective.
- Ivermectin 12 mg single dose, to repeat after 2 weeks
- Pyrantel pamoate 10 mg/kg base once (max. 1 g); to repeat in 2 weeks
- Vanquin® (pyrvinium) may also be used as an alternative to mebendazole. The faeces may
Since the eggs can adhere to all objects e.g. underclothing, sheets and so on, these should be changed. In a family it is best to treat all the family members, even those without symptoms.

Capillaria philippinensis

Summary

- Infections with *Capillaria philippinensis* are rare, but potentially fatal
- Transmission by eating infected fish
- Endogenous multiplication resulting in chronic malabsorption and diarrhoea

Life cycle

*Capillaria philippinensis* is a nematode which causes severe infections. The parasite was discovered in 1960 in Luzon, an island in the Philippines. Subsequently it was also found in Thailand, Indonesia, Egypt, Japan, Taiwan, Korea and Iran. It is a parasite of fish-eating waterbirds. The infection occurs due to eating infected fish which live in fresh or brackish water. The larvae are found in the muscles of the fish. It is an intestinal nematode which has an intermediate host (most nematodes don’t). After developing to adult forms the parasites, which are 2 to 4 mm long, live in the mucosa of the small intestine. The worm is capable of multiplication in the human intestine (cf. *Strongyloides*). This phenomenon may lead to severe infection (high worm load). The incubation period can be very long (many months). Chronic watery diarrhoea, malabsorption and cachexia follow. The diarrhoea can be high volume (several litres per day). Ascites, pleural fluid and severe electrolyte imbalance including hypokalaemia may occur. The infection is sometimes fatal if not treated in time.

Diagnosis and treatment

Diagnosis is made by means of faecal examination. Often it is necessary to analyse multiple stool samples before eggs are found. Intestinal biopsy can show worm fragments. Every infection must be treated promptly with mebendazole, 200 mg x 2 per day for 20 days or albendazole x 10 days. Cooking fish prevents the infection. Eating raw fish is a culinary habit in many Asiatic countries and this is difficult to change.
Oesophagostomiasis

Nematodes of the genus *Oesophagostomum* (*O. bifurcum*, *O. aculeatum*, *O. stephanostomum*) are widely distributed intestinal worms of monkeys. In some regions humans are accidental final hosts. Foci of *Oesophagostomum bifurcum* infections occur commonly in parts of West Africa (Northern Ghana and Togo) with very high prevalence in some villages. The eggs are morphologically identical to those of hookworms. The larvae develop when the eggs land on the ground, progressing through stages 1-3 in 5 to 7 days. Probably a number of stage 3 larvae can resist long periods of dehydration. Stage 3 larvae are swallowed with food or water and penetrate the human intestinal wall. They then develop further inducing abscesses with a necrotic content (*helminthoma*). The worms may cause severe intestinal lesions, including eosinophilic granulomas in the intestinal wall (mostly caecum) and mesentery, deep abscesses and peritonitis. Epigastric or periumbilical masses may result.

As soon as the worms become adult they return to the intestinal lumen where they attach to the mucosa and mate. Adult worms in the intestinal lumen do not cause illness. In veterinary medicine the illness is known as “pimply gut” which refers to countless abscesses under the serosa.
Anisakiasis

Adult *Anisakis simplex* have been found in the stomachs of whales, seals, sea lions, walruses and dolphins. Humans are incidental hosts and the human “equivalent” of anisakiasis for sea animals is ascariasis. The eggs are eliminated with the faeces. In sea water the eggs hatch after embryonation after which the released larvae penetrate small crustaceans e.g. copepods or krill, which then in turn are eaten by fish or cephalopods. *Anisakis* larvae are usually restricted to the fish viscera in vivo only infesting the muscles after the fish has been killed, particularly if the fish is not promptly gutted and cleaned after its death. Humans become infected by eating undercooked or raw infected marine fish. The parasites which measure about 2-3 cm in length attach themselves to the gastric or intestinal mucosa by their anterior parts as far as the muscularis mucosa. This makes them visible during endoscopy.

In humans the parasites do not reach the adult stage and usually die off spontaneously after 3 weeks. The dying organism induces an inflammatory reaction and a tissue abscess develops with a predominance of eosinophils. **Gastric pain and nausea/vomiting** may occur within a few hours after eating infected fish or cephalopod but symptoms may have a late onset with abdominal pain appearing up to three weeks later. Late manifestations have rarely been described (several weeks to months) and are due to more distal intestinal infections. The infection is sometimes confused initially with appendicitis, stomach ulcer, duodenal ulcer, stomach cancer or Crohn’s disease. Rarely the worms perforate the intestinal wall and are found in the peritoneum. Eosinophilia is present. Approximately 95% of all cases in the world, which amounts to some 2000 cases annually, occur in Japan. Many different species of *Anisakis* larvae are being recognized as the cause of urticaria and hypersensitivity reactions after eating fish. The worm can in fact trigger quite dramatic hypersensitivity reactions even after it is dead. The first signs of an allergic reaction usually occur 60-120 minutes after ingestion, but may be delayed for up to 6 hours later probably due to passage of the food bolus through the gastro-intestinal tract. This means that urticaria and angio-oedema may occur at night. The diagnosis of allergy to *Anisakis simplex* is based on (1) a compatible anamnesis such as urticaria or angio-oedema after consumption of saltwater fish, (2) a positive skin prick test, (3) specific IgE against *Anisakis simplex* via radio-immunoassay, (4) negative reactions to the proteins of fish. There are some people who have antibodies to *Anisakis* without ever having exhibited
Therapy of anisakiasis consists of mechanical removal by means of surgery (in case of intestinal obstruction) or endoscopic extraction. Ivermectin and albendazole therapy has been suggested.

Thorough cooking to 70°C or adequate freezing to -20°C for a minimum of 72 hours are the best preventive measures.

Dracunculiasis

*Dracunculus medinensis* or Guinea worm, is a nematode that was distributed in the past in several African countries north of the Equator as well as in Central Asia, India and the Arabian Peninsula. During the slave trade cases were introduced into the New World but subsequently the disease disappeared spontaneously. In 1986 the total number of active cases was estimated to be
around 3,500,000 and the infection occurred in 20 countries. In 1993 there were 23,735 cases. The last foci in India and Yemen were eradicated in 1996 and 1997, respectively so the disease is now only found in Africa. In 2004, a total of 16,026 cases were reported. Southern Sudan, Northern Ghana and eastern Mali (regions Mopti, Kidal, Gao and Timbuktu) are the three last strongholds of the disease.
Map of the area endemic for Guinea worm.
Year after year, the map changes due to progress in the eradication programme.
Guinea worm
Guinea worm removal
Guinea worm (Dracunculus medinensis), life cycle

Humans acquire the infection by drinking fresh water containing infected small water fleas (Cyclops sp). After several moults in the water flea, infective larvae are produced. When humans drink water containing infected copepods, the vector is digested in the stomach. The infective larvae penetrate the stomach or the intestine and start maturation in the peritoneum. After 3 months copulation occurs. The male dies and the female grows further to reach her adult length of 60 to 100 cm after approximately 1 year. The long maturation period of approximately one year is required to coincide with the annual peaks in Cyclops numbers.

A female worm tends to be localised subcutaneously and causes a painful blister on the skin, usually on the lower legs or feet. The lesion occurs as a result of toxic secretions from the papillae around the parasite’s mouth. When the blister bursts it creates an ulcer. When the human host wades in fresh water, the female parasite discharges several hundreds of thousands of larvae. Each time the ulcer comes into contact with water, the female slides out further and releases more larvae a process that repeats itself over a number of weeks until the whole worm is “used up”. This process is slow, painful and disabling. The pain is alleviated by contact with cold water. This can be seen as a mechanism for promoting the survival of the parasite as a species because the victim looks for water to relieve the pain. The adult worm dies approximately 3 weeks after its emergence. After its death it will calcify and become visible on an X-ray, for example as an irregular calcified coiled string of about 2 mm diameter which should be distinguished from vascular calcifications.

The best approach is to remove the adult worm in its entirety. The adult worm can be coiled around a stick and one turn made daily. To accelerate expulsion, it is best to keep the wound constantly moist, for example with wet compresses. This however requires approximately 14 days. Surgical removal under local anaesthesia has been described.

Prevention is based on three approaches: safe drinking water, health information (people with wounds should not enter the water) and control of the vector (temephos (Abate®) is an organophosphate harmless to humans but kills the vector Cyclops.

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Cestodes

Taeniasis

Summary

- *Taenia saginata*: infection only via beef with larvae, resulting in an adult intestinal worm
- Infection with *Taenia solium* larvae present in pork results in an adult intestinal worm: vague abdominal symptoms or asymptomatic
- Feco-oral infection via human feces containing *Taenia solium* eggs results in cysticercosis: epilepsy, subcutaneous nodules, nodules located in muscles, etc.
- *Taenia asiatica*: resembles *Taenia saginata*, but is transmitted via pigs. No cysticercosis in humans.

Life cycle
Helminthiasis | 85

Eating insufficiently cooked infected beef (*Taenia saginata*) or pork (*T. solium*) leads to infection with adult tapeworms. Humans are the natural final host and the only carriers of these cestodes, and thus also the only distributors of their eggs. The adult worms live in the small intestine and are several meters long. The pre-patent period is approximately 3 months.

A third species of human *Taenia* has been described in Asia (*Taenia asiatica*). The clinical importance of this has still to be determined. At present insufficient is known about *T. asiatica*. The adult worm is morphologically very similar to *T. saginata*. The life cycle of this cestode is different, however. Unlike *T. saginata*, which causes infections in the skeletal muscles of cattle, *T. asiatica* affects the liver, omentum, serosa and lungs of pigs. At present, *Taenia asiatica* does not seem to cause neurocysticercosis in humans, but more study is needed.
Clinical aspects

Below, the symptoms present due to infection with an adult worm are described.

