الاستاذ الدكتورة مي حميد كوان

Genus *Fasciola:*

Fasciola hepatica also known as the **common liver fluke** or sheep liver fluke is a parasitic trematode (fluke or flatworm, a type of helminth) of the class Trematoda, phylum Platyhelminthes. It infects the livers of various mammals, including humans. The disease caused by the fluke is called fasciolosis or fascioliasis, which is a type of helminthiasis and has been classified as a neglected tropical disease.[1]Fasciolosis is currently classified as a plant/food-borne trematode infection, often acquired through eating the parasite's metacercariae encysted on plants.[2] *F. hepatica*, which is distributed worldwide, has been known as an important parasite of sheep and cattle for decades and causes significant economic losses in these livestock species, up to £23 million in the UK alone.[3] Because of its relatively large size and economic importance, it has been the subject of many scientific investigations and may be the best-known of any trematode species. *F. hepatica's* closest relative is *Fasciola gigantica*. These two flukes are sister species; they share many morphological features and can mate with each other.[4]

Classification:

Scientific classification	
Kingdom:	Animalia
Phylum:	Platyhelminthes
Class:	Trematoda
Subclass:	Digenea
Order:	Echinostomida
Suborder:	Distomata
Family:	Fasciolidae
Genus:	*Fasciola*
Species:	***F. hepatica***

Prevalence:

Currently, *F. hepatica* has one of the widest geographical spread of any parasitic and vector-borne disease. Originating in Europe, it has expanded to colonize over 50 countries, covering all continents except Antarctica.[22] In contrast, *F. gigantica* is generally considered more geographically constricted to the tropical regions of Africa, Asiaand the Middle East, there is some overlap between the two species.[23]

Climate affects both *F. hepatica* itself and its definitive host, the snail. For example, the development of *F. hepatica* miracidia and larvae, and the reproduction of *Galba truncatula*, require a temperature range of 10-25 °C. In addition to this, they both require high levels of moisture in the air, as both are at risk of desiccation. Due to this, the prevalence, along with the intensity of infection, of *F. hepatica* is primarily dependent on rainfall levels and temperature.[22]

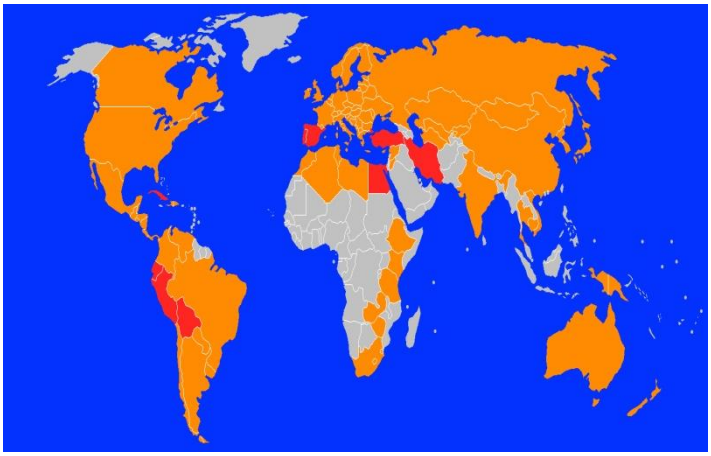


Fig1:fasciola hepatica prevalence,countries in red colour are those a high pervalence

Anotomy and morphology:

Fasciola hepatica is one of the largest flukes of the world, reaching a length of 30 mm and a width of 13 mm (*Fasciola gigantica*, on the other hand, is even bigger and can reach up to 75 mm).[10] It is leaf-shaped, pointed at the back (posteriorly) and wide in the front (anteriorly). The oral sucker is small but powerful and is located at the end of a cone-shape projection at the anterior end. The acetabulum is a larger sucker than the oral sucker and is located at the anterior end.[8]

Tegument:

