An overview of Fascioliasis: Epidemiology, clinical manifestations, diagnosis and treatment

Una visión general de Fasciolosis: epidemiología, manifestaciones clínicas, diagnóstico y tratamiento

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Abstract

Fasciola hepatica is a liver fluke that can cause the zoonotic disease called fascioliasis. There are about 17 million people infected and 91.1 million at risk of infection around the world. Fascioliasis is considered one of the neglected tropical diseases that affects the poorest people in the world. The disease occurs mainly in the liver and biliary tract. After suspecting the infection, the diagnosis is confirmed by serology and stool examination. Treatment with a single dose of triclabendazole is highly effective (cure rates ≥ 90%). Further research should be focused on uncovering the real burden of this parasitic disease and specifically to assess the control of this parasitosis by using rapid diagnostic tests and possibly massive drug administration programs (i.e. triclabendazole) in endemic areas.

Key words: Fascioliasis | Fasciola | Diagnosis | Treatment (source: DeCS BIREME)

Resumen

Fasciola hepatica es un trematode del hígado que causa la enfermedad zoonótica llamada fasciolosis. Existen más de 17 millones de personas infectadas y 91.1 millones en riesgo de infección alrededor del mundo. Fasciolosis es considerada una de las enfermedades tropicales desatendidas que afecta a los más pobres de América Latina. Fasciola ocasiona la infección principalmente en hígado y tracto biliar. Después de sospechar en esta infección, el diagnóstico se confirma por serología y examen de heces. Una dosis única de triclabendazol es un tratamiento altamente efectivo (tasas de curación ≥ 90%). Futuras investigaciones deben de enfocarse en revelar la carga real de esta enfermedad parasitaria y específicamente evaluar el control de esta parasitosis empleando exámenes de diagnóstico rápido y posiblemente programas de administración masiva de drogas (ej. triclabendazol) en zonas endémicas.

Palabras clave: Fasciolosis | Fasciola | Diagnóstico | Tratamiento. (source: DeCS BIREME)
Introduction

Fascioliasis is a parasitic disease caused by the liver flukes *Fasciola hepatica* or *F. gigantica* (Trematoda: Fasciolidae). Fascioliasis is the vector-borne disease with the widest latitudinal, longitudinal and altitudinal distribution known. This disease is endemic in more than 51 countries, about 17 million people are infected and 91.1 million at risk of infection around the world. Thus, the World Health Organization (WHO) has included Fascioliasis into the list of important human parasitic diseases. The geographical distribution of this liver fluke is determined by the intermediate host (*Lymnaea sp.*) and other conditions such as climate, alimentary behaviors and poverty. Peru is one of the countries with the highest estimated number of people infected. First is Egypt with 830,000; followed by Peru with 742,000 and Bolivia with 360,000.

The actual number of cases seen in clinical practice is undoubtedly underestimated since most infections are subclinical and only complicated cases are reported in the literature. Different liver-related complications have been reported in people from endemic areas such as Argentina, Venezuela, Chile, Ecuador, Mexico, Turkey, Thailand, Tunisia, Lebanon and non-endemic countries such as Japan, Korea and U.S.A. Lack of awareness of Fascioliasis among physicians can delay the diagnosis and treatment which can lead to complications by the disease.

In terms of reporting endemic areas of fascioliasis, researchers should follow this classification: (1) cases imported to areas where neither human nor animal fascioliasis is transmitted; (2) autochthonous, isolated, non-constant cases sporadically infected in areas where animal fascioliasis is present; (3) endemic fascioliasis (hypo ≤ 1%, meso 1-10%, hyper-endemic ≥ 10%); (4) epidemic fascioliasis: (i) in animal endemic areas and (ii) in human endemic areas.