Most carriers of adult worms are asymptomatic. The length of an adult worm is usually ≤5 m for *T. saginata* (however, it may reach up to 25 m) and 2 to 7 m for *T. solium*. Some people present nausea, anorexia or epigastric pain. The loose segments of *T. saginata* (not of *T. solium*) may actively creep outside through the anus, and cause local discomfort. Each segment contains approximately 60,000 eggs. *Taenia* may have a role in malnutrition (5 to 7 cm of worm has to be produced every day, for which food is needed), but only if there are also other reasons for malnutrition. In only 15% of patients peripheral eosinophilia is present. Note that while many humans can carry *T. solium* adult worms without any apparent effect, these people are the only source of eggs. When ingested, these eggs can produce larvae both in the natural host and in humans. The larvae are the cause of cysticercosis in both pig and human. Human-to-human transmission can therefore take place so that cysticercosis can occur in people who do not eat pork or who have no pigs in their surroundings.

Diagnosis of infection with an adult worm.

Finding proglottids in the feces, or a history of motile proglottids crawling out of the anus is important. Eggs are sometimes found in the stools. The eggs are sticky and easily get onto the peri-anal skin. They can be detected in the peri-anal region with a Scotch tape test. There is no morphological difference between the eggs of *T. saginata* and those of *T. solium*. Differentiation can be made by the proglottids: a uterus with 10 branches or less in the dangerous *T. solium* and a highly branched uterus (12 or more) in the harmless *T. saginata*. *Taenia* antigens may be found in the feces. Only rarely can the tapeworm’s head be discovered. The undamaged scolex of *T. solium* bears two rows of hooks. The scolex of *T. saginata* is hookless. However, dysmorphic tape worms are sometimes encountered.

Treatment

- Niclosamide (Yomesan®) 4 tablets each of 500 mg will be taken together and chewed well. If the patient should vomit there is a theoretical risk that *T. solium* eggs will pass back into the stomach, activate and subsequently give rise to cysticercosis.
- Praziquantel (Biltricide®), in a very low dose (5-10 mg/kg), is also very effective. Praziquantel in a higher dose can sometimes provoke complications – such as sudden neurological symptoms – should cysticerci be present in the brain. This complication seems however extremely rare in endemic areas where praziquantel mass treatment is used to control schistosomiasis.

For successful treatment, the scolex must be destroyed and eliminated; a residual scolex can result in
regrowth of the entire tapeworm. Some experts recommend purgative treatment to be associated with antihelminthic drugs to have more probability to obtain the scolex in the stool, but this method is far from being universally accepted.

Cysticercosis

Summary

- Infection by *T. solium* eggs followed by development of cysticerci (= larvae) in the body.
- Symptoms depending on localization of the larvae.
- Neurocysticercosis with epilepsy is a common complication.

General

At the end of the 19th century cysticercosis was still occurring frequently in Europe. At that time cysticercosis was found in 2% of the autopsies in Berlin. Nowadays the disease has virtually disappeared in the West. There are still occasional imported cases. Approximately 50 million people worldwide are estimated to have cysticercosis infection, although subclinical infection may underestimate this number. The disease occurs in regions where pigs are kept and eaten (thus not in Muslim regions). In many poor areas pigs are not kept in a pigsty, but run about in the open. This is encouraged in some areas, so that the animals function as a kind of free waste-disposal system. These are generally also places where the sanitary facilities are inadequate. The animals can become infected from human faeces via coprophagy. Insufficient meat control is an important risk factor in endemic regions. Not cooking meat through is another risk factor. Cases of cysticercosis in non-endemic regions may sometimes occur via infection from the carriers of adult worms who have come from endemic regions. If these infected migrants are employed in a household they may cause infections in their new surroundings (e.g. Mexican women who go to work in households in the USA).

Life cycle

When larval *Taenia solium* infect a human they develop into an adult tapeworm. In contrast, if the eggs of *Taenia solium* are swallowed (food or water infected with human feces) the larvae
(oncospheres) which emerge from them penetrate the intestinal wall and spread throughout the whole body via the blood stream. Therefore note that cysticercosis is caused by infected human faeces and not directly by eating insufficiently cooked pork. People with cysticercosis do not necessarily have an adult tapeworm. Auto-infection in humans infected with an adult *Taenia solium*, is a possibility, however. In approximately 40% of people with cysticercosis an adult worm is found in the intestinal tract. The larvae migrate to various tissues and within 2 months convert into what are known as bladder worms (cysticerci). The typical bladder worm is a small ellipsoidal bag measuring 5-15 mm surrounded by a white translucent membrane. This bag contains clear fluid and a single round head, the protoscolex. When the cysticerci die off they are absorbed or encapsulated and calcify. Each egg produces 1 cysticercus. Larval multiplication does not occur. In the brain, cysticerci can become extremely large (many centimeters diameter) when they develop in the ventricles (racemose form, see below).

Cysticerci which are present in pork, evaginate normally in the human intestine to then grow to full adult worms. Evagination is also possible, (but rare) in the human eye and intraventricular evagination may occur in the brain. These are sites where no inflammatory capsule is formed around the parasite. Evagination does not occur in the muscles or in the cerebral parenchyma.

**Clinical aspects**

Symptoms vary greatly, depending on the location of the cysticerci and the immune response of the individual. Small cysts may be found in the muscles, subcutis, eyes and in other tissues, where they are usually asymptomatic but may cause discomfort when inflamed. They appear as small nodules (5-10 mm). Sometimes they are much larger (e.g. 30 mm or even larger). In neurocysticercosis (NCC) there are parenchymal, subarachnoidal, intraventricular, spinal and ocular forms. Racemose cysticercosis is an aberrant development form of the parasite similar to a bunch of grapes. Live cysticerci in the central nervous system often cause remarkably few symptoms. When the parasites degenerate there may be focal encephalitis and oedema. Sometimes they may trigger a severe inflammatory response within a few days, which can be fatal. In the brain they often cause late-onset epilepsy (common in Mexico and South America). Adult-onset seizures in endemic regions are therefore highly suggestive of neurocysticercosis. This can manifest itself as focal seizures (Jacksonian epilepsy). This is often followed by postictal confusion or transient paralysis (Todd’s paralysis) and/or speech ± vision problems. Todd’s paralysis usually disappears within 48 hours. Intraventricular cysts may cause obstructive hydrocephalus. According to a recent meta-analysis, the main syndromes caused by NCC by order of frequency are epilepsy (80%), focal deficits (15%), intracranial hypertension (10%) and cognitive declines (5%). Mixed locations (parenchymal + meningeal) are common, but spinal localization is rare. Chronic meningitis, paralysis of cranial nerves,
spinal cord lesions and mass effects may occur. Psychiatric symptoms, encephalitis-like, are possible in case of severe infection. All these neurological problems may be acute or delayed forms. Focal calcifications are detectable 8 months to 10 years after infection. Larvae cannot be regarded as dead, unless the lesion is completely calcified.

Radiograph of an arm, showing elongated oval calcifications, typical of cysticercosis (calcified cysts in muscle).
Taenia solium, calcified cysticerci in the muscles of the legs. Such lesions are typically oval and elongated when localised in a muscle.

Table: Symptoms of neurocysticercosis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>23-98%</td>
</tr>
<tr>
<td>Meningism</td>
<td>29-33%</td>
</tr>
<tr>
<td>Papilloedema</td>
<td>48-84%</td>
</tr>
<tr>
<td>Convulsions</td>
<td>37-92%</td>
</tr>
<tr>
<td>Abnormal mental state</td>
<td>74-80%</td>
</tr>
<tr>
<td>Focal deficits (motor and/or sensory)</td>
<td>3-36%</td>
</tr>
<tr>
<td>Ataxia</td>
<td>5-24%</td>
</tr>
<tr>
<td>Myelopathy</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Cerebral nerve defect</td>
<td>1-36%</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>5-34%</td>
</tr>
</tbody>
</table>

**Diagnosis**

Diagnosis is made by means of excision of skin nodules or by using serological techniques, including antigen detection. Antibody and antigen detection may be carried out on cerebrospinal fluid as well as serum, but are often negative if only one or two lesions are present. Lesions can be demonstrated by radiology, such as radiography targeting the soft tissues (shoulder and thigh muscles) and X-ray of the skull. In muscles, the calcified cysts tend to be elongated ovals.

MRI scanning of the brain is clearly superior to CT from a diagnostic point of view and scolices can sometimes be visualized through MRI. Living cysticerci are seen on a CT scan as hypodense lesions which are not enhanced by IV contrast. Degenerating cysticerci are sometimes isodense or hyperdense with an edematous ring-shaped zone which can be enhanced by IV contrast. They may disappear within 3 months. Sometimes the diagnosis can only be made by stereotactic brain biopsy. The parasite is often surrounded by an inflammatory infiltrate with plasma cells. Immunoglobulins
may accumulate in the cytoplasm of reactive plasma cells, and form prominent eosinophilic inclusions (Russell bodies). They are however not specific for cysticercosis.

Serology is available and EITB (enzyme-linked immunoelectrotransfer blot assay) uses affinity-purified glycoprotein antigens fractionated by electrophoresis which performs better than ELISA. Antigenic tests have been also developed, reflecting the presence of viable cysts (if their numbers is sufficient however), in contrast to antibody detection tests reflecting only (past) exposure. Field-adapted lateral flow antigen-based diagnostics are being evaluated.

