

Current status of diagnosis and treatment of hepatic echinococcosis

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Abstract

Echinococcus granulosus (*E. granulosus*) and *Echino-*

coccus multilocularis (*E. multilocularis*) infections are the most common parasitic diseases that affect the liver. The disease course is typically slow and the patients tend to remain asymptomatic for many years. Often the diagnosis is incidental. Right upper quadrant abdominal pain, hepatitis, cholangitis, and anaphylaxis due to dissemination of the cyst are the main presenting symptoms. Ultrasonography is important in diagnosis. The World Health Organization classification, based on ultrasonographic findings, is used for staging of the disease and treatment selection. In addition to the imaging methods, immunological investigations are used to support the diagnosis. The available treatment options for *E. granulosus* infection include open surgery, percutaneous interventions, and pharmacotherapy. Aggressive surgery is the first-choice treatment for *E. multilocularis* infection, while pharmacotherapy is used as an adjunct to surgery. Due to a paucity of clinical studies, empirical evidence on the treatment of *E. granulosus* and *E. multilocularis* infections is largely lacking; there are no prominent and widely accepted clinical algorithms yet. In this article, we review the diagnosis and treatment of *E. granulosus* and *E. multilocularis* infections in the light of recent evidence.

Key words: *Echinococcus granulosus*; *Echinococcus multilocularis*; Liver; Ultrasonography; Albendazole

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Core tip: *Echinococcus granulosus* and *Echinococcus multilocularis* infections are the most common parasitic diseases of the liver. They could be asymptomatic for many years. Most of the asymptomatic patients are diagnosed incidentally. Ultrasonography is important in diagnosis. There is no standardized and widely accepted treatment approach.

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INTRODUCTION

Cystic echinococcus (CE) is a parasitic illness, caused by infection with *Echinococcus granulosus* (*E. granulosus*) in its larval stage^[1]. Although the disease occurs worldwide, it is endemic in Africa, South America, and Eurasia^[2-4]. The liver is the most commonly affected organ; however, the lungs, spleen, kidney, brain, and breasts may be involved^[5]. Mortality from CE is usually due to the development of complications and is reported to be 2%-4%^[6,7]. The disease course is typically slow and most CE patients remain asymptomatic for several years. In addition, due to non-specific symptoms, the diagnosis is often incidental^[8]. Hepatic alveolar echinococcus (AE) referring to the intrahepatic growth of the larvae of *Echinococcus multilocularis* (*E. multilocularis*) is a rare yet serious disease. When the epidemiology of AE is analyzed, it is striking that the disease is encountered in the northern hemisphere only^[9].

Complications of the echinococcal disease include allergic reactions to the dissemination of cyst contents due to spontaneous, traumatic or iatrogenic rupture, secondary infection, and cholangitis^[3,10-12]. While most CE patients have a single cyst, 20%-40% tend to harbor multiple cysts^[13].

Although a wide range of treatment methods have been identified (medical, percutaneous, monitoring, and surgical), a standardized treatment protocol has yet to be defined.

In this article, we present an update on the diagnosis and treatment of the CE and AE diseases in the liver in the light of emanating evidence.

E. GRANULOSUS INFECTION

Life cycle

E. granulosus is a small sized tapeworm with 10 different genotypes. The definitive host of this parasite is the dog and other members of canids; the intermediate hosts include members of the ungulates such as sheep, goat, and pigs. The adult parasites localize in the liver of the definitive host; eggs are excreted *via* the stool of the host. Upon oral ingestion of the eggs by the intermediate host, the eggs hatch within the stomach and intestine. Oncosphere larvae emerge and cling onto the small intestine by its hooks. Subsequently, the oncosphere larvae migrate to organs such as the liver and lungs through the blood and lymph vessels. Humans are accidental hosts and not essential to the life-cycle of *Echinococcus*. Infection occurs after the oral ingestion of eggs. The eggs grow inside the host organs and form a cyst (hydatid cyst). Hydatid cysts are round in shape and

are usually filled with a clear fluid. The inner part of the cyst features a germinating membrane while the outer part features a laminated layer. In time, the parasite matures and evokes a granulomatous inflammatory reaction which leads to walling off of the cyst by fibrous tissue. In time, budding (germination) occurs from the germinative membrane and blisters are formed (Figure 1). The protoscolices, which occur inside the organ that the definitive host consumed, open up and *Echinococcus* matures into adult from clinging onto the intestine of the definitive host, thus completing the cycle^[14-17] (Figure 2).