Life cycle

The adult *F. hepatica* flukes are large, flat, brown and leaf-shaped, measuring approximately 25 to 30 mm by 10 to 15 mm. The eggs are oval (yellow-brown) and measure approximately 130 to 150 by 60 to 90 μm. The adult fluke lives in the hepatic bile ducts of the host. Animals susceptible (hosts) to *Fasciola* species include mainly cattle, sheep, pigs, buffaloes, donkeys, and less commonly horses, dogs, goats, llamas, alpacas, dromedaries and camels. Humans can act as a reservoir of *Fasciola* in highly endemic areas. The life cycle begins when the eggs of the parasite (from stools) are deposited in tepid water (22-26°C). Then, miracidia appear, develop, and hatch in 9-14 days to invade freshwater snails (*Lymnaea sp.*) where they multiply as sporozoites and redia during a period of 4-7 weeks. Later, free-swimming cercaria are released from the snail and can be attached to some plants in contact with contaminated water such as watercress, water lettuce, alfalfa, mint, parsley, khat, among others. Free-swimming cercaria may remain suspended in the water and encyst over a few hours. Therefore, infection of the human host begins after consumption of plants or water contaminated with the metacercariae. In the first week, the larvae excyst in the duodenum; migrate through the bowel wall and peritoneal cavity. At week 4, the juvenile larvae penetrate the liver through the Glisson’s capsule, initiating the acute larval, hepatic, and invasive stages of human infection which can last about 3 to 5 months. Finally, the larvae reach the large hepatic and common bile ducts where they become in adult flukes. Extrahepatic or ectopic infections may be seen when larvae migrate to other parts of the body. Adult flukes resides for years (between 9 and 13.5 years) in the hepatic and common bile ducts and occasionally in the gallbladder. Adult worms start producing eggs at 4 months of infection (with a range of 3-18 months). These eggs are passed with the bile through the biliary tract to the sphincter of Oddi, intestines and stools (to continue the life
cycle). Of note, acute and chronic stages can overlap, which may occur in people from endemic areas, and it may be not unusual to find eggs in stool samples when the patient clinically has the acute infection.\textsuperscript{1,2,20,21,22,23}

**Risk factors and high-risk populations**

The main source of infection is the consumption of raw vegetables contaminated with metacercariae such as watercress, lettuce, alfalfa juice, mixed green salads or contaminated water from irrigation man-made channels (Table 1).\textsuperscript{29} In non-endemic areas, fascioliasis can be acquired by consuming imported vegetables from endemic areas.\textsuperscript{29} Women are more affected than men, have more severe infections and hepatobiliary complications.\textsuperscript{30} Children are affected more than adults.\textsuperscript{31} Other high-risk populations include farmers and vegetarians. Occasionally, travelers may acquire the infection if contaminated raw vegetables are consumed during a trip to endemic countries.\textsuperscript{29} Treatment of contaminated plants with high doses of potassium permanganate decreases metacercariae viability and could be used to prevent infection.\textsuperscript{32}

**Clinical manifestations**

Fascioliasis has two clinical phases, acute and chronic. Signs and symptoms depend on worm burden, duration and phase of infection. Chronic infection is usually asymptomatic. The acute infection can present with an acutely ill person seeking medical attention (i.e. acute cholecystitis-like picture in the emergency room). The clinical manifestations are so variable that a mild right upper quadrant may lead to a step-by-step work up that can lead to the final diagnosis of fascioliasis.\textsuperscript{33} A summary of clinical manifestations, laboratory data and imaging of fascioliasis is presented in Table 2.