The most important **differential diagnoses of cerebral ring-shaped lesions:**

- Cerebral toxoplasmosis
- Hydatid cyst
- Ectopic worms (Paragonimus, Schistosoma)
- Amoebiasis
- Tuberculosis and cryptococcosis
- Bacterial abscesses, septic emboli, nocardiosis
- Glioma, lymphoma, metastasis
- Haemangioma

**Treatment**

Therapy of neurocysticercosis is extremely complex and depends on the cysticerci stages (viable, degenerating, calcified) and localizations (intra- or extra-parenchymal). It remains a rather controversial area. Expert advice and a multidisciplinary approach are often required. The most important is to treat the symptoms first, mainly the seizures with anti-epileptic drugs (up to 2 years after the last seizure, like for other epilepsy). Medical treatment, when indicated, is based on administration of praziquantel (50 mg/kg/day) or albendazole (15 mg/kg/day) for 2 weeks, but in case of multiple cysticerci (>3), association of both drugs was found superior in seizure reduction.

In adequately selected patients (see below), antihelminthic therapy may reduce the risk of generalized seizures by 67% as well as of the number of seizures, and lead to complete resolution of the lesions at CT/MRI in a substantial proportion of patients. But in real life, the outcome is rarely this favourable. It is important to note that when the bladder worms die off they cause a local tissue reaction. Neurological symptoms may therefore exacerbate (generally on the 2nd to 4th day of treatment) and can be very difficult to manage where there are no neurosurgical facilities or neuro-
imaging. This effect can be mitigated by starting dexamethasone 1 day before the other drugs, maintained up to one month (a dose of 8 mg/day seems optimal), before it’s slowly tapered down. Albendazole does not interfere with carbamazepine (Tegretol®) or phenytoin (Diphantoin®). Corticosteroids reduce the blood level of praziquantel and increase albendazole levels, but this is probably of no clinical importance.

Recently the benefit of medical therapy has been questioned. Probably many patients with infections recover spontaneously. When treating neurocysticercosis, it is important to know beforehand whether there are intra-ocular lesions. Degeneration of a cysticercus in the retina, together with accompanying inflammation, may lead to acute blindness. Surgical removal via vitrectomy should be considered, but such a procedure is not without risk.

Today, experts recommend antihelminthic drugs only in case of viable (symptomatic) cysts without inflammation and degenerating cysts with inflammation (to accelerate involution). Granulomatous cysts and those already calcified, for which symptomatic treatment and steroids are sufficient, do not benefit from antihelminics. More and more a segregation is made between intra-parenchymal NCC, where medical therapy may be carefully proposed, except when there are too many lesions (contra-indicated because of the high risk of diffuse cerebral oedema), and extra-parenchymal (intraventricular, meningeal, spinal, ocular,...) NCC where neurosurgery is almost always required (due to risk of intracerebral obstruction and hydrocephalus) in combination with longer antihelminthic treatment at higher dose (extraparenchymal cysticerci are usually less susceptible to medication). Sometimes a ventriculoperitoneal shunt must be inserted in obstructive hydrocephalus. Shunt blockage is common if the cerebrospinal fluid contains large amounts of protein. Appropriate treatment of NCC is nearly unfeasible without adequate diagnostic/surgical facilities, and impossible without an initial careful neuro-imaging assessment. In remote, low-resource settings, it is often preferable to just treat the complications (epilepsy) with a symptomatic antiepileptic therapy, rather than using an etiologic treatment without possibility of monitoring or neurosurgical intervention.

Prevention

Since humans are the only reservoir for adult T. solium the disease can be controlled by improved sanitation and hygiene, in particular by controlling pollution with human faeces. Human carriers should be treated. To reduce the number of carriers of Taenia solium, proper statutory meat inspection should be carried out. Furthermore, meat should be heated to above 56°C or stored for at least 10 days at -10°C (requiring a freezer). Eating raw or insufficiently cooked pork should be discouraged. If there is a patient with cysticercosis, it is best to investigate whether the patient, close family members, domestic staff and friends are carriers of adult T. solium and constitute a possible
source. A faecal examination and an antigen-capture ELISA test are used for screening. If positive, a CT scan of the brain is carried out (detection of cysts in the brain).

Pigs can be treated with a single administration of oxfendazole, a benzimidazole. Vaccination of pigs is under study, and appears to be efficacious under controlled environments. There should be a strong recommendation that pigs not be allowed to run free. They are coprophagic. If humans do not compost their faeces, but use them directly as pig fodder or on the fields, the animals will become infected. Composting kills the eggs. Washing hands with soap after using the toilet should be encouraged. Parasitic infections in which faeces play a part, are a taboo subject in some communities. A control program needs to take account of this. There is no vaccine for human protection against T. solium. However, vaccines are available to prevent T. saginata infection in cattle and T. ovis in sheep.

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Cystic echinococcosis

Summary

- Infection from eggs in dog feces.
- Larvae form large cysts with internal daughter cysts.
- Cysts in the liver and lungs, rarely in other organs.
- Often asymptomatic, sometimes symptoms due to pressure upon surrounding organs.
- Risk of rupture with anaphylaxis or dissemination.

General

There are several tape worms in the genus *Echinococcus*: *E. granulosus*, *E. multilocularis*, *E. vogeli*, *E. oligarthus*, *E. shiquicus*. The most important and frequent one is *E. granulosus*, causing cystic echinococcosis or hydatid disease. *Echinococcus granulosus* is a small tapeworm (a few mm long) which infects dogs and other canines. Its distribution is world-wide. In some regions the problem is very important such as North Kenya around Lake Turkana and Kyrgyzstan and the surrounding central Asiatic republics. Various animals (sheep, goats, cattle, pigs) may become infected with the eggs in dog faeces. In the animal’s intestine the larva (called “oncosphere”) emerges from the egg. It penetrates the intestinal wall and is carried by the venous blood towards the portal vein. After development of the parasite, hydatid cysts are formed in internal organs. The cycle is completed
when a dog has the opportunity to eat offal containing hydatid cysts. In the dog’s intestine adult *E. granulosus* then develop, after which egg laying can begin. Each hydatid cyst leads to multiple adult worms.

Humans are accidental hosts. If humans take water or food contaminated by dog faeces, they will develop one or more hydatid cysts. The cyst contains fluid and daughter cysts and is known as a hydatid cyst. On the inside of each cyst is a germinal membrane. From this membrane countless protoscolices (small heads) develop. There is thus multiplication at the larval stage. A capsule of connective tissue is formed around the cyst. This capsule consists of the cyst wall together with the germinal membrane. The majority of cysts are found in the liver and lungs, but other locations are also possible (brain, bones, spleen, kidneys). These are often continuously growing cysts, which may produce pressure on surrounding organs, may rupture or die off and calcify. When the parasite has died and disintegrated the hooks which were situated at the former heads remain in the sandy fluid of the dead cyst, and these can be seen under a microscope. This is useful if there is doubt concerning the nature of a cystic lesion.

**Clinical aspects**

Humans are generally infected faecal-orally during childhood. The cysts grow very slowly, about 1 to 2 cm per year. The carrier may remain asymptomatic for a long time and symptoms are unusual before the cyst has reached 10 cm in diameter, at least in the liver, its preferred localization. There may be mechanical consequences. Pressure on surrounding organs leads to various symptoms and complaints. Hepatic cysts may lead to an enlarged liver with local discomfort, obstructive icterus with or without cholangitis. If localization is in the central nervous system this produces symptoms of a brain tumour, epilepsy, compression of the spinal cord or brain stem and even eosinophilic meningitis if there is spillage. If situated in the skeleton there is often bone pain, sometimes with fractures. This has to be differentiated from ordinary bone cysts or tumours. Lung cysts are usually asymptomatic, but sometimes there is a cough and thoracic discomfort. Renal cysts are sometimes found by chance and may cause unilateral kidney destruction. Allergic reactions may also occur, such as urticarial rash, bronchospasm, anaphylactic shock after rupture of a cyst (which may be spontaneous, after trauma or during surgery). After rupture there may be dissemination of the protoscolices in the peritoneum or pleura. Mechanical aspiration of a cyst may sometimes lead to rupture with allergic shock and dissemination.

**Diagnosis**

Plain X-ray of the abdomen (crescentic calcifications), X-ray of the lungs or CT scan. Ultrasound of the
liver shows a round or oval hypodense zone with retro-acoustic intensification. The cyst can contain septa or daughter cysts. The wall may appear split (the endocyst separated from the pericyst) or it may be partially or completely calcified. Sometimes the cyst appears heterogeneous and produces a pseudo-tumorous image. Sometimes the diagnosis is made during surgery. In case of doubt as to the nature of a cystic mass, the content of the lesions may be examined for the presence of hydatid sand or the presence of the typical small hooks which remain after the protoscolices degenerate. Serology may be negative in the case of well encapsulated liver cysts and lung cysts. Sometimes the serology is positive or the titer increases during treatment due to leakage of the cyst content and release of antigen which cause the immune response to increase.

**Ultrasound**

Various types of cysts can be identified by ultrasound. The following signs are regarded as pathognomonic for cystic echinococcosis (CE):

- Unilocular, anechogenic round or oval lesions with a pronounced laminated membrane or with snow-like inclusions.
- Multivesicular cysts or cysts with multiple septa with a wheel-like appearance.
- Unilocular cysts with daughter cysts which may exhibit a honeycomb appearance.
- Cysts with floating laminated membranes (“water-lily sign”) which may also contain daughter cysts.