The outer surface of the fluke is called the tegument. This is composed of scleroprotein and its primary function is to protect the fluke from the destructive digestive system of the host.[11] Its also used for renewal of the surface plasma membrane and the active uptake of nutrients.[12] On the surface of the tegument there are also small spines. Initially, these spines are single pointed, then, just prior to the fluke entering the bile ducts, they become multipointed. At the anterior end of the fluke the spines have between 10 and 15 points, whereas at the posterior end, they have up to 30 points.[13] The tegument is a syncytial epithelium. This means it is made from the fusion of many cells, each containing one nucleus, to produce a multinucleated cell membrane. In the case of *F. hepatica*, there are no nuclei in the outer

cytoplasm between the basal and apical membranes. Thus, this region is referred to as anucleate. Instead, the nuclei are found in the cell bodies, also known as tegumental cells, these connect to the outer cytoplasm via thin cytoplasmic strands. The tegumental cells contain the usual cytoplasmic organelles (mitochondria, Golgi bodies and endoplasmic reticulum).[14] The tegument plays a key role in the fluke's infection of the host. Studies have shown that certain parts of the tegument (in this case, the antigen named Teg) can actually suppress the immune response of the mammalian host. This means that the fluke is able to weaken the immune response, and increase its chances of a successful infection. A successful infection is needed in order for the fluke to have enough time to develop into an adult and continue its lifecycle.[15]

Digestive system:

The alimentary canal of *F. hepatica* has a single mouth which leads into the blind gut; it has no anus. The mouth is located within the anterior sucker on the ventral side of the fluke. This mouth leads to the pharynx, which is then followed by a narrow oesophagus. The oesophagus, which is lined with a thin layer of epithelial cells, then opens up into the large intestine. As there is no anus, the intestine branches, with each branch ending blindly near the posterior end of the body.[16] It has been shown that flukes migrate into smaller capillaries and bile ducts when feeding within the host. They use their mouth suckers to pull off and suck up food, bile, lymph and tissue pieces from the walls of the bile ducts.[16] *F. hepatica* relies on extracellular digestion which occurs within the intestine of the host. The waste materials are egested through the mouth. The non-waste matter is adsorbed back in through the tegument and the general surface of the fluke. The tegument facilitates this adsorption by containing many small folds to increase the surface area.[16]

Respiratory system:

F. hepatica has no respiratory organs: the adult flukes respire anaerobically (without oxygen). Glycogen, taken from within the host is broken down via glycolysis to produce carbon dioxide and fatty acids. This process provides the fluke with energy.[17] In contrast, the free-living miracidia stages of the parasite generally develop within oxygen rich environments. It is therefore believed that the free-living stages of the parasite respire aerobically, to gain the most energy from their environment.[18]

Excretory system:

F. hepatica's excretory system contains a network of tubules surrounding one main excretory canal. This canal leads to the excretory pore at the posterior end of the fluke. This main canal branches into four sections within the dorsal and ventral regions of the body. The role of *F. hepatica's* excretory system is excretion and osmoregulation.[17] Each tubule within the excretory system is connected to a flame cell, otherwise known as protonephridia. These cells are modified parenchyme cells. In *F. hepatica* their role is to perform excretory, but more importantly, osmoregulatory functions. Flame cells are therefore primarily used to remove excess water.[17]

Nervous system and sensory organs:

The nerve system of *Fasciola hepatica* consists of a pair of nerve ganglia, each one is located on either side of the oesophagus. Around the oesophagus is a nerve ring. This nerve ring connects the two nerve ganglia together. The nerves stem off from this ring, reaching all the way down to the posterior end of the body. At the posterior end, one pair of nerves become thicker than the others, these are known as the lateral nerve cords. From these lateral nerve cords, the other nerves branch. Sensory organs are absent from *F. hepatica*.[19][20]

Reproductive system:

F. hepatica adult flukes are hermaphrodite, this means each fluke contains both male and female reproductive organs. The male and female reproductive organs open up into the same chamber within the body, which is called the genital atrium. The genital atrium is an ectodermalsac which opens up to the outside of the fluke via a genital pore.[19] The testes are formed of two branched tubules, these are located in the middle and posterior regions of the body. From the epithelium lining of the tubules sperm is produced. The sperm then passes into the vas deferens and then into the seminal vesicle. From the seminal vesicle projects the ejaculatory duct and this is what opens up into the genitalatrium, many prostate glands surround this opening.[19] On the right hand side of the anterior testis there is a branched, tubular ovary. From here, a short oviduct passes to the vitelline duct. This duct connects, via a junction, the ovaries, the uterus and the yolk reservoir. From this junction, the uterus opens into the genital atrium, this opening is surrounded by Mehlis glands. In some flukes, the terminal end of the uterusis strengthened with muscles and spines.[19]

F. hepatica reproduces both sexually, via the hermaphrodite adult flukes, and also asexually. The miracidia can reproduce asexually within the intermediate snail host.[21]