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**Table 1. Risk factors for *F. hepatica* infection in Peru.**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds Ratio = OR (Confident Interval CI 95%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivariate analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drinking emollients</td>
<td>5.2 (1.7-15.6)</td>
<td>(p&lt;0.05)</td>
</tr>
<tr>
<td>Living close to irrigation channels</td>
<td>17.2 (2.8-106.7)</td>
<td>(p&lt;0.05)</td>
</tr>
<tr>
<td>Eating salads</td>
<td>3.3 (1.2-9.0)</td>
<td>(p&lt;0.05)</td>
</tr>
<tr>
<td>Drinking alfalfa juice</td>
<td>4.5 (1.7–11.1)</td>
<td>(p&lt;0.001)</td>
</tr>
<tr>
<td>Familiarity with aquatic plants</td>
<td>4.3 (1.7–10.5)</td>
<td>(p&lt;0.001)</td>
</tr>
<tr>
<td>Univariate Analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water supply from channels</td>
<td>2.4 (1.1-5.3)</td>
<td>(p=0.03)</td>
</tr>
<tr>
<td>Consumption of aquatic plants</td>
<td>2.5 (1.1-5.6)</td>
<td>(p=0.03)</td>
</tr>
<tr>
<td>Breeding 5 or more cattle</td>
<td>2.5 (1.15-5.6)</td>
<td>(p=0.03)</td>
</tr>
<tr>
<td>Owning dogs</td>
<td>3.2 (1.3-8.1)</td>
<td>(p=0.01)</td>
</tr>
<tr>
<td>Defection site in fields</td>
<td>2.6 (1.3-5.6)</td>
<td>(p=0.01)</td>
</tr>
<tr>
<td>Familiarity with aquatic plants</td>
<td>3.9 (1.8-8.3)</td>
<td>(p&lt;0.001)</td>
</tr>
<tr>
<td>Breeding 5 or more sheep</td>
<td>0.3 (0.1-0.7)</td>
<td>(p=0.003)</td>
</tr>
</tbody>
</table>

References. 24-27
Acute infection

The classic triad of the acute infection consists of hypereosinophilia, right upper quadrant pain (“Murphy sign”) and fever. This phase lasts between 3 to 5 months, and ends when the larvae reach the large hepatic and common bile ducts. Parasites migrate through the liver parenchyma and digest hepatic tissue, causing hemorrhage and inflammation. Migration tracks can be observed in histological sections. Flukes sometimes die, leaving cavities filled with necrotic debris that are eventually replaced by scar tissue. When imaging is available, multiple hypodense lesions can be seen on computed tomography (CT), mimicking metastases. Hypereosinophilia is seen in the majority of cases. Absence of eosinophils can be found in the very early stage of the acute disease. A sudden raise on the eosinophil count can be seen few days later. Thus, repeating an eosinophil count in the blood in 3-5 days later may be justified when fascioliasis is strongly suspected. Hyperbilirubinemia is absent in the acute phase, which distinguishes it from viral hepatitis. Other manifestations are anorexia, weight loss, nausea, vomiting, cough, diarrhea, urticaria, lymphadenopathies and arthralgias. Occasionally the juvenile larvae reach other anatomic locations such as the subcutaneous tissue, pancreas, eye, brain, stomach wall, among others.

Chronic infection

The chronic phase begins when the parasite reaches the bile ducts. Eggs are produced by adult flukes and reach the environment through the stools. Most of the patients are asymptomatic. When symptoms are present these include recurrent right upper quadrant abdominal pain, nausea, vomiting, jaundice and urticaria, all of which reflect biliary obstruction. In this stage, the liver contains large dilated, thick-walled and calcareous bile ducts with yellowish brown bile. By microscopic examination, the bile ducts have a thickened hyperplastic wall with marked fibrosis. In endemic areas, increase levels of liver function tests can be a clue of Fascioliasis. In Egypt, it was found that patients with fascioliasis had significant liver enzymes abnormalities, such as elevation of alanine transaminase (ALT) in 21.5%, aspartate transaminase (AST) in 21.9%, total bilirubin in 16.5%, gamma-glutamyl transferase (GGT) in 80.6%, and alkaline phosphatase in 76.4%. Excluding viral hepatitis, *F. hepatica* infection is a significant cause of cholestasis in endemic areas. This fluke may also cause acute eosinophilic cholecystitis along with pruritus and intermittent jaundice. The parasites may cause abscesses and appear as intrahepatic cystic lesions in imaging, which could mimic echinococcosis. Bacterial overinfection in these cysts containing adult parasites is a complication of the chronic phase. Recent studies in a rat model with chronic fascioliasis have shown that there is a significant increased risk for bacterobilia and gallstones. Even after successful treatment, the abdominal pain and weight loss may persist in 2-4% of patients for months. Eosinophilia may be absent in half of the chronic cases. Thus, eosinophilia is not a major criterion for fascioliasis in the chronic phase. The adult parasites may ulcerate the biliary tract causing hemobilia. Granulomatous chronic inflammation has been also described by the parasite ova in the liver and other locations. A study suggested that the infected host may have persistent immune suppression and be at risk for other infections. Liver fibrosis is another complication well described in animals and humans. At a molecular level, *F. hepatica* cathepsine-L1 has been associated with tissue-invasion through its collagenolytic and proteolytic activity. This translates in hepatic fibrosis in experimental rat models, by increasing the collagen type I gene expression. *F. hepatica* infection causes also bile duct hyperplasia, increased levels of proline, and type I and III collagen in the liver, which are similar as those observed in
cirrhosis and wound healing. Last, but not least, around 9.1% of cirrhotic patients in an endemic country (Peru) were positive for Fas2-ELISA, suggesting a previous or current infection by *F. hepatica*. In conclusion, there is substantial evidence to suggest that chronic fascioliasis may be associated with liver fibrosis.