Ultrasound is also of utmost importance to stage the liver cysts according to the 2010 WHO classification (see Fig 2 below), between active (or early: CE1 and CE2), transitional (C3a and C3b) and inactive (or late: CE4 and CE5) lesions. This has immediate implication for the prognosis and treatment of cystic echinococcosis.
**WHO Classification of hepatic hydatid cysts**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CL</strong></td>
<td>Unilocular anechoic cystic lesion without any internal echoes and septations</td>
</tr>
<tr>
<td><strong>CE 1</strong></td>
<td>Uniformly anechoic cyst with fine echoes settled in it representing hydatid sand</td>
</tr>
<tr>
<td><strong>CE 2</strong></td>
<td>Cyst with multiple septations giving it multivesicular appearance or rosette appearance or honey comb appearance with unilocular mother cyst; this stage is the active stage of the cyst</td>
</tr>
<tr>
<td><strong>CE 3</strong></td>
<td>Unilocular cyst with daughter cysts with detached laminated membranes appearing as water lily sign; this is the transitional stage of the cyst</td>
</tr>
<tr>
<td><strong>CE 4</strong></td>
<td>Mixed hypo and hyperechoic contents with absent daughter cysts, these contents give an appearance of ball of wool sign indicating the degenerative nature of the cyst</td>
</tr>
<tr>
<td><strong>CE 5</strong></td>
<td>Arch-like thick partially or completely calcified wall; this stage of cyst is inactive and infertile</td>
</tr>
</tbody>
</table>

**Treatment**
Waiting

Many cysts remain stable, calcify or even involute spontaneously. Small, calcified cysts in the elderly can usually be left untreated. As a whole, a wait and see attitude is recommended for CE4 and CE5.

Surgery

Pericystectomy or partial liver resection. Sometimes what is known as the “frozen-seal” method is applied. Using liquid nitrogen, a funnel is frozen onto the liver capsule to prevent accidental spillage. The liver is opened and the cyst content evacuated. During the operation, lavage is carried out with a scolicidal agent. Surgery is the treatment of first choice for large cysts (> 10 cm), for CE2-CE3b lesions, if there is superinfection or communication with the biliary tract. For extrahepatic cysts, surgery is always the treatment of first choice. Albendazole is administered ideally prior to surgery (but optimal timing is unknown, up to 4 weeks), and praziquantel is given at the time of the operation. This is done in order to diminish the risk of disseminated infection in case of accidental rupture or spillage during operation. Post-operative complications are not unusual.

Medication

Mebendazole is no longer used (only at high dose, in case of albendazole toxicity). Long-term therapy with albendazole (e.g. 800 mg daily for 6 to 9 months, blocks glucose uptake by the parasite) is usually used alone for CE1 and CE3a lesions < 5 cm and in combination with PAIR or surgery for bigger lesions or in CE2 and CE3b lesions. It is used in extended duration for inoperable and/or disseminated disease. Previously this was given in cycles, but nowadays the medication is administered daily without interruption. The efficacy of medical therapy varies greatly (overall cure rate of 30%) and clearly leaves much to be desired. Higher levels of albendazole sulphoxide (ricobendazole), the chief active metabolite, may be obtained by higher dosage, ingestion with a fatty meal, or by combination with praziquantel or cimetidine [cimetidine inhibits the breakdown of both albendazole and praziquantel]. Albendazole cannot be used during pregnancy. The combination albendazole (10-15 mg/kg daily divided in two doses) with praziquantel (40 mg/kg once a week) is probably more effective than either drug alone.

PAIR

Percutaneous treatment with the PAIR technique (puncture-aspiration-injection-reaspiration) can be used for CE1 and CE3a lesions. Daughter cyst should be ruled out, since their presence reduces the
likelihood of successful treatment with PAIR. Experienced surgeons can perform a laparoscopic variant of this technique. In hospitals where the necessary equipment is available, after detection of a cyst an endoscopic retrograde cholangiography is carried out. This permits determination of whether there is any communication between the cyst and the biliary tract. Under ultrasound or CT guidance the cyst is punctured transhepatically with a fine needle. The cystic pressure can be measured. Vital cysts have a pressure of 8-75 cm water. Dead cysts have a low pressure (0-2 cm water). Subsequently 10-15 ml of cystic fluid is aspirated. Live protoscolices are actively motile upon microscopic examination. Biochemical analysis of the fluid for the presence of bilirubin is carried out to exclude communication with the biliary three. If there is sufficient evidence of active echinococcosis, the remaining cystic fluid is aspirated. Afterwards a protoscolicidal agent is injected (generally 95% ethanol or 15-20% hypertonic salt). As a guideline the amount injected should by 1/3 of the volume of the aspirated fluid. After 10 to 30 minutes the cyst content is then aspirated again. The risk of rupture, dissemination or anaphylaxis is minimal if there is at least 1 cm (preferably 2 cm) between the liver capsule and the cyst wall.

If there is a cyst-to-biliary tract fistula, the PAIR technique cannot be used due to the risk of sclerosing cholangitis. It is advisable to begin albendazole one week before and to continue administering this until 4 weeks after the procedure. PAIR cannot be used for extra-hepatic lesions. Those who have no experience with PAIR are advised to leave this to an expert as the complication rate is quite high.

**Prevention**

De-worm dogs and prevent them from eating offal.

Keep dogs out of slaughterhouses.

The first results of a recombinant vaccine (EG95) administered to sheep and goats, are encouraging, and show protection of 83-100% for these animals.

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**Echinococcus multilocularis**

*Echinococcus multilocularis* or fox tapeworm is closely related to *E. granulosus* (dog tapeworm). The parasite occurs in the northern hemisphere, often in regions with a cold climate such as Alaska, the Alps, Siberia, north-west China and central Turkey. The eggs of the parasite are cold-resistant.
Transmission by sleigh dogs is known. Treatment of these draught animals with praziquantel reduces the transmission to humans. In the wild there is a cycle between canines (including fox, wolf, etc.) and various rodents, including mice. Domestic dogs and cats may also become infected. Humans become infected accidentally by faecal-oral transmission, e.g. by eating contaminated berries, or drinking water contaminated with fox faeces. After infection with eggs the larvae develop, resulting in alveolar hydatidosis of the liver and other organs. The cysts may calcify, but usually continue to grow slowly and constantly and are similar to a malignant growth. Metastasis may occur. There may be growth through to the diaphragm and into the inferior vena cava. Treatment is difficult and involves liver surgery and/or long-term therapy with antihelmintics (even life-long in inoperable cases).

**Hymenolepis nana**

In 1921 Saeki demonstrated direct transmission (i.e. without intermediate host) of *H. nana* in humans, in contrast with *H. diminuta* for which human infection requires ingestion of infected insects. *H. nana* occurs in foci and has a cosmopolitan distribution. The highest prevalence of this cestode is found in hot, dry regions. People become infected by swallowing an egg (faeco-oral transmission) or by accidentally swallowing an insect (flea, weevil) which acts as intermediate host. An intermediate host is not essential for infection. Humans are the only definitive host. The adult worm is found in the lumen of the small intestine. The adult parasite is smaller than *H. diminuta*: it only measures 2-4 cm (dwarf tapeworm). The strobila contains 100 to 200 proglottids. The course of infection is almost always asymptomatic, but marked hypereosinophilia can be present. Malignant transformation of *H. nana* has been described in an HIV-infected patient in 2015, being a novel disease mechanism of a neoplasm in invertebrates invading human tissue. The treatment of choice is praziquantel.

**Trematodes**

**Introduction**

The trematodes are flatworms which are of great importance in tropical pathology. They may affect various organs. They have at least two suckers, one oral and one ventral (*Heterophyes* has three). The oral sucker surrounds the mouth. The intestinal system has a blind ending. They have no blood
circulation. Oxygen is absorbed by diffusion. Most trematodes are hermaphrodites and thus possess both male and female genitalia. They have a cirrus (penis). The function of the Laurer canal is unclear, but it is probably a vestigial vagina. Cross-fertilization and self-insemination are both possible. There are exceptions, e.g. schistosomes have separate sexes. After leaving the ovary, the eggs are fertilized and subsequently surrounded by yolk in the ootype (an extension of the vitelline duct). Several concentric eggshells are formed. The eggshells then undergo a chemical reaction, a kind of tanning process, which makes them tough and harder. In this way the egg acquires its typical form, and becomes more resistant to conditions in the outside world, which are often unfavorable.

### Localisation

<table>
<thead>
<tr>
<th>Localisation</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal lumen</td>
<td>Large intestinal fluke (<em>Fasciolopsis buski</em>)</td>
</tr>
<tr>
<td></td>
<td>Small intestinal flukes (<em>Metagonimus</em>, <em>Heterophyes</em>)</td>
</tr>
<tr>
<td>Lungs</td>
<td>Lung fluke (<em>Paragonimus</em>)</td>
</tr>
<tr>
<td>Bile ducts</td>
<td>Large liver flukes (<em>Fasciola hepatica</em> and <em>F. gigantica</em>)</td>
</tr>
<tr>
<td></td>
<td>Small liver flukes (<em>Opisthorchis</em>, <em>Clonorchis</em>, <em>Dicrocoelium</em>, <em>Amphimerus</em>)</td>
</tr>
<tr>
<td>Blood vessels</td>
<td>Blood flukes (<em>Schistosoma</em> sp.)</td>
</tr>
</tbody>
</table>

**Intestinal flukes**

Various trematodes are found as adult worms in human intestines. Examples are *Fasciolopsis buski*, *Metagonimus yokogawai*, *Heterophyes heterophyes*, *Echinostoma* sp., *Gastrodiscoides* sp. Most infections are asymptomatic or provoke vague abdominal symptoms. Only in severe infestations (high worm load) are there likely to be signs of malabsorption. Eosinophilia is common. Diagnosis can only be made by examining the faeces for parasites. As a general rule most of these infections can easily be treated with praziquantel.
Lung flukes

Paragonimus sp.

Summary

- Transmission via eating infected crabs and crayfish
- Symptoms resembling pulmonary tuberculosis or chronic bronchitis
- Sometimes ectopic localization
- Diagnosis via detection of eggs in sputum

General

The parasite occurs in Southeast Asia and the Far East, in Central and West Africa. In America its distribution is limited to Central America and the north of South America. Usually *P. westermani* is reported, but there are a number of other species which can cause infection in humans (*Paragonimus africanus, P. bangkokensis, P. heterotremus, P. hueitungensis, P. kellicotti, P. mexicanus, P. miyazakii, P. ohirae, P. philippinensis, P. sadoensis, P. skrjabini, P. uterobilateralis)*.
Map showing areas endemic for Paragonimus westermani, P.kellicotti and P.africanus. Copyright ITM

Life cycle
Paragonimus westermani, life cycle. Courtesy of CDC, Division of Parasitic Diseases.

