

## REVIEW

## THERAPEUTIC OPTIONS, EVOLUTION, AND FOLLOW-UP IN LIVER HYDATIDOSIS: A LITERATURE REVIEW

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### Abstract

*Hydatidosis is a disease affecting most commonly liver and lungs, and it is caused by the infection that, in humans, is due to the larval stage of the Echinococcus granulosus. These complexes generate cystic hydatid disease characterized by unilocular cystic lesions. The disease spreads mostly in geographical areas with a large amount of livestock, and it is closely associated with dogs. The mechanic action produced on the tissues by the progressive growth of the cyst, even if with certain limitations, relates to the entity of the symptomatology. The diagnosis can be based on abdominal ultrasonography, which represents the golden standard and serology, or using more refined techniques such as Magnetic Resonance Imaging or Computed Tomography. The optimal treatment for hepatic cystic echinococcosis has not been fully determined, but it can follow a conservative method (benzimidazoles therapy, percutaneous evacuation, or a watch and wait policy) and a surgical way (by open or laparoscopic cyst approach). The prognosis is favorable in cases of unique cysts, in a location where it is easily removed by surgical intervention or if it positively responds to pharmacological treatment or to Percutaneous Aspiration Injection and Reaspiration (PAIR) technique.*

**Keywords:** *hydatidosis, echinococcus, liver, surgery*

### Introduction

Hydatid echinococcosis is a parasitic infectious disease that has its favorite target organs in the liver and the lungs. The symptomatology depends on the mechanic action produced on the tissues by the progressive growth of the cyst. Thus, it can remain asymptomatic or generates symptoms if the cysts are expanded [1]. The most used classifications for the diagnosis and the differentiation of the cysts are the Gharbi's and World Health Organisation classifications [2] (Table I)

Gharbi classification	World Organisation classification	Health
I	CE1	
II	CE3A	
III	CE2 and CE3B	
IV	CE4	
V	CE5	

**Table I: Equivalence between Gharbi's and World Health Organisation classifications**

The optimal treatment for hepatic cystic echinococcosis has not been fully determined [3], but the criteria for the treatment of choice

should be based on [4]: patient's characteristics (age, pregnancy, surgical risk evaluation, associated pathologies, patient's desire); cyst's features (number, localization, size, features, presence or absence of complications); the experience of the physician, and the therapeutic options available.

The physician has two available strategies to treat the patient with: the conservative method (Benzimidazoles, Percutaneous Therapy, Watch and Wait), and a surgical way (by open and laparoscopic approach).

The prognosis is favorable in cases of unique cyst development in a location where it is easily removed by surgical intervention or if it positively responds to pharmacological treatment or to "PAIR". However, possible complications can lead to the worsening of the prognosis [5].

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## Materials and Methods

We have reviewed the relevant articles using the PubMed/Medline and Google Scholar databases.

We have used the following keywords: „hydatid“ OR „echinococcosis“ AND „liver“ OR „hepatic“.

Our study took into consideration publications and researches from the last 20 years.

The main purpose of the current study is to detail the epidemiological and clinical features of liver hydatid cystic disease.

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## Goals of the treatment

The principles of treatment aim to establish an early intervention, to prevent potential secondary complications, as well as the eradication of the parasite and the prevention of the disease's recurrence and reducing to a minimum its morbidity and mortality.

It is imperative that the therapy chosen by the physician takes into consideration all possible side effects such as the spillage of scolices, and the management of any complication associated with this, the patient's general status, the features of the liver hydatid

cyst as seen under examination and the possible differential diagnoses [6].

## Conservative Treatment

### *Benzimidazoles*

The systemic chemotherapy using the anti-helminthic drugs, known as Benzimidazoles, represent the main medical treatment of echinococcal hepatic disease.

Albendazole (ABZ), with a dosage of 10-15 mg/kg/day, given twice a day by oral route, is the golden standard [7] because of its ability to be rapidly absorbed from the gut and metabolized in the liver that, in turn, gives rise to the active form of the drug. The drug is better concentrated in the fluid of the cyst if compared to the Mebendazole, the second most common drug used in liver hydatid disease treatment.

The recommendations about dose and regimen vary from continuous treatment lasting 3-6 months to monotherapy for the immediate postoperative discontinuation. These drugs are indicated only in complicated lesions and not in the case of an inactive calcified cyst.

Albendazole in combination with Praziquantel has a more effective outcome than the monotherapy with Albendazole in the setting of preoperative treatment of intra-abdominal hydatidosis [8].

Therefore, additional percutaneous and surgical therapy should be considered in conjunction with the medical treatment.

### *Percutaneous Therapy*