Clinical presentation

Most patients have an asymptomatic disease course. The most important reason for this is the slow growth rate of the cysts (1-5 mm per year). Therefore, symptoms usually develop in adulthood^[13,14,18]. The most common presenting symptoms are discomfort in the right upper quadrant of abdomen and loss of appetite. Other symptoms may include pain caused by an increase in the size of the cyst, anaphylactic reaction^[11] induced by the rupture of the cyst, hepatitis, and cholangitis due to biliary obstruction caused by the daughter vesicles^[19], secondary infection of the cyst, embolism^[14], and subphrenic or intracystic abscess^[13]. In 90% of the patients, the cysts open into the biliary tract, which causes the complications listed above^[20]. In approximately 10% of cases, intraperitoneal rupture of the cyst induces anaphylaxis. In addition, secondary CE may develop due to the rupture of the cyst, and this may lead to a much larger mass developing over a relatively short period^[13]. Patients are usually diagnosed incidentally during radiological examination conducted for complaints unrelated to CE. During physical examination, hepatomegaly, palpable mass in one right upper quadrant, and abdominal distension may be encountered as well.

For patients who develop hepatitis, colic pain, portal hypertension, acidity, pressure in inferior vena cava, and Budd-Chiari syndrome, liver hemangioma, liver cysts, adenoma, liver abscess, hepatocellular cancer, liver metastasis, and in addition, liver *Echinococcus* should be taken into account during the differential diagnosis of the masses that are found in the liver^[21,22].

Diagnosis

Most of CE patients at the asymptomatic early stage are diagnosed incidentally. Diagnosis relies on imaging and immunological tests. Ultrasonography is a convenient tool for diagnosis that indicates the location, number, and size of the cysts with relative ease^[2,3,13,18,23,24].

However, small-sized cysts may not be detected by ultrasonography. The criteria for classification of liver cysts on ultrasonography, which were first developed by Gharbi in 1981, were improved by the World Health Organization (WHO) in 2001 (WHO-IWGE)^[25,26] (Tables 1 and 2). The WHO classification includes cysts of unknown origin and includes modified subtypes of the Types 2 and 3 cysts^[14]. There are three categories of cysts: Active,

Table 1 The Gharbi classification of hydatid cysts

Type	Characteristics
I	Unilocular cyst, wall and internal echogenicities
II	Cyst with detached membrane (water-lily sign)
III	Multivesicular, multiseptated cyst, daughter cyst (honeycomb pattern)
IV	Hererogeneous cyst, no daughter vesicles
V	Cyst with partially or completely calcified wall

Table 2 The World Health Organization classification of hydatid cysts

WHO stage	Characteristics	Activity
CE1	Unilocular, anechoic cyst with double line sign	Active
CE2	Multiseptated "rosette-like" "honeycomb pattern" cyst	Active
CE3a	Cyst with detached membrane (water-lily sign)	Transitional
CE3b	Daughter cysts in solid matrix	Transitional
CE4	Hererogeneous cyst, no daughter vesicles	Inactive
CE5	Solid matrix with calcified wall	Inactive

WHO: World Health Organization.

transitional, and inactive^[27]. Types 1 and 2 cysts are considered "active" while Type 3 cysts are considered "transitional". Types 4 and 5 cysts are categorized as "inactive"^[27]. However, this classification has changed with the long term results of the medical and percutaneous treatment and the usage of the high-field magnetic resonance spectroscopy. Type 3 cysts, which are considered transitional, are further divided into two sub-groups: CE3a (separated endocysts) and CE3b (solid type containing daughter vesicle)^[7,28]. Some studies have suggested that CE3a cysts are inactive while CE3b cysts are active^[14,29]. Ultrasonography may also be used for monitoring of the lesion. For patients who have received treatment, post-treatment follow-up examinations every 3-6 mo until stabilization of the cyst, and annual examinations thereafter, are recommended. In general, a period of 5 years without recurrence is considered sufficient^[30]. Magnetic resonance imaging (MRI) and computer tomography (CT) may be required in some cases, where ultrasonography fails to provide a definitive diagnosis. These include obese patients, patients with subdiaphragmatic cyst or secondary infection of cysts, complicated cases such as biliary fistula, cases with extra-abdominal spread, and patients who have a common disease. CT and MRI are particularly useful for pre-operative and follow-up examinations. Use of MRI for diagnosis and follow-up examination is known to be superior to CT^[28,31,32].