Table 2. Clinical manifestations, laboratory data and imaging in Fascioliasis

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
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<tbody>
<tr>
<td>I. Clinical manifestations</td>
<td>I. Clinical manifestations</td>
</tr>
<tr>
<td>Prolonged fever (weeks or months)</td>
<td>Abdominal pain in right upper quadrant</td>
</tr>
<tr>
<td>Abdominal pain (mostly upper abdomen)</td>
<td>Biliary colicky</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Recurrent or intermittent jaundice</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Urticaria</td>
</tr>
<tr>
<td>II. Laboratory</td>
<td>II. Laboratory</td>
</tr>
<tr>
<td>Marked eosinophilia</td>
<td>Eosinophilia (only 50% of cases)</td>
</tr>
<tr>
<td>Anemia</td>
<td>Cholestasis</td>
</tr>
<tr>
<td>Anicteric hepatitis</td>
<td>Possible jaundice</td>
</tr>
<tr>
<td>III. Imaging</td>
<td>III. Imaging</td>
</tr>
<tr>
<td>Biliary hemorrhage or hemobilia</td>
<td>Hepatic abscesses</td>
</tr>
<tr>
<td>Subcapsular liver hematoma</td>
<td>Liver fibrosis and cirrhosis</td>
</tr>
<tr>
<td>Hepatic rupture</td>
<td>Necrotic granuloma of liver</td>
</tr>
<tr>
<td>Hepatic abscesses</td>
<td>Cystic hepatic tumors</td>
</tr>
<tr>
<td>Track-like lesions of liver in CT</td>
<td>Cholangitis</td>
</tr>
<tr>
<td></td>
<td>Choledocolithias</td>
</tr>
<tr>
<td></td>
<td>Eosinophilic or achalcolous cholecystitis</td>
</tr>
</tbody>
</table>

References.27,29,30,36.

**Diagnosis**

a) Acute infection. This stage of infection can be diagnosed by serology. Fas2-ELISA (cathepsin L1-based antibody) has a sensitivity of 92.4% and specificity of 83.6%, better performance than Western blot and Arc II. If serology is not available readily, a significant clinical improvement and decreasing levels of eosinophils in the 3 to 5 days after an empirical therapeutic trial of triclabendazole can be used as diagnostic criterion. 29

b) Chronic phase. The gold standard test for the chronic infection is the visualization of *Fasciola* eggs in the stools of the infected host. A sedimentation technique is recommended to be performed in a serial of stools specimens from different days (at least 3 samples) in order to increase the likelihood of detecting the eggs in the stools. The intermittent deposition of parasite ova in the biliary duct can decrease the sensitivity of the parasitological technique. The preferred technique is the Rapid Sedimentation Technique (RST) described by Lumbreras is easy to perform, highly sensitive,
Once the infection is resolved by death of the parasite or after treatment, popcorn-like calcifications can be seen in the liver parenchyma. Magnetic Resonance Imaging (MRI). T2-weighted turbo-spin-echo image MRI shows a homogenously hyperintense area located in the subcapsule and containing multiple hypointense areas. T1-weighted 3D gradient-echo imaging displays homogeneous contrast-enhancement. The hypodense lesions observed with CT are of hypointense signal in T1-weighted and hyperintense in T2.