Adult worms live in the lungs. Eggs pass to the outside with the sputum. If sputum is swallowed, eggs may also be found in faeces. Once in the outside world and in water, miracidia (first-stage larvae) emerge from the eggs. They penetrate snails, where they undergo a transformation. After 3 to 5 months cercariae (second-stage larvae) leave the snail and penetrate crabs. Here the cercariae develop into metacercariae (third-stage larvae). It is this form which is infectious for the definitive host. Paragonomiasis is a zoonosis of carnivorous animals. Humans are only an exceptional host. They become infected by eating raw fresh-water crabs and river crayfish which contain infectious metacercariae. Excystation occurs in the duodenum. The larvae bore through the intestinal wall and migrate via the abdominal cavity and diaphragm to the lungs. There they develop into adult worms. The worms form a cavity 1 to 4 cm in diameter. Egg-laying begins 8 to 10 weeks after infection. The worms may also migrate to ectopic sites. An individual generally carries ≤20 worms, which can
persist within humans for 20 years. Paragonimus got its name from the shape with ‘gonads at the side’.

**Clinical aspects**

Mild infections are asymptomatic. In the acute stage (invasion and migration of the larvae) there may be diarrhoea, abdominal pain, urticaria and eosinophilia. This is followed by fever, thoracic pain, cough, dyspnoea and malaise. The chronic illness resembles chronic bronchitis and TB. There is spasmodic cough (especially after exertion) with expectoration of blood stained sputum, as well as dyspnoea sometimes with wheezing and pleural pain. When the parasite is located in an ectopic site (brain, peritoneal cavity, liver, subcutaneous region, etc.), causing an eosinophilic abscess, the symptoms depend on the place where the worms are.

**Diagnosis**

Diagnosis is by detecting the eggs. The eggs often need to be concentrated (e.g. mix sputum + water + potassium hydroxide, then centrifuge and examine the sediment). Differential diagnosis includes tuberculosis of the lungs, Loeffler’s syndrome, pulmonary abscess, chronic bronchitis, melioidosis, histoplasmosis, coccidiodomycosis, lung carcinoma and lung metastases. If sputum is swallowed, eggs may also be found in the faeces. Serology has a sensitivity and specificity > 90 percent.

**Treatment**

Praziquantel 75 mg/day for 3 days is very effective. Triclabendazole is an alternative. In cases of cerebral localization higher doses must be given but only under the protection of steroids due to the risk of epileptic fits secondary to perilesional oedema.

**Liver flukes**

**Summary**

- Small liver flukes: eating infected fish leads to cholangitis, icterus, eosinophilia, cancer of the bile duct
- Large liver flukes: eating contaminated plants leads to cholangitis, icterus, eosinophilia
Small liver flukes: Clonorchis, Opisthorchis and Metorchis

*Opisthorchis viverrini* and *Clonorchis sinensis* (= *Opisthorchis sinensis*) occur in Asia. Eggs eliminated in the bile and faeces are taken up by snails. After further development in these animals, they leave the mollusk and penetrate freshwater fish (metacercariae). Humans become infected by eating raw fish such as carp. After the larvae are released in the duodenum, they migrate directly via the main bile duct to the intrahepatic bile ducts. Thus, there is no tissue passage. The parasites are approximately 1 to 2 cm long and can live for 20 years. Dogs and cats form a reservoir.

There may or may not be symptoms, depending on the worm load and location of the worms. Intermittent pain may occur around the liver which is sometimes enlarged. If bacterial superinfection occurs, febrile suppurating cholangitis results. If impaction with obstruction of the main bile duct occurs, there will be progressive icterus. In long-existing cases of infestation with *Clonorchis sinensis*, secondary biliary cirrhosis and carcinoma of the bile duct (cholangiocarcinoma) may develop. The diagnosis is made by detecting eggs in the faeces. A concentration technique is necessary. However, if bile duct is obstructed, no eggs can be detected. Sometimes duodenal intubation is necessary (aspiration of bile containing eggs). Serology may be helpful. The treatment consists of praziquantel. A new drug, tribendimidine, appeared very promising for both *Opisthorchis* and *Clonorchis* in recent phase 2 trial.

Large liver flukes: Fasciola hepatica and F. gigantica

General
Infection with these large liver flukes is quite wide-spread among animals. For example, *Fasciola hepatica* causes liver rot in sheep. The encapsulated larvae (metacercariae) are found on all kinds of
plants such as water cress (*Nasturtium officinale*), etc. After infected plants have been consumed the larvae are released in the small intestine, migrate within the hour through the intestinal wall to the peritoneal cavity and then bore through the liver capsule about 5 days later. After further migration in the liver, they reach the bile duct after approximately 7 weeks and remain there, laying their eggs. These are transferred via the bile to the intestine, and then excreted with the faeces. A single liver fluke can lay up to 20,000 eggs a day but usually produces smaller numbers. It should be noted that fertilized eggs can be produced by a single liver fluke (they are hermaphroditic).

Eggs often remain viable for months and can overwinter. Survival for more than 2 years has been demonstrated at a temperature of 2°C. Fierce heat and drying out kills the eggs. At a temperature of approximately 25°C (the optimum temperature) eggs develop in about three weeks. There is much variation in the rate at which eggs are released, which is an advantage to the parasite, since a particular habitat will remain infectious over longer periods. Under the influence of specific stimuli a 130 µm long larva (miracidium) emerges from the egg. This is covered with cilia and is immediately mobile in water. It can easily swim for hours. The larva has eye spots and is highly phototropic (it swims towards the light). This prevents the larva from wasting time and energy exploring the bottom of the pond, where the intermediate host (usually *Lymnaea trunculata*) is not to be found. This is unlike *F. gigantica* where the miracidium actively swims away from light to find *L. natalensis*, which lives deeper down. If the larva does not find the correct snail within 24 hours its glycogen reserves are exhausted and the larva dies. If a miracidium arrives some 15 cm from a snail, there is pronounced chemotaxis and the larva swims directly to the host and penetrates it. The next development takes place within the snail. These snails can survive long periods of drought (via aestivation) and long-term cold (via hibernation). Inside the snail, the miracidium develops into a sporocyst and then into rediae, a stage named after the Italian physician Francesco Redi (1688). The rediae measure approximately 1-3 mm, are mobile and may cause significant damage in the snail (if the infection is severe the snail dies). After 4-7 weeks the first cercariae emerge from the rediae; they measure 250-350 µm and leave the snail. The cercariae swim around in the water, to encyst within 2 hours on particular plants. Each cercaria then changes into a metacercaria (plural metacercariae). Due to the amplification phase in the snail, a single egg can produce 4000 metacercariae. Metacercariae can survive for more than a year on pasture. They are destroyed by heat and drought (the effect of long hot summers).

**Clinical aspects**

Symptoms are present mainly during the migration period: fever, pain in the liver region, hepatomegaly, urticarial, eosinophilia. After this period symptoms are generally mild or absent. Sometimes there is cholangitis and obstructive jaundice. If raw goat’s or sheep’s liver is eaten, adult
worms can sometimes attach to the throat, resulting in local irritation (halzoun).

**Diagnosis**

The diagnosis is made by detecting the eggs in faeces or duodenal aspirate (eggs appear approximately 12 weeks after infection). Repeated specimens are often necessary in view of the small number of eggs which are produced daily. If an individual has eaten infected sheep’s liver, he/she can have eggs in the faeces, although no real infection occurs (spurious infection). Ultrasound or CT scan of the liver may show a clustering of hypo reflective or hypo dense tunnels in the liver parenchyma (these are inflamed bile ducts). Sometimes it is possible to actually visualize the moving worms. Via laparoscopy, one can sometimes find slowly migrating worm tracts. The specificity of serology is lowered by cross-reactivity with other helminths.

**Treatment**

The therapy is problematical at present.

- Praziquantel is not sufficiently active.
- **Triclabendazole (Fasinex®, Egaten®) 10 mg/kg taken in one dose** together with a fatty meal is becoming the treatment of choice. Triclabendazole-resistant F. hepatica strains are already known in cattle.
- Nitazoxanide is an alternative drug. The dose is 500 mg BD for 1 week.
- Artemisinine may become an alternative. Worm burden reductions of 99-100% were observed with a single dose of the drug.

LAST UPDATED BY ADMIN ON JULY 15TH, 2022

**Blood flukes**

**Schistosomiasis**

**Summary**

- Schistosomiasis (or bilharziasis): infection with small blood flukes
- S. haematobium, S. mansoni, S. japonicum are the most common
- S. intercalatum (closely related to S.guineensis) and S. mekongi are of regional importance
Hybrid species (*S. bovis*-*S. haematobium*) are occasionally found in humans. Certain species of fresh water snails are intermediate host. Transmission via skin contact with fresh water containing larvae (cercariae) released by intermediate host. Mainstay treatment with praziquantel, active against adult worms only. Artemisinin derivates are active against immature schistosomes. Symptoms depend upon worm load (number of worms), anatomical location of parasites, duration of infection and host immune system reactions. Short-lasting pruritus after transcutaneous infection is possible (swimmer’s itch). Acute schistosomiasis syndrome or “Katayama syndrome” a few weeks to months after primary infection (beginning of egg production). Fever, cough, influenza-like symptoms, abdominal pain, hypereosinophilia, splenomegaly. Ectopic localizations with e.g. neurological lesions may occasionally occur after primary infection, but also during chronic infection. Chronic lesions due to *S. mansoni* and *S. japonicum*: abdominal discomfort, bloody diarrhea, hepatic fibrosis with portal hypertension, esophageal varices, ascites, hepatosplenomegaly - no risk for colon carcinoma. Chronic lesions due to *S. haematobium*: hematuria, hydronephrosis, renal insufficiency, genital lesions, right heart decompensation due to pulmonary hypertension secondary to lung fibrosis. Increased risk for bladder carcinoma.