There are no workups amongst the routine blood workups that may be used specifically for CE. Hyperbilirubinemia and increased levels of alkaline phosphatase and gamma glutamyl transferase may indicate opening of the cyst into the biliary tract^[15,30,33]. Although EC is



Figure 1 Daughter vesicles of *Echinococcus granulosus*.

a parasitic infection, eosinophilia may not be always present. Serologic diagnostic methods are used to support the radiological diagnosis and for follow-up assessment. The immunological response to the disease tends to vary from one individual to another. Rugged and intact cysts tend to show minimal immune response, while leaking or ruptured cysts tend to evoke a strong immune response^[2,34,35].

The indirect hemagglutination (IHA) is usually non-specific and is of value in tandem with other investigations such as enzyme-linked immunosorbent assay (ELISA) and immunoblotting^[36]. Concomitant use of IHA and ELISA is associated with diagnostic sensitivity rates up to 85%-96%^[37-41]. Immunoblotting is generally used to confirm the diagnosis in cases where IHA and ELISA findings are not definitive^[14]. *E. granulosus* antigen B and antigen 5 (Ag5) are the most specific antigens used for immunological diagnosis^[2,35]. However, these immunological methods often show cross reactivity with other parasitic antigens or with non-parasitic diseases such as malignancy or liver cirrhosis^[15,42-45]. Sensitivity of the serological tests tends to vary with the location, stage, and size of the cyst^[11].

While seronegativity is observed in 20% of patients with CE, those with multiple cysts are usually seropositive. Rate of seronegativity is relatively higher in patients with CE1, CE4, and CE5 cyst types as compared to those with CE2 and CE3 types. Moreover, seropositive patients may continue to remain so for more than 10 years despite treatment^[14,46-48]. This may lead to unnecessary treatment and an increase in costs.

Percutaneous fine needle aspiration (FNA) biopsy under ultrasound guidance is used in suspected cases with equivocal radiological and serological test results. Observing the protoscolices and cyst membranes, or Echinococcal antigen or DNA in aspirated fluid confirms the diagnosis^[49]. Percutaneous procedure requires meticulous care due to the associated risk of anaphylaxis; informed consent of the patient should be obtained prior to the procedure^[50]. Anaphylaxis risk of FNA is 2.5%^[51]. In order to prevent secondary CE, pretreatment with albendazole for 4 d prior to the biopsy and continuation of treatment for one month after the biopsy are recommended^[20,52].

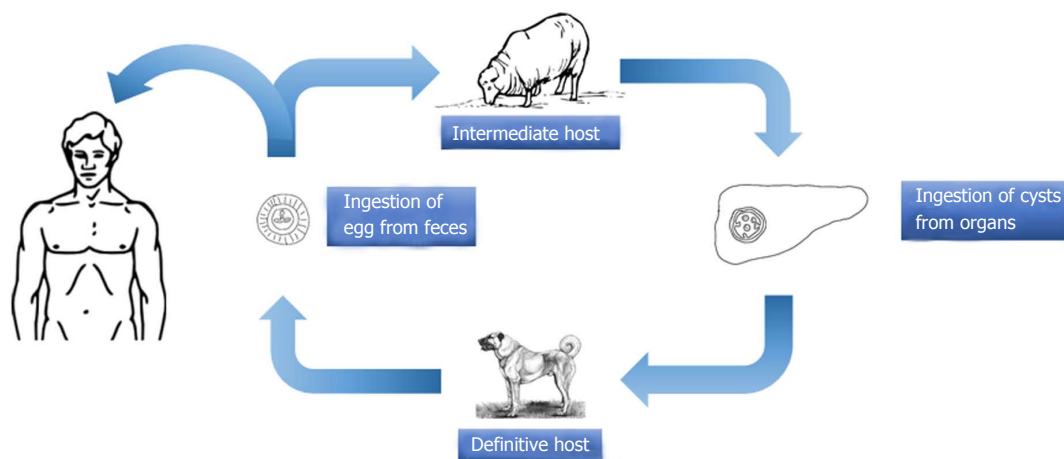


Figure 2 Life cycle of *Echinococcus granulosus*.