Complications of Fascioliasis

Some complications of this parasitic infection are biliary obstruction and choledocolithiasis. Occasionally, this fluke can be found in the gallbladder, during elective cholecystectomies, or after draining an infected gallbladder (purulent cholecystitis). Out of 162 post-cholecystectomized cases in an endemic area, about 1.2% were found to have the adult parasite in the gallbladder. Adult parasites can also be found by endoscopic retrograde cholangiopancreatography (ERCP) and the removal of them can help to relieve biliary obstruction. After surgical or endoscopic removal of the parasite, a single dose of triclabendazole is recommended in order to complete the treatment. Fascioliasis can mimic echinococcosis when a pseudocyst is formed in the liver parenchyma and represent a challenge for clinicians in endemic areas where both parasites co-exist. Fascioliasis can also present as cancer-like disease even in non-hepatic structures such as the colonic wall, neck, epidural space, eye, breast and pancreas.

Cholangitis is another complication from this parasitic disease. The most common organisms identified in an animal model were Escherichia coli 45%, Enterococcus faecalis 45% and Klebsiella pneumoniat 10%, which are similar organisms causing biliary infections in humans. It is recommended a single antibiotic

The Kato-Katz technique is a novel technique that can also detect eggs of the fluke. In a study performed in rats, the sensitivity of FLOTAC was 92.6% when compared to sedimentation techniques (63-85.2%) but the sedimentation method resulted in higher mean faecal egg count than FLOTAC (P<0.05). An abdominal Ultrasound (U/S). Findings in the acute phase include focal areas of increased echogenicity, multiple nodular or irregular lesions of variable echogenicity, or a single complex mass in the liver resembling malignancy mimicking metastases or cancer. An abnormal liver U/S showing a complex cystic lesion warrants a work up for fascioliasis or other parasitic disease such as Echinococcus spp. In the chronic phase, the U/S has a poor sensitivity to detect the adult parasites. Only in about 14% of people with chronic Fascioliasis the adult parasites were visualized by U/S. CT scan. The most common CT findings include multiple hepatic metastases-like lesions which change in position, attenuation, and shape in time. Also has been described hepatomegaly, track-like hypodense lesions with subcapsular location, subcapsular hematoma and cystic calcifications. The hepatic lesions correlate with time of infection. During the first month of infection, early infection is associated with contrast enhancement of Glisson’s capsule due to inflammation produced by the juvenile parasite penetrating the liver capsule. After the first month of infection, multiple hypodense abscess-like lesions along with low-density serpiginous, tortuous, tunnel-like branching lesions ranging from 2 to 10mm are correlated with parasite migration through the liver. After 3 months, single non contrast-enhanced hypodense irregular mass can be seen resembling a peripheral necrotic granuloma.
such as beta-lactam/lactamase inhibitor (i.e. piperacillin / tazobactam) for mild to moderate infections or a carbapenem (i.e. meropenem) for severe infections. Ideally, antimicrobial therapy should be adjusted according to the organism identified with susceptibilities to common antimicrobials.

**Treatment**
Triclabendazole is the treatment of choice for both phases of fascioliasis. A single oral dose of 10 mg/kg has a cure rate above 90%. The most frequent adverse event is biliary colic caused likely by the passage of dead or dying parasites through the bile ducts. Antispasmodics may ameliorate the abdominal pain and should be used in most cases at the beginning of the therapy. Clinicians in endemic areas are encouraged to rule out fascioliasis in a patient with hepatomegaly, eosinophilia and fever. Clinical response to a single empiric dose of triclabendazole in unclear cases, might support the diagnosis of Fasciola infection.

Another drug evaluated for fascioliasis is nitazoxanide but cure rate is disappointingly low, about 40-60%, so that it is not recommended for the treatment of this infection. Albenzole, metronidazole and praziquantel have lower cure rates and are not recommended.

**Conclusions**
Fascioliasis is endemic in several continents and it may cause significant morbidity in some cases. Sensitive diagnostic tests and effective therapy are available. Despite this evidence, fascioliasis is still a neglected tropical disease that affects the poorest people in Latin America and other parts of the world. Further research should focus in evaluating burden of this disease and control strategies in endemic areas, such as rapid diagnostic tests and massive drug administration using triclabendazole.

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**References**


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