**General**

The infection was first described by Dr. Theodore Bilharz (1825-1862) when he was working in the Kasr-el-Aini hospital in Cairo. Schistosomiasis or bilharziasis (this terminology should be abandoned) is a disease caused by flatworms (trematodes or flukes). There are 3 main species which infect humans: *Schistosoma haematobium*, *S. mansoni* and *S. japonicum*. There are a few other species that infect humans, but these are less widespread: *S. mekongi* and *S. intercalatum*. Approximately 200 million people throughout the world are infected, a minority of whom are severely infected.

Both males and female worms have two suckers. The more anterior one surrounds the mouth. Bilharz mistakenly took the two suckers for two mouths and thus called the worm Distomum (“two mouths”). Five species of schistosomes are known to infect humans and lay eggs (complete their life cycle). Infections with *Schistosoma mansoni*, *S. japonicum*, *S. mekongi*, and *S. intercalatum* are associated with intestinal lesions and chronic hepatic fibrosis. *S. haematobium* infection mainly results in fibrosis, strictures and calcification of the urinary tract.
Eggs reach the outside world via the faeces or urine. Each egg contains a larva that possesses numerous cilia. In a fresh microscopic preparation, a larva can be seen moving in the egg. If an egg reaches fresh water, the larva (synonym miracidium) is released. If the eggs do not reach the water, the larvae die rapidly, except in the case of *S. japonicum*. The latter can survive for up to 80 days outside the body (importance for hibernating). After swimming around for a while, a miracidium penetrates a snail (each parasite species is restricted to its own range of host snails). After two generations in the snail in the form of primary and later daughter sporocysts, a very large number of larvae each with a bifurcated tail, known as cercariae, is released. There is asexual proliferation in the snail, therefore one miracidium can produce up to 100,000 cercariae (etymology Gr. “kerkos” = tail). Cercariae live for 48 to 72 hours. Infection is acquired via skin contact with contaminated water. These larvae can actively penetrate the skin in 3 to 5 minutes. Cercariae penetrate the skin of humans or, in the case of *S. japonicum*, humans and other mammalian hosts that act as reservoirs for
infection.

Once in the human body, the cercariae lose their bifurcated tail and develop further into schistosomula. After migration through the dermis and the lungs, they reach the liver. Copulation occurs in the blood vessels of the liver (in contrast to other trematodes, schistosomes are not hermaphroditic but have separate sexes). Afterwards, the worms migrate upstream to their final destination: the superior mesenteric venules in the case of *S. mansoni*, the inferior mesenteric and superior hemorrhoidal venules in the case of *S. japonicum*, or the vesical plexus and veins draining the ureters in the case of *S. haematobium*. Egg production starts (300 to 3000 per day, depending on the species) four to six weeks after infection. The eggs mature in approximately one week and remain alive for 3 weeks (longer in the case of *S. japonicum*). The eggs contain a miracidium that is motile (cilia). The movement can be seen in fresh microscopic preparations. The adult worms are not carried away by the flow of blood because they are attached to the vascular wall with two suckers per worm. The short, wide male contains the longer thinner female in a sort of groove, the gynaecophoric canal. It was previously thought that this was a single animal with a split body. This continuous “embrace” led to the parasite’s name [schistos = split; soma = body]. The male is approximately 10 mm and the female 20 mm long. The mean life span of the adult worms is 3 to 7 years, but some can survive for up to 20 years. The theoretical reproduction potential of one schistosome pair is up to 600 billion schistosomes. For *S. haematobium* and *S. mansoni*, humans are the most important reservoir. *S. japonicum*, however, is predominantly a parasite of animals (water buffalo, dog, pigs, etc).

**Geographical distribution**

<table>
<thead>
<tr>
<th>Schistosome</th>
<th>Distribution</th>
<th>Site of infection</th>
<th>Snail Host</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. mansoni</em></td>
<td>Africa, Middle East, South America</td>
<td>GI-tract, mostly colon</td>
<td>(Biomphalaria sp)</td>
</tr>
<tr>
<td><em>S. haematobium</em></td>
<td>Africa, Middle East</td>
<td>Urinary tract</td>
<td>(Bulinus sp)</td>
</tr>
<tr>
<td><em>S. intercalatum</em></td>
<td>Central Africa</td>
<td>GI-tract, mostly rectum</td>
<td>(Bulinus sp)</td>
</tr>
<tr>
<td><em>S. japonicum</em></td>
<td>Southeast Asia and Far East</td>
<td>GI – small intestine</td>
<td>(Oncomelania sp)</td>
</tr>
<tr>
<td><em>S. mekongi</em></td>
<td>Mekong basin</td>
<td>GI-tract</td>
<td>(Tricula sp – syn. Lithoglyphopsis)</td>
</tr>
</tbody>
</table>
Global distribution of countries where human schistosomiasis is transmitted. Source Bruno Gryseels and colleagues

**Vector**

Each *Schistosoma* species has its own snail species as a vector: see table above. These snails require well-defined ecological conditions to thrive. The average temperature plays a role. If it is too cold, the snails cannot proliferate. There is thus practically no transmission above 1800 meters, where the water temperature is too low. Some snail species resist periods of long-term drought. This explains the occurrence of schistosomiasis in locations where there is only abundant water during the rainy season. At these sites, there is naturally no transmission during the dry season.
Biomphalaria alexandrina. This snail can harbor Fasciola gigantica and Schistosoma mansoni (bilharzia). Copyright ITM

Snails. Bulinus truncatus / Bulinus africanus, host for Schistosoma haematobium, bilharzia. Copyright ITM
**Hosts**

<table>
<thead>
<tr>
<th>Schistosoma Species</th>
<th>Hosts</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. mansoni</em></td>
<td>principally humans, also baboons and rodents</td>
</tr>
<tr>
<td><em>S. haematobium</em></td>
<td>principally humans, rarely monkeys</td>
</tr>
<tr>
<td><em>S. intercalatum</em></td>
<td>only humans</td>
</tr>
<tr>
<td><em>S. japonicum</em></td>
<td>animals: water buffaloes, dogs, cats, rats, pigs, etc., also humans</td>
</tr>
<tr>
<td><em>S. mekongi</em></td>
<td>dogs, sometimes humans</td>
</tr>
</tbody>
</table>

**Immunologic aspects of schistosomiasis.**

Longstanding epidemiological and clinical observations indicate that people living in endemic areas acquire some form of immune resistance after years of exposure. However it is not clear if true immunity is acquired or if the reduction in number of infections can be explained by reduced water contact after adolescence.

Comparative studies of reinfection after curative treatment have demonstrated that children are far more susceptible than adults and that these differences cannot be explained by quantified water contact patterns. Numerous studies in humans and in animal models suggest that acquired immunity would be mediated by IgE against larval and adult worm antigens, which stimulate eosinophils to release cytotoxines targeting schistosomulae.

Cellular immune responses against eggs and the enzymes they release are responsible for most schistosomiasis-related pathology. The granulomatous reactions around the eggs are orchestrated by CD4 T-cells and involve eosinophils, monocytes and lymphocytes. A shift from a predominantly $T_{h1}$ reaction in early stages of the infection to a “modified” $T_{h2}$ profile in chronic infections would account for the regression of the granulomas and their replacement by collagen. This has important implications for targeted mass treatment. Heavily infected children often present with non-fibrotic hepatomegaly due to its $T_{h1}$ nature, and this pathology is usually reversible upon treatment. Likewise in early urinary schistosomiasis, haematuria seen in children promptly disappears after treatment with praziquantel.

**Clinical aspects**
Pathophysiology

Schistosoma mansoni egg-induced granulomas in the liver of an infected mouse. Eggs are roughly 120-180 μm long, 45-70 μm wide. From The Lancet

Pathology depends on the stage of the infection. Chronic symptoms are related to the total worm load (= number of worms in the body). Usually, light infections are asymptomatic. The likelihood of symptoms increases with an increase in the degree of infection. Sometimes parasites are found at ectopic sites (e.g. spinal cord), in which case there can be severe consequences, even in mild infections. Most people in endemic areas acquire some immunity over the course of the years. Many adults exhibit few signs of infection. This immunity is directed towards new infections, against schistosomula. Adult worms are covered in an unusual skin (“tegument”) that displays few parasite proteins on its outer membrane. As a result, the immune system usually takes little notice of the adults. In addition, certain human molecules, such as those which determine blood type, can stick to the surface of the worms, further shielding the parasite from the immune system. The immunological reaction directed towards the eggs produces cytokines which induce a host Th-2 immune response, leading to an eosinophilic granulomatous reaction, responsible for most pathology.
Clinical, Swimmer's itch. A local cutaneous itch can occur where cercariae penetrate. Slight erythema and pruritic papules develop, but will disappear spontaneously. This is well known with S. mansoni, S. haematobium and with S. japonicum. The itch is more frequent and violent in infections with animal schistosomes, probably because the cercariae die after penetration in humans (e.g. avian schistosomiasis, which also occurs in areas with a moderate climate).

Acute schistosomiasis (or “Katayama fever”) is caused by primary infection with schistosomes and represents a hypersensitivity reaction to maturing schistosomules (and probably also to antigens released from the eggs). It usually occurs 3 to 8 weeks after initial infection. It can be mild or severe, with one or more of the following symptoms: fever, general discomfort, abdominal pain, diarrhea, vomiting, flu-like syndrome with muscle and joint pain, severe dry cough, wheezing, urticaria and sometimes lymph node enlargement and hepatosplenomegaly. There is nearly always a marked eosinophilia of > 1000/µL. Katayama fever is less frequent and milder in S. haematobium infections.