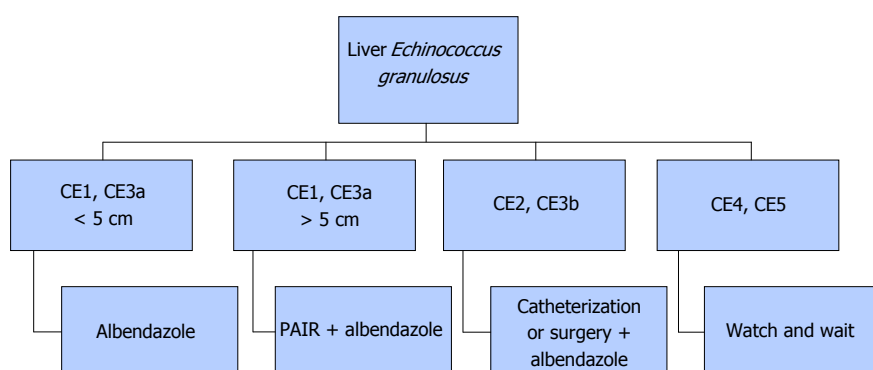


Figure 3 Treatment algorithm for *Echinococcus granulosus* infection. PAIR: Puncture, aspiration, injection of a scolecidal agent, and reaspiration.

Treatment and management of *E. granulosus* infection

The treatment options for CE included surgery, percutaneous treatment, medical pharmacotherapy, and monitoring^[10]. In the literature, there is no randomized clinical study that compares the treatment methods with each other. Therefore, there is no standardized and widely accepted treatment approach for CE either^[14]. The treatment planning is done according to the WHO diagnostic classification. In case CE1 and CE3a cysts are < 5 cm in diameter, albendazole alone may suffice, while for cysts exceeding 5 cm in size, the puncture, aspiration, injection of a scolecidal agent, and reaspiration (PAIR) treatment in tandem with albendazole is preferred. Types CE2 and CE3b cysts are treated by catheterization or surgery. For types CE4 and CE5 inactive cysts, monitoring is often sufficient^[10] (Figure 3).

Medical treatment: Exclusive medical pharmacotherapy is used in special cases where surgical or percutaneous treatment (such as elderly patients, cases with high comorbidity, patients who opt out of surgical and percutaneous treatment, and inoperable cases) is not suitable, or as an adjunct to surgical and percutaneous treatment.

Ever since benzimidazoles became available for use in 1970s, therapeutic efficacy of albendazole and mebendazole for larval stage of *E. granulosus* has been

proved^[14]. At present, albendazole is the most commonly used drug in the treatment of *E. granulosus* infection^[53]. The dose of albendazole is 10-15 mg/kg per day and the treatment usually lasts for 3-6 mo. Efficacy of mebendazole is comparable to that of albendazole, but requires higher doses for a longer period of time, due to its poor absorption^[53-55]. The dose of mebendazole is 40-50 mg/kg per day for the patients who can not use albendazole.

With benzimidazoles, the duration of treatment is 3-6 mo without interruption for CE1, CE3a cysts that are < 5 cm^[10,56]. Studies have demonstrated that 28.5%-58% of patients who undergo medical treatment are cured, and that cure rates do not increase with the increase in the duration of treatment^[54,57-61].

According to the recommendations of WHO, the medical treatment should be initiated 4-30 d prior to the surgical operation and continued for at least 1 mo thereafter for albendazole, and at least 3 mo for mebendazole. Medical pharmacotherapy is also indicated in patients with spontaneous or traumatic ruptured of cysts. In these cases, too, albendazole should be used for at least 1 mo or mebendazole for 3 mo^[62-64].

In a large study (929 cysts) of the effectiveness of medical therapy in late stages, albendazole therapy was associated with a significantly higher incidence of degenerative changes than that with mebendazole the-

rapy (82.2% vs 56.1%; $P < 0.001$). However, the relapse rates were comparable between the two groups^[65].

Headache, nausea, neutropenia, hair loss, and hepatotoxicity are the most commonly reported side effects of albendazole and mebendazole. Monthly monitoring of leukocyte counts and liver function tests is recommended in patients who experience significant side effects. Contraindications to medical treatment include liver failure, pregnancy, and bone marrow suppression^[13].

Praziquantel has protoscolicidal activity and can be used for treatment of CE, either as a standalone therapy or in combination with albendazole. A study suggested higher efficacy of the combination of praziquantel plus albendazole^[66]. More studies on the efficacy of praziquantel are required.

Percutaneous treatment: The percutaneous treatment methods defined in the 1980s for liver CE continue to be popular today^[67-70]. These are classified under two main categories. The first and more popular one is the PAIR method^[71]. This method is based on the destruction of the germinal membrane by use of a scolicedal agent. However, PAIR is not a suitable method for cysts that contain daughter vesicles and for multi-vesicular cysts that have a higher solid content^[7,69,72].