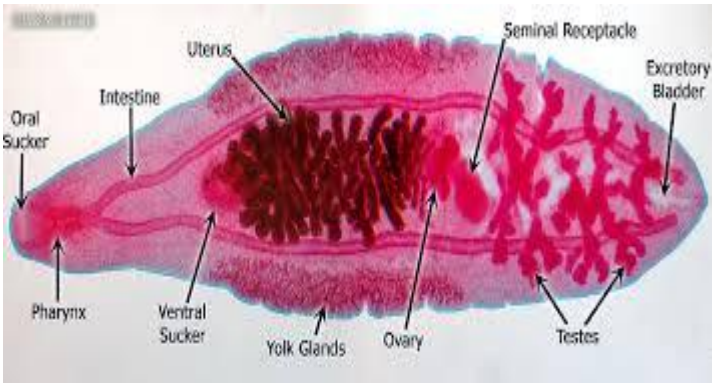


Fig3:anatomy of fasciola hepatica

fig2:mouth part of fasciola hepatica

Life cycle:

Fasciola hepatica occurs in the liver of a definitive host and its life cycle is indirect. Definitive hosts of the fluke are cattle, sheep and buffaloes. Wild ruminants and other mammals, including humans, can act as definitive hosts as well.[5] The life cycle of *F. hepatica* goes through the intermediate host and several environmental larval stages.[6] Intermediate hosts of *F. hepatica* are air-breathing freshwater snails from the family Lymnaeidae. Although several lymnaeid species susceptible to *F. hepatica* have been described, the parasite develops only in one or two major species on each continent. *Galba truncatula* is the main snail host in Europe, partly in Asia, Africa and South America. *Lymnaea viator*, *L. neotropica*, *Pseudosuccinea columella* and *L. cubensis* are most common intermediate hosts in Central and South America.[4][5]Several other lymnaeid snails may be naturally or experimentally infected with *F. hepatica* but their role in transmission of the fluke is low.

The metacercariae are released from the freshwater snail as cercariae, and form cysts on various surfaces including aquatic vegetation. The mammalian host then eats this vegetation and can become infected. Humans can often acquire these infections through eating freshwater plants such as watercress. Inside the duodenum of the mammalian host, the metacercariae are released from within their cysts. From the duodenum, they burrow through the lining of the intestine and into the peritoneal cavity. They then migrate through the intestines and liver, and into the bile ducts. Inside the bile ducts, they develop into an adult fluke.[8] In humans, the time taken for *F. hepatica* to mature from metacercariae into an adult fluke is roughly 3 to 4 months. The adult flukes can then produce up to 25,000 eggs per fluke per day.[9] These eggs are passed out via stools and into freshwater. Once in freshwater, the eggs become embryonated, allowing them to hatch as miracidia, which then find a suitable intermediate snail host of the Lymnaeidae family. Inside this snail, the miracidia develop into sporocysts, then to rediae, then to cercariae. The cercariae are released from the snail to form metacercariae and the life cycle begins again.

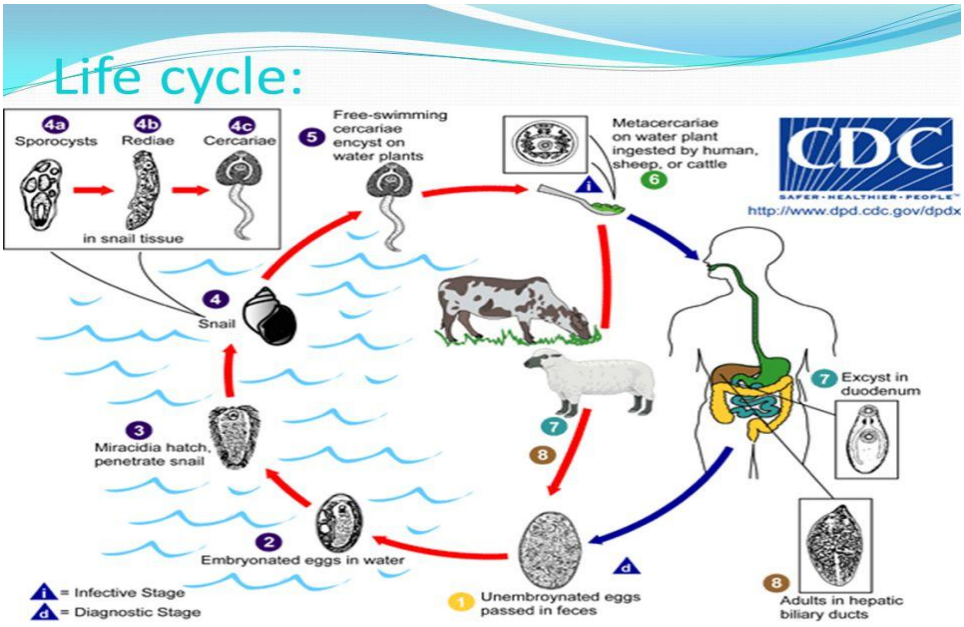


Fig4:life cycle of fasciola hepatica

Parasitic adaptations:

Fasciola hepatica's tegument protects it from the enzymes of the host's stomach, whilst still allowing water to pass through.[26] Free-swimming larvae have cilia and the cercariae have a flagella-like tail to help them swim through the aquatic environment and also allow them to reach the plants on which they form a cyst.[24] To attach within the host, *F. hepatica* has oral suckers and body spines. Their pharynx also helps it to suck onto the tissues within the body, particularly within the bile ducts.[27] The adult fluke's respiration is anaerobic, this is ideal as there is no oxygen available in the liver.[17] *F. hepatica* is adapted to produce a large number of eggs, this increases its chances of survival, as many eggs are destroyed on release into the environment. Also, *F. hepatica* is hermaphrodite, thus all flukes can produce eggs, increasing the number of offspring produced by the population.[19]

The genome for *Fasciola hepatica* was published in 2015. *F. hepatica's* genome, at 1.3 Gb, is one of the largest known pathogen genomes. The genome contains many polymorphisms, and this represents the potential for the fluke to evolve and rapidly adapt to changes in the environment, such as host availability and drug or vaccine interventions

Immunology of *Fasciola hepatica*:

Although many mammalian species may be infected with *Fasciola*,there is variation in the degree of susceptibility to infection and in the ability to mount an effective immune response For example, sheep often die from acute fasciolosis while some infections may last for as long as 11 years (Pantelouns, 1965)

Different genetic backgrounds may be causative in the differing levels of susceptibility to infection (Boyce et a l , 1978) In contrast, cattle rarely die from infection with liver fluke, and display a " self cure" between 9 and 26 months after infection This self-cure, in chronically infected cattle This immune strategy employed may be due to the observed thickening by calcification of This self-cure may be due to the observed thickening by calcification of the bile duct walls, in chronically infected cattle This immune strategy employed by cattle is not observed in sheep, and may explain the higher mortality rates associated with infection of sheep In general, infection in humans tends to cause high morbidity, and persists in hosts for lengthy periods (Maizels et a l , 1993) rather than causing high mortality rates.

. Infection with *F hepatica* induces a predominant Th2 response It has been observed that Th cell clones specific for *F hepatica* enhanced IgG synthesis through IL-4 expression (Brown et a l, 1999),. a characteristic Th2 cytokine response The capacity to produce IgG2 is associated with the production of INF-Y(Estes et a l , 1994) and as a result of a polarised Th2 response, IFN-y, and consequently IgG2 is inhibited This observation is consistent with the polarised Th2 response observed in chronically infected animals (Clery et a l1996) *Fasciola* infection Elevated levels of protection against exprenmental challenge have been associated with IgG2 antibodies (Mulcahy et a l , 1998), however this protective response is down-regulated in the polarised Th2 response characteristic of infection with *F hepatica* Susceptibility to a secondary infection and chromcity is a common feature of *Fasciola* infection For example, the relationship between pathogenesis of disease and host immune responses was observed in primary and secondary *F hepatica* infections o f goats (Martinez-Moreno et a l , 1999) The extent to which the necropsy, was similar in animals during primary and secondary infections however liver damage was much more severe

In secondarily infected animals. Primary infection was observed to evolve to chronic fasciolosis that did not induce the development of resistance, as animals were highly susceptible to secondary infection, exhibiting severe and acute hepatic lesions that ultimately led to the death of some of the animals (Martinez-Moreno et a l , 1999). It was also observed that secondary infection failed to induce any difference in either IgG response or in the composition of cellular infiltrate of hepatic lesions, although lesions were more extended in the secondarily infected animals. There was no significant correlation between the level of antibody titres and the number of flukes recovered at necropsy, suggesting that antibodies have no protective function against Fasciola infection in primary or secondary infection (Martmez-Moreno et a 1999) this correlates with the observations by Dalton et a l , (1996) who reported that no correlation was observed between antibody titres and protection against F hepatica.