Diagnosis and treatment of acute (symptomatic) schistosomiasis

- Katayama fever tends to occur in patients who are not previously exposed, although in the case of S. japonicum this syndrome can also occur on re-infection.
- History of recent exposure, freshwater contact in endemic area < 10 weeks before symptom onset.
- Respiratory disorder and/or abdominal discomfort with fever and hypereosinophilia (DD trichinellosis, fascioliasis, filariasis, Strongyloides hyperinfection, etc.). Acute schistosomiasis is the most common cause of fever with hypereosinophilia in travelers returning from endemic areas, almost exclusively after a stay in sub-Saharan Africa.
- Eggs usually only appear in the faeces or urine after 6 to 12 weeks. Failure to detect eggs thus does not rule out acute schistosomiasis.
- Serum antibody tests may turn positive from 6 weeks after infection, but often much later.
- In acute schistosomiasis, the performance of PCR based genomic tests and of soluble schistosome antigen tests in blood and urine is still a research object.
- Treatment of acute schistosomiasis consists of steroids in the acute symptomatic phase, and additionally with praziquantel once symptoms are subdued with steroids. Repeat the course of praziquantel after a 3-4 months. Praziquantel is only active against adult worms.

Ectopic localisations

Central nervous system schistosomiasis occurs by ectopic worm or egg dissemination via the bloodstream through retrograde venous flow into the Batson vertebral epidural venous plexus, which
connects the portal venous system to the spinal cord and cerebral veins. When eggs and/or adult worms cause lesions of the spinal cord, transverse myelitis (principally *S. haematobium* and *S. mansoni*) or brain lesions (principally *S. japonicum*) ensue. These take the form respectively of spastic paraparesis and CVA or space-occupying lesion (hemiplegia, epilepsy, etc...). Urgent treatment consists of steroids for several weeks to months to limit the local inflammatory reaction. Treatment with praziquantel has to be given while continuing steroids. Sometimes eggs can reach the skin, where they can cause papular dermatitis. This rare condition can only be diagnosed by biopsy. Even rarer is localization in the vocal chords, with nodules and hoarseness.

In acute schistosomiasis, a form of localized hypersensitivity encephalopathy may occasionally occur and requires steroids for effective initial treatment.

**Symptoms in chronic infections**

**General**

The live larvae (miracidia) in the eggs excrete proteolytic enzymes that digest the surrounding tissues. In this way, eggs can reach the rectal lumen or the bladder after their migration through the intestinal mucosa (*S. mansoni* and *S. japonicum*) or the bladder mucosa (*S. haematobium*). In general 50% or less of the eggs are eliminated with the faeces or urine. The remaining eggs either die locally or are transported with the venous blood until they reach the liver or another organ where the blood vessels become too small for their further passage. At this point the eggs and digestive juices which they secrete can cause local inflammation. The lesions of chronic schistosomiasis can be explained almost exclusively by the local inflammatory reaction to these eggs (formation of granulomata containing numerous eosinophils). Inflammation granulomata can reach up to 100 x the size of the original egg. Fibrous thickening and loss of elasticity of the tissues occurs. If massive infestation is present pseudopolyps occur in the intestine or bladder. The symptoms in chronic schistosomiasis differ according to the location.

**Intestinal lesions**

Diarrhoea sometimes with some blood and mucus, can be caused by *S. mansoni* and *S. japonicum*. Pseudopolyps can occur in the colon. There is no increased incidence of intestinal cancer. In severe chronic infections, fibrosis of the intestine can occur. *S. mekongi* and *S. intercalatum* are also found in the intestine but usually does not cause severe pathology.
Hepatosplenic schistosomiasis

When *S. mansoni* eggs are carried in the portal venous bloodstream as far as the liver they cause a physical obstruction of the bloodstream. Local inflammation around the eggs exacerbates this. The result is increased pressure in the portal circulation (portal hypertension). Clinically it takes the form of:

- Collateral circulation with oesophageal varices and increased venous markings on the abdominal skin, principally around the navel (umbilicus), the so-called “caput medusa”. Eggs can also reach other organs subsequently via this collateral circulation (lung).
- Ascites is a late sign.
- Because the eggs obstruct the branches of the portal venous system and fibrosis occurs around these foreign bodies, periportal fibrosis develops. This is also known as Symmers pipestem fibrosis which is seen years later in the course of the infection. The white fibrotic bands in the liver are in fact long and hollow like pipestems (in the center is a branch of the portal vein). Liver function remains surprisingly well preserved for a long time (normal blood coagulation, no severe hypoproteinemia, no hepatic encephalopathy, no gynaecomastia). This stands in contrast with chronic aggressive hepatitis B and alcoholic cirrhosis. *S. japonicum* lesions are usually more severe because the worms produce ten times more eggs per day (3000 as opposed to 300) than *S. mansoni*. People with severe, chronic infections often die from bleeding from oesophageal varices.

Renal and urinary tract lesions

*S. haematobium* eggs lie grouped together in the bladder wall and surrounding organs (rectum, prostate, vagina, cervix, ovaries). This leads to the formation of very small (sandpaper-like) to a few mm large fleshy polyps and ulcerations. *S. haematobium* infection is a cause of genital lesions which are often mistaken for “warts”. The lesions in the urinary tract cause blood to be passed in the urine. In endemic areas this occurs typically in children of school age. The severity of the haematuria and proteinuria is related to the degree of infection. Ureteral strictures occur mostly in the distal third (mainly in the intravesical part). Ureteral obstruction can occur with resultant hydro-ureter and hydronephrosis. Because of the impairment of the normal anatomical relations vesico-ureteral reflux can also occur. Initially these lesions are still reversible. *S. mansoni* can give rise to a deposition of immune complexes in the kidney leading to glomerulonephritis. This happens in about 0.5% of cases usually in those with severe infections. In *S. haematobium* schistosomiasis the bladder wall can thicken. This resembles the thickening that can occur in tuberculous cystitis, chronic interstitial cystitis, radiation cystitis, chronic chemical cystitis or as a result of muscular hypertrophy with
obstruction due to prostatic hypertrophy or neoplasia or with a neurogenic bladder. At a later stage in bladder schistosomiasis, calcification of the dead eggs in the bladder wall occurs which is clearly visible on X-ray film.

Bladder calcifications due to Schistosoma hematobium

Bladder carcinoma

In highly endemic areas of *S. haematobium*, there is an increased incidence of bladder carcinoma. This is manifested around the 4th or 5th decade of life. It principally involves a highly malignant squamous cell carcinoma which can occur anywhere in the bladder wall (in contrast to transitional cell carcinoma that occur later in life and is located principally in the trigonum). There may be a relationship with increased carcinogen concentrations (DNA alkylating nitrosamines) due to frequent bladder infections with nitrate-reducing bacteria, due to smoking tobacco or due to the local production of nitrosamines via activated macrophages.
Late consequences

After severe chronic infection, the following serious problems can occur:

- Reduced bladder capacity.
- Increased incidence of bladder carcinoma, especially in tobacco smokers.
- Lesions of the female genitalia with cervical erosions, papillomatous lesions, sterility, increased risk of ectopic pregnancy and sexually transmitted diseases such as HIV.
- Lesions of the male genitalia e.g. localization in the ductus spermaticus.
- Irreversible obstruction of the urinary tract with hydro-ureter and hydronephrosis.
- Renal stones can form. Recurrent bacterial urinary infections are frequent, including *Salmonella*.
- Nephrotic syndrome can occur, as well as hypertension.
- Finally, chronic renal insufficiency may ensue.
- Remember that chronic glomerulonephritis can be caused by *S. mansoni* which is localized in the intestines (and eggs in the liver); This is secondary to the deposition of immune complexes in the renal glomeruli.

**Cardiac and pulmonary lesions**

*S. haematobium* eggs can reach the systemic circulation and only rarely reach the portal circulation. This parasite is not a cause of hepatosplenomegaly. These eggs then reach the lungs. The same can happen with severe portal hypertension when *S. mansoni* or *S. japonicum* eggs reach the lung via the collateral circulation. Inflammation occurs in the lungs resulting in fibrosis and pulmonary hypertension. Right heart failure then occurs with development of cor pulmonale with congested jugular veins, peripheral edema and congested swollen liver. It used to be common in Brazil and Egypt but less so in recent years.

**Association with other infections**

Patients with schistosomiasis (*S. mansoni*, *S. haematobium* and *S. japonicum*) are at increased risk of being *Salmonella* carriers. These bacteria are found in the intestinal tract of the worm. Urinary schistosomiasis often results in recurrent bacterial urinary tract infections.

Genital schistosomiasis is an independent risk factor for HIV infection since eggs can induce inflammation leading to development of ulcerative lesions in the female reproductive tract.
Diagnosis

Microscopy

The definitive diagnosis is established by the detection of eggs in the stools or urine with or without concentration techniques. The weight of a stool specimen that can be examined by direct microscopy is approximately 2 to 4 mg. In view of the small volume, egg excretions of up to 100,000 eggs per day can be missed. Only severe infections are detected in this way. The Kato-Katz method (cellophane impregnated with glycerol and malachite green) uses a larger quantity of stool (25 to 50 mg). The method is simple and more sensitive but more cumbersome. Low-grade infections can still be missed. Concentration of ova in faeces or urine can be done by a range of techniques.

Schistosoma mansoni egg with a large lateral spine. Copyright ITM
The sensitivity of the laboratory tests can be problematic. It is dependent on the quantity of sample which it is feasible to routinely examine. A sample of 10 ml urine is equivalent to approximately 1/100 of the daily production and thus theoretically makes it possible to detect even a mild infection if it is assumed that at least 100 eggs/worm pair/day are found in the urine. With more than 50 eggs/10 ml there is almost always (microscopic) hematuria and proteinuria and this number has therefore been taken as the accepted threshold for distinguishing between mild and more severe infections. A stool smear by contrast, examines only 2 mg out of a total quantity of feces which for an adult in a tropical environment, may be estimated as 200-400 g/day. In this case therefore only 1/100,000 - 1/200,000 of the daily quantity of stool excreted is examined.