Secondary percutaneous treatment modalities include catheterization of the cyst with a broad tube to remove the solid contents of the cyst as well as the daughter vesicles. Several catheterization methods such as percutaneous evacuation, a modified catheterization technique, and dilatable multi-function trocar have been described^[73-75]. This treatment method can be used for treatment of Types CE2 and CE3a cysts and for post-PAIR relapsing cysts^[76].

A review of percutaneous CE treatment ($n = 5.943$) revealed a 0.03% incidence of lethal anaphylaxis and 1.7% incidence of allergic reactions^[49]. Using albendazole starting from 4 h prior to the percutaneous treatment until 30 d after the percutaneous treatment is convenient^[10].

The PAIR treatment is a less invasive method than surgery. In selected patients (CE1 and CE3b) success rates of up to 97% have been reported; the reported mortality and morbidity rates have varied from 0%-1% to 8.5%-32%^[77-80]. In a study of ethanol plus PAIR treatment ($n = 231$), only one case of relapse was reported^[80]. Eleven percent to thirteen percent of patients undergoing PAIR tend to develop fever and rash; however, the risk of anaphylaxis is quite low^[77,81].

PAIR treatment is not recommended for the cysts which are containing materials that can not be absorbed, cysts which carry the risk of spread into the abdominal cavity, cysts that have already opened into the peritoneal cavity or biliary tract, and inactive and calcified cysts^[7].

The relation of the cyst with the biliary tract should be examined prior to administration of scolicedal agent. Although no cases of scolicedal agent-related cholangitis after PAIR procedure have been reported, several such

cases have been reported after surgical procedure^[82-84]. The commonly used scolicedal agents used during PAIR are hypertonic saline and ethanol^[14]. Successful intra-cystic application of albendazole and mebendazole solutions as scolicedal agents during PAIR has been reported in sheep^[85].

The reported success rate of percutaneous treatment plus albendazole in non-complicated cysts is similar to that of surgery but has the advantage of a shorter duration of hospital stay^[86]. In a retrospective comparison of conservative surgery and PAIR, the incidence of biliary fistula and residual cavity relapse was considerably lower with the latter^[87].

Surgical treatment: While surgical treatment was once the most commonly used treatment modality, it is currently, to a large extent, reserved for complicated cysts (such as cysts that develop biliary fistula or perforated cysts) or is applied to the cysts that contain daughter cysts (CE2, CE3b). In addition, it is a suitable treatment option for superficial cysts that are smaller than 10 cm or are at high risk of rupture and for cases not suitable for percutaneous treatment^[7,10,53,88]. The surgical treatment options include open surgery and laparoscopic surgery^[5,89,90]. Open surgical options include radical and conservative surgery. Radical surgery refers to the removal of the cyst along with the pericystic membrane (Figure 4) and may also include liver resection if indicated. Conservative surgery includes removal of the cyst contents only, while the pericystic membrane is retained (Figure 5). Omentoplasty, external drainage, or obliteration of the residual cavity by imbricating sutures from within (capitonnage) is used for drainage from the residual cavity. The complication rates of the surgical treatment options vary between 3%-25%, while the recurrence rates vary between 2% and 40%^[89,91-93]. The complication and recurrence rates tend to differ based on the location and size of the cyst, as well as the experience of the surgeon and the selected treatment method.

It is not clear which one of the given treatment options is the safest and the most effective. However, recurrence and complication rates tend to be higher with conservative surgery as compared to those with radical surgery^[94]. Many retrospective studies have revealed similar results^[93,95].

The recurrences usually occur due to failure of complete removal of the endocysts and/or their dissemination during the surgery. For this reason, special attention should be paid to prevent spread during the operation^[96,97]. Of note, spread during the surgery may also lead to other complications such as anaphylaxis.

The most common complication of liver EC is the infection and the contact with the biliary tract. The contact of the cyst with the biliary tracts is encountered in 3%-7% of all cases^[98]. A relationship between cyst size and its contact with the biliary tract has been reported. In cases where the radius of the cyst is > 7.5 cm, the sensitivity



Figure 4 An example of pericyclectomy material.

of the contact of the cyst with the biliary tract is reported to be 73% while its specificity is indicated to be 79%^[99]. Prior to intraoperative administration of drugs in the cyst, the relation of the cyst with the biliary tract should be ascertained as protoscolicidal agents are known to induce sclerosis, cholangitis, and pancreatitis.