Animals chronically infected with *F hepaticado* not acquire a protective immune response (Clery et a l , 1996), and it has been suggested (Ortiz et a l , 2000) that animals with chronic infections remain as susceptible to *Fasciola* infection as naive animals A similar response to re-infection has also been observed in sheep (Chauvm et a l , 1995) in expreriments in which infected animals did not develop resistance against secondary infection While immunohistochemical features of *Fasciola* infection appear to suggest vigorous cellular responses against the invading parasite (Martmez Moreno et a l , 1999), these responses are not observed to be protective, as there is no evidence of effective destruction of Fasciola flukes at any stage of development The effector mechanism of protective immunity has not been clearly established, however reported data suggests that it may occur at the early stage of infection in three different sites, the wall of the intestine (Charbon et a l 1991), the peritoneal cavity (Burden et a l , 1983) and the liver surface o f the parenchyma (Keegan & Trudgett, 1992) The effector response is eosinophils,) believed to be mtnc oxide-mediated killing which involves attachment o f the effector cells neutrophils and macrophages) to the tegument (Spithill et a l , 1997) Eosmophiha is a common feature o f *Fasciola* infection, and eosinophils have been observed in close association with the surface of damaged newly excysted juveniles (NEJ), suggesting a role for this cell type in resistance to *Fasciola* infection (Burden et a l , 1983) However, Hughes (1987) remarked that there is only circumstantial evidence which shows eosinophils are functional in the killing o f *F hepatica* NEJ's Furthermore, it has been demonstrated The (in vitrothat eosinophils fail to induce irreversible damage on NEJ *of F hepatica*(Glauert et al 1985) fact that the immune responses are induced, but are ineffective against *Fasciola* implies that the immune response is ineffective due to a defensive *Fasciola* implies that the immune response is ineffective due to a defensive capability o f the parasite (O'Neill et a l , 2001).

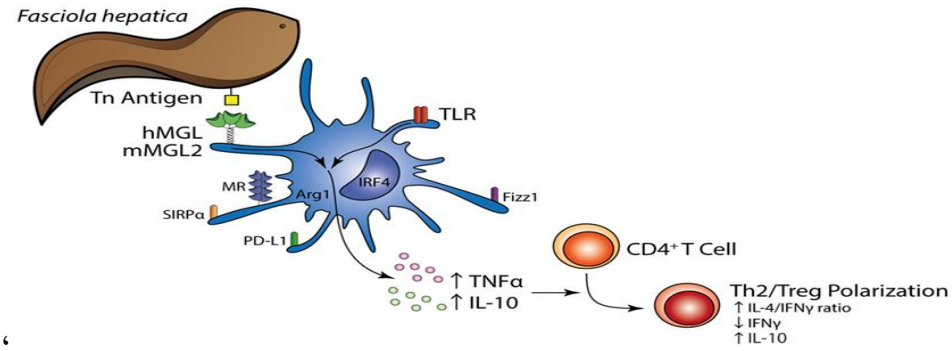


Fig5:immunity of *fasciola hepatica*

Fasciolosis:

Both *F. hepatica* and *F. gigantica* can cause fasciolosis. Human symptoms vary depending on if the disease is chronic or acute. During the acute phase, the immature worms begin penetrating the gut, causing symptoms of fever, nausea, swollen liver, skin rashes and extreme abdominal pain.[32] The chronic phase occurs when the worms mature in the bile duct, and can cause symptoms of intermittent pain, jaundice and anemia.[32] In cattle and sheep, classic signs of fasciolosis include persistent diarrhea, chronic weight loss, anemia and reduced milk production.[33] Some remain asymptomatic. *F. hepatica* can cause sudden death in both sheep and cattle, due to internal hemorrhaging and liver damage.[3]

Fasciolosis is an important cause of both production and economic losses in the dairy and meat industry. Over the years, the prevalence has increased and it is likely to continue increasing in the future.[34] Livestock are often treated with Flukicides, which are chemicals toxic to flukes. The two chemicals used are triclabendazole and bithionol. Ivermectin, which is widely used for many helminthic parasites, has low effectivity against *F. hepatica*, as does praziquantel.[35][36] For humans, the type of control depends on the setting. One important method is through the strict control over the growth and sales of edible water plants such as watercress. This is particularly important in highly endemic areas. Some farms are irrigated with polluted water, hence, vegetables farmed from such land should be thoroughly washed and cooked before being eaten.[8]

The best way to prevent Fasciolosis is by reducing the lymnaeid snail population or separating livestock from areas with these snails.[33] These two methods are not always the most practical, so control by treating the herd before they are potentially infected is commonly practiced.