The severity of infection is reflected by the egg load. In S.mansoni infection, egg loads of less than 100 eggs per gram feces (epg) are considered mild and severe infections have more than 400 epg. A
mild infection is equivalent to more than 5 eggs/Kato smear. For this reason the WHO recommends the Kato method with which it is possible to examine 25 to 50 mg of stools, sufficient to discover all severe infections. It is however clear that even with this technique many milder infections are missed. It is important that a positive smear always indicates an infection which is already fairly severe.

There are several other flotation and sedimentation concentration methods which allow detection of lighter degrees of infection. For instance the FLOTAC stool concentration method is about 10 times more sensitive for S. mansoni egg detection than the Kato-Katz. The sensitivity is also affected by fluctuations in the quantity of eggs in the excreta. This is the case for excretion of S. haematobium eggs which peaks around midday. Specimens taken between 10 a.m. and 2 p.m. are therefore optimal for examination. During the evening hours and the night elimination falls to a minimum. This periodicity is the result of contractions of the muscle wall of the bladder which itself is affected by drinking/meals and exercise and not by the production of eggs (which occurs continuously). In the case of intestinal schistosomiasis this systematic factor has little if any importance.

An additional source of error is that the elimination of eggs in the same person can vary considerably from day to day, making the individual diagnosis more difficult. The consequence is that a negative parasitological examination even with sensitive techniques is only of limited value. In a severely infected person, on average high egg loads are found and only rarely low egg loads. The opposite is true for people with low worm loads. Taking fecal specimens on different days is better than examining several smears from 1 stool.

**Serology**

Serology based on the detection of antibodies, does not distinguish between active and previous infections. Positive serological tests with low titers which cannot be confirmed parasitologically probably indicate either (1) an old, cured infection, (2) an infection with a very low worm load, (3) an infection by worms of a single sex or (4) cross-reactivity with other worm species. Antibodies are usually detectable before eggs are detectable.

**Antigen detection**

Circulating antigen detection tests (circulating anodic and cathodic antigen CAA and CCA) have been developed, as a means to detect schistosomiasis. Antigen can be detected in serum as well as in urine (in urine also for S. mansoni). Many research groups are evaluating such antigenic tests in the tropical fields under rapid test formats (RDT) based on lateral flow immunochromatography. A
recently developed CCA dipstick test (in urine) has been consistently found much more sensitive in detecting infection with *S. mansoni* than conventional stool microscopy (Kato-Katz concentration).

**Polymerase chain reaction**

PCR based molecular techniques are currently being developed for population surveys and for clinical use. Due to sophistication and costs this technique is still restricted to research and reference labs. The sensitivity and specificity of different formats and sequence targets are being evaluated.

**Medical imaging**

Complications can be detected by means of ultrasound (e.g. hydrenephrosis). The degree of liver involvement can also be determined echographically. This may be of epidemiological importance for example in control programs. Ultrasound is the only possible technique for establishing a non-invasive sensitive and specific diagnosis of hepatic lesions in hepato-intestinal schistosomiasis. The lesions are pathognomonic and can even be seen in children with surprisingly low egg excretion. There is a clear relationship between the presence of ultrasound lesions and the mean excretion of eggs.

Symmers hepatic fibrosis can become symptomatic in later life when the parasite load has become low and it can even be difficult to detect that there is an infection. Clinical differences between cirrhosis and Symmers hepatic fibrosis are relative: youth of the patients, more pronounced splenic enlargement in Symmers hepatic fibrosis, general health preserved for longer even after hematemesis, hepatic enlargement predominantly of the left liver lobe.

Bladder calcifications may be visible on a standard radiograph of the abdomen and on CT-scan.

**Biopsy**

**Rectal snip or rectal biopsy** consists in removing 1 to 3 fragments of superficial tissue with biopsy forceps under endoscopic control from sites where small hemorrhages or other suspicious lesions are seen. These tissue specimens are placed between two glass slides and examined immediately in a drop of water without fixation. Histological examination has a lower diagnostic yield as the section of tissue examined is much thinner. The sensitivity of a rectal snip is good and curiously, better for *S. haematobium* than for *S. mansoni*. In travel medicine this examination is more sensitive, particularly in the case of *S. haematobium* than examination of the urine or stools because the patients involved are mainly adults with a low worm load with few eggs. Rectal snip detects eggs that have accumulated over a period of weeks, months or years under the rectal mucosa. The distinction
between dead and living eggs is important. When living eggs are examined immediately after sampling in an unstained biopsy the moving cilia of the miracidia can easily be seen. The rectal biopsy technique is not used so often in endemic areas where attention is directed particularly to children. Rectal snip data are not quantitative.

**Other biopsies:** Needle biopsy or surgical biopsy of the liver cannot confirm the diagnosis in all cases and is dangerous in patients with a bleeding tendency. Cystoscopy can be used to visualize bladder lesions. Eggs are found in bladder biopsies and sometimes in cervix or skin.

**Treatment**

**Praziquantel (Biltricide®)**

Praziquantel (PZQ) is the first choice treatment. The standard dose is one 600 mg tablet per 15 kg or 40mg/kg body weight. Usually it is given as a single dose but doses can be be taken 4 to 6 hours apart to minimize side-effects. A single dose reduces the parasite load by more than 80%. Treatment cost is low and makes repeated mass treatment an attractive option to reduce the parasite load.

Praziquantel kills the adult worms not the immature schistosomules or the eggs. Praziquantel is undoubtedly the most effective medication with the fewest side-effects for the treatment of all species of schistosomes. The drug seems less effective in regions of West Africa where there has been a recent invasion of the parasite possibly due to rapid re-infections. Diminished sensitivity or resistance to praziquantel are other possibilities but not a major issue so far. Apart from its activity against all human schistosomes including *S. mekongi*, *S. intercalatum* and *S. mattheei*, praziquantel is also very effective against most infections due to trematodes (except *Fasciola*) and cestodes but not roundworms. There are no contra-indications and no major toxicity has been reported. It may be given in hepatic insufficiency. The drug however is not recommended during the first three months of pregnancy. Side-effects include abdominal pain, vomiting, diarrhea and fever; probably caused by the reaction to the dead worms. In very severe infections cases of rectorrhagia are observed. In patients with a hemorrhagic diathesis, this could be dangerous. There is a major risk if cysticercosis is present in the region since serious complications (seizures) can occur as a consequence of the death of cysticerci in the CNS following administration of the medication. In spinal and cerebral schistosomiasis, praziquantel always follows prolonged corticosteroid treatment.

Praziquantel has no effect on eggs and immature worms. Tissue-dwelling eggs can be excreted for several weeks after treatment. During the same period prepatent or newly acquired infections can become productive. The preferred timing of follow-up is therefore 4-6 weeks after initial treatment to
kill the meanwhile matured schistosomes. Katayama fever is primarily treated with corticosteroids to suppress the hypersensitivity reaction and with praziquantel to eliminate matured worms.

**Other drugs used in the past** (and still available in some countries) for schistosomiasis

- Niridazole (Ambilhar®)
- Metrifonate (Bilarcil®)
- Oxamniquine (Vansil®)

Praziquantel has become however the first-choice treatment everywhere in the world. Some of these second-line drugs might become important again if resistance to PZQ would emerge.

**It should be also noted** that the artemisinin derivatives have “preventive” effect on *S. mansoni* and *S. japonicum* (being mostly active on schistosomulae). Mefloquine is another antimalarial drug with some partial efficacy on *Schistosoma* larvae and adult worms (all species). Several small studies have demonstrated short-term reduction of egg load with both drugs in particular when they are combined. Whether these drugs can be used in addition to praziquantel for schistosomiasis treatment or prevention (in malaria-free areas or in returning exposed travelers) still remains to be thoroughly studied before any new recommendation can be made.

**Prevention**

The main objective for schistosomiasis control is the **reduction of morbidity** which is based on the reduction of the worm load. No vaccine is yet available. Attention is focused on detection and treatment and vector control. Mass treatment can be undertaken with yearly administration of praziquantel (treat everyone without screening). Selective treatment of infected people can also be carried out following active screening. Treatment can be restricted to a particular group (e.g. all schoolchildren or children from specific school years). Passive screening (all those people who attend a health center) is also possible. Control of morbidity should not be seen separately from **control of transmission**.

Health education is not effective if it is not associated with an improvement in sanitary conditions in the district. The avoidance of contact with contaminated water is only possible if there is an alternative. Hence the importance of a technical infrastructure and its maintenance (washing areas, showers, toilets, footbridges over canals etc). It is obvious that these are only meaningful if they are accepted and used. The erection of numerous bridges over canals and the use of water pumps (drinking water, washing areas) reduce contact with potentially contaminated water. Water pumps
should be of a design that allows inexpensive local repairs to be made.

It is also possible to try to **control the vectors**. Snails like mud and the presence of water plants. If there is a large amount of deep shadow in places where the vectors are present, the latter will have less food (snails eat algae and plants, which are dependent on photosynthesis). No shadow at all, however, will reduce egg production. Control of water plants and vegetation involves infrastructural changes. Covering over irrigation channels can limit snail populations. Cleaning of canals or the use of concrete for irrigation canals can be useful. Snail control by chemical molluscicides cannot be sustained in the long-term (too expensive and too much collateral ecological damage). The efficacy of biological control of the vector still needs to be demonstrated. The use of certain plants with a molluscicidal effect is being studied, e.g. the soapberry **Endod** (*Phytolacca dodecandra*).