In case of preoperative evidence of opening of the cyst into the biliary tract, sphincterotomy by endoscopic retrograde cholangiopancreatography (ERCP) prior to surgery decreases the risk of postoperative external fistula from 11.1% to 7.6%^[100]. When the relation of the cyst with the biliary tract is noticed during the surgery, presence of a cystic component within the biliary branches or within the common biliary duct should be checked. For this, intraoperative cholangiography is often required. In addition, the width of the biliary tract would be in normal range if there is no cystic component within the biliary branches or within the common biliary duct. The biliary tracts, which can be clearly seen through the cyst, should be sutured. In case there is a cystic component inside the biliary tract, the biliary tract would be widened. In such cases, removal of the cystic components within the biliary branches and applying T-tube or choledochoduodenostomy is recommended^[101,102]. In addition, postoperative bilioma or high flow biliary fistula requires ERCP and sphincterotomy along with nasobiliary drainage or biliary stenting^[103,104].

The most commonly used protoscolicidal agent during the surgery is 20% hypertonic saline. The hypertonic saline should be in contact with the germinal membrane for at least 15 min. Albendazole, ivermectin, and praziquantel can also be used as protoscolicidal agents^[105,106]. In a recently conducted *ex vivo* research, use of selenium nano-particles (250-500 $\mu\text{g}/\text{mL}$) as a protoscolicidal agent for 10-20 min showed good results^[107].

Intraoperative dissemination of the mass in the peritoneum should be rinsed with hypertonic saline. Postoperative albendazole for 3-6 mo plus praziquantel for 7 d is recommended^[108].

In a retrospective review of conservative surgery methods ($n = 304$), use of external drainage was associated with a statistically significant increase in com-

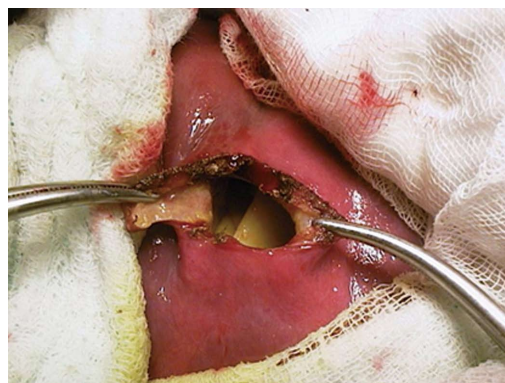


Figure 5 An example of conservative surgery.

plication rates as compared to patients who received omentoplasty or capitonnage^[109]. In another randomized clinical trial and one retrospective study, patients who received omentoplasty in addition to the conservative surgery showed fewer complications as compared to patients with external drainage^[5,110].

The first laparoscopic surgery for CE was reported in 1992^[111]. While the laparoscopic surgery offers some advantages such as shorter duration of hospital stay, lesser postoperative pain, and lower infection rates, it is applicable only to selected cases. Further laparoscopic procedures are associated with an increased risk of intraoperative dissemination of the cyst contents due to the increased pressure inside the mass^[5,88]. No studies comparing open surgery with laparoscopic surgery were retrieved on the literature search. Appropriate patient selection is critical to the success of laparoscopic surgery. Deep-seated cysts in the hepatic parenchyma, posterior cysts close to the vena cava, multiple cysts (> 3), and cysts with calcified walls are unsuitable for laparoscopic surgery^[88,112-114].

Monitoring: Some studies suggest that inactive cysts, such as CE4 and CE5, require no treatment^[7,49,76]. However, more studies in this regard are required.

***E. MULTILOCCULARIS* INFECTION**

Life cycle

E. multilocularis is a small cestode. The definitive hosts of the sylvatic cycle are feral carnivores, and the definitive hosts of the synanthropic cycle are domestic cats and dogs. The fully grown parasites within the small intestine of the definitive host excrete their eggs with the feces of the definitive host. Upon ingestion of the eggs by intermediate hosts such as small rodents, echinococcal metacestodes form alveolar structures with multiple vesicles of different sizes within the liver. Humans get infected after oral ingestion of eggs^[3,17]. Each vesicle has a structure, similar to the cysts of *E. granulosus*^[115]. Potential complications include the formation of pseudocysts due to fluid accumulation or central necrosis. Small cysts usually do not contain liquid within them and