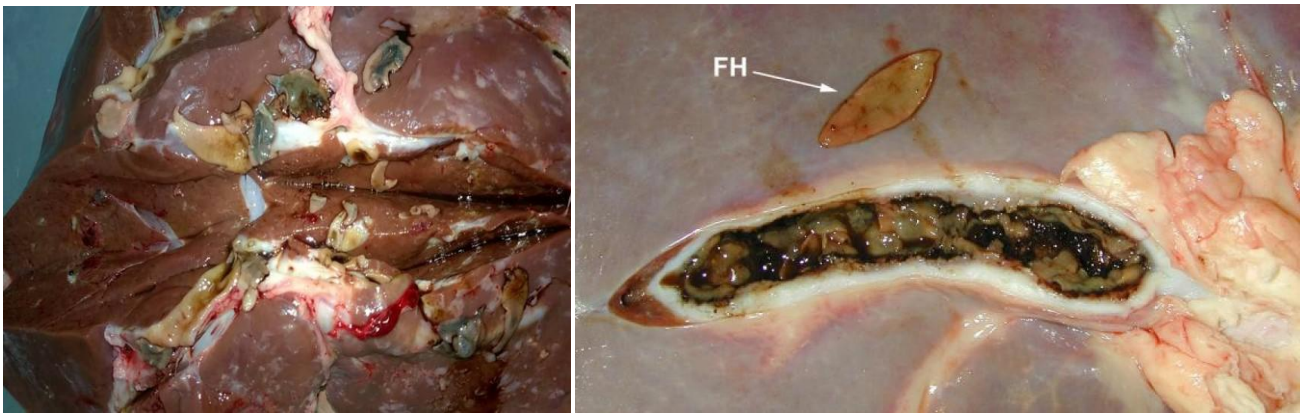


Fig6,7:detection F.hepatica in liver and intestin

Diagnosis:

A diagnosis may be made by finding yellow-brown eggs in the stool. They are indistinguishable from the eggs of *Fascioloides magna*, although the eggs of *F. magna* are very rarely passed in sheep, goats, or cattle. If a patient has eaten infected liver, and the eggs pass through the body and out via the faeces, a false positive result to the test can occur. Daily examination during a liver-free diet will unmask this false diagnosis.[37]

An enzyme-linked immunosorbent assay (ELISA) test is the diagnostic test of choice. ELISA is available commercially and can detect anti-hepatica antibodies in serum and milk; new tests intended for use on faecal samples are being developed.[38] Using ELISA is more specific than using a Western blot or Arc2 immunodiffusion.[29] Proteases secreted by *F. hepatica* have been used experimentally in immunizing antigens.[3

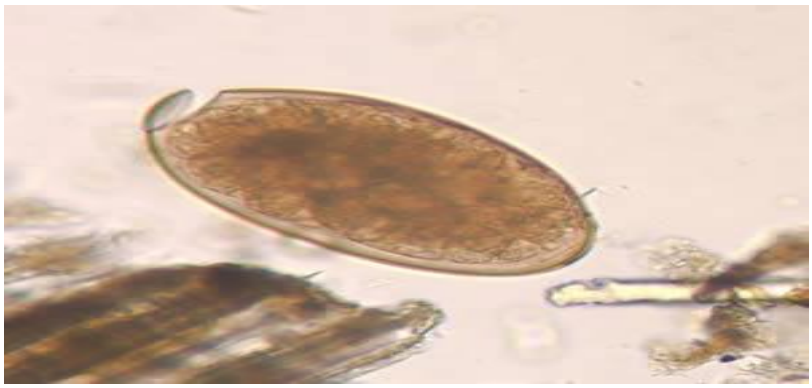
‘ 

Fig8:fasciola hepatica egg

Treatment:

The first step is to make sure the diagnosis is correct. For more information, patients should consult their health care provider. Health care providers may consult with CDC staff about the diagnosis and treatment of fascioliasis.

The drug of choice is triclabendazole. In the United States, this drug is available through CDC, under a special (investigational) protocol. The drug is given by mouth, usually in one or two doses. Most people respond well to the treatment.