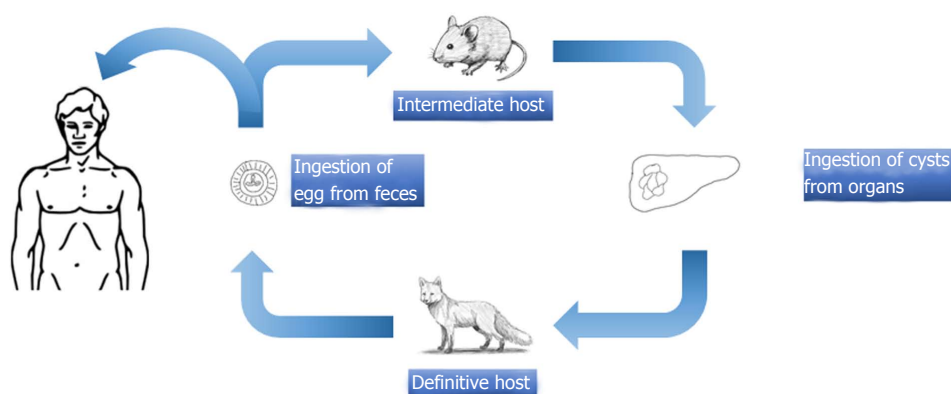


Figure 6 Life cycle of *Echinococcus multilocularis*.

are semisolid in structure^[16] (Figure 6).

Clinical symptoms of *E. multilocularis* infections

The latent period for infection in which the patients are asymptomatic lasts around 5-15 years and is rather longer compared to the CE. In general, the AE is set into the right lobe of the liver and its size may vary from a few millimeters to 20 cm^[11,13]. The AE may spread locally or metastasize to the brain, bones, and lungs *via* blood^[115]. Extrahepatic manifestations are rare in primary disease^[11]. The typical presenting symptoms include fatigue, weight loss, abdominal pain, and signs of hepatitis or hepatomegaly. Up to one-third of patients suffer from hepatitis and abdominal pain^[115-117]. The prognosis for untreated cases or cases with incomplete treatment is grim; liver failure, splenomegaly, portal hypertension, and acidity may occur in advanced stages. The life expectancy may extend up to 20 years with treatment^[118].

Diagnosis of *E. multilocularis* infection

The radiological imaging methods are the main methods of diagnosis of AE and the serologic examinations are used to support the diagnosis^[3,4,10,119]. Ultrasonography is the diagnostic method of choice. On ultrasonography, a pseudotumoral mass with hypo and hyperechoic areas together that contain irregular, limited, and dispersed calcifications is diagnostic^[120,121]. Doppler ultrasonography may be useful for imaging of biliary tracts and vascular infiltrations. Although CT renders the anatomical details in a better manner, MRI is considered the best method to determine invasion of the contiguous structures^[120-122]. Percutaneous cholangiography is an important method for diagnosis in order to view the relation between the alveolar lesions and the biliary tracts. In addition cranial and thoracic imaging should be required to rule out extra-hepatic involvement in AE patients^[120]. Despite the fact that the fluorodeoxyglucose positron emission tomography can be used for diagnosis, negative results do not necessarily mean that the parasite is active^[123]. The WHO classification developed for *Echinococcus* is based on the imaging methods and aims to establish standardization in the diagnosis and treatment

of the disease^[3,10,124]. WHO-IWGE PNM classification system resembles the TNM classification used for the tumors^[3,124]. P indicates the size and location of the parasite within the liver, N indicates the adjunct organ involvement while M indicates distant metastasis (Table 3).

The immunological diagnostic methods are helpful for diagnosis as well as for monitoring the effectiveness of the treatment^[125,126]. The serological investigations for AE (ELISA or IHA test) are more specific than the ones used for the diagnosis of CE (antigens Em2 and Em II/3-10 are highly specific to AE)^[127]. However, EM2-ELISA may remain positive for many years even in the treated cases as the EM2 antigen is present in inactive lesions. The most active component of AE is the protoscolex that has EM16 and EM18 antigens. The activity of the lesion can be obtained by using those antigens in immunoblot tests^[128]. In addition, EM18 is helpful for distinction between AE and CE^[2]. In some studies, AE patients had high levels of IgG1 and IgG4 antibodies and their IgG4 antibody levels decreased after treatment. Therefore, an increase in IgG4 levels may be a surrogate marker of reactivation of the parasite^[129-132]. Demonstration of alveolar vesicles in the samples extracted by percutaneous needle biopsy in suspected cases helps confirm the diagnosis. Although PCR imaging of the *E. multilocularis* DNA in the liver biopsy samples has high positive predictive value, negative results do not necessarily rule out the presence of an active parasite^[10]. There are several studies evaluating the serologic agents best suited for post-treatment follow-up^[133,134].

Treatment and management of *E. multilocularis* infection

AE is comparatively difficult to treat than CE. The main treatment modalities are medical pharmacotherapy and surgery (Figure 7).

Surgical treatment is the primary method for AE; radical resection is often required for hepatic lesions. Conservative and palliative surgery is not recommended since they offer no advantage over medical pharmacotherapy^[135,136]. Treatment is based on pre-operative assessment and the disease stage as per the WHO-IWGE PNM classification^[124]. Liver transplantation is an option for patients with advanced stage liver failure,

Table 3 PNM classification of *Echinococcus multilocularis*^[146]

P	Hepatic localization of the metacestode
Px	Primary lesion unable to be assessed
P0	No detectable hepatic lesion
P1	Peripheral lesion without biliary or proximal vascular involvement
P2	Central lesions with biliary or proximal vascular involvement of one lobe
P3	Central lesions with biliary or proximal vascular involvement of both lobes or two hepatic veins or both
P4	Any lesion with extension along the portal vein, inferior vena cava or hepatic arteries
N	Extra-hepatic involvement of neighbouring organs
Nx	Not evaluable
N0	No regional involvement
N1	Involvement of neighboring organs or tissues
M	Absence or presence of distant metastasis
Mx	Not completely assessed
M0	No metastasis on chest radiograph and computer tomography brain scan
M1	Metastasis present

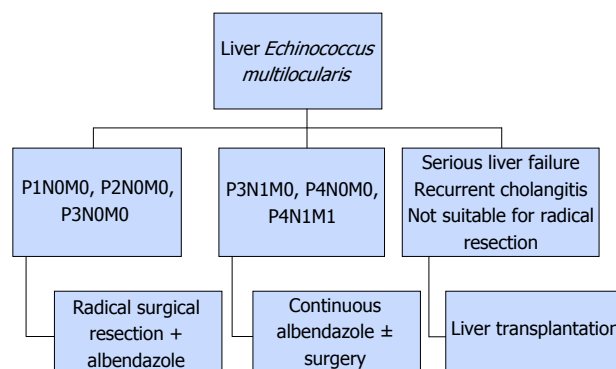
patients that have recurrent cholangitis, and patients unsuitable for radical surgery. Extrahepatic spread of AE during surgery is particularly hazardous in liver transplant recipients, due to drug-induced immunosuppression^[10]. These patients are at risk of relapse^[137].

Although there is no information regarding the effectiveness of pre-operative pharmacotherapy, it is generally used for liver transplant recipients. Postoperative albendazole is recommended in all patients for at least 2 years^[30,137]. Although there are alternative drugs such as mebendazole, praziquantel, and amphotericin, none is as effective as albendazole^[138,139]. In a recently conducted study, it was revealed that nitazoxanide has no effect on the treatment of AE^[140].

Optimal duration of albendazole treatment in patients not treated by surgery is not clear. However, cases have been documented where albendazole was continuously used for up to 20 years without any complications^[10]. The use of albendazole in patients who do not undergo surgical treatment increases the 15-year survival from 0% to 53%-80%^[141-145]. Interventions such as endoscopic sclerosis of the varicose veins of the esophagus and stent implantation may be required during treatment^[53].

CONCLUSION

E. granulosus and *E. multilocularis* infections are the most common parasitic diseases that involve the liver. Due to the typical slow growth, these often present in adulthood. Their symptoms include right upper quadrant abdominal pain, chlorosis, cholangitis, and anaphylaxis due to cyst rupture. AE is one of the most fatal helminthic infections. Ultrasonography plays a special role in diagnosis. WHO classification is used for staging and treatment selection. Immunological diagnostic methods are used to support the diagnosis. Cysts smaller than 5 cm (WHO stages CE1 and CE3a) are treated with albendazole only, while PAIR plus albendazole therapy is recommended for cysts > 5 cm.

**Figure 7** Treatment algorithm for *Echinococcus multilocularis* infection.

PAIR treatment for patients with CE2 and CE3b cysts is associated with frequent relapses. Therefore, broad tube percutaneous treatment should be considered in these cases. During open surgery and percutaneous treatment, all necessary efforts should be made to prevent dissemination of cyst contents; albendazole should be used at least for 4 d prior to such procedures and for 1 mo after the procedures. For AE, despite the fact that albendazole is not used preoperatively, postoperative treatment for 2 years is recommended. For CE, radical surgery is reported to be more effective than conservative surgery. For AE, the radical treatment option is also recommended as palliative surgery offers no advantages over medical treatment. Despite the fact that the general templates regarding the treatment seem clear, the lack of randomized clinical studies that compare the treatment options leads to failure in the selection of treatment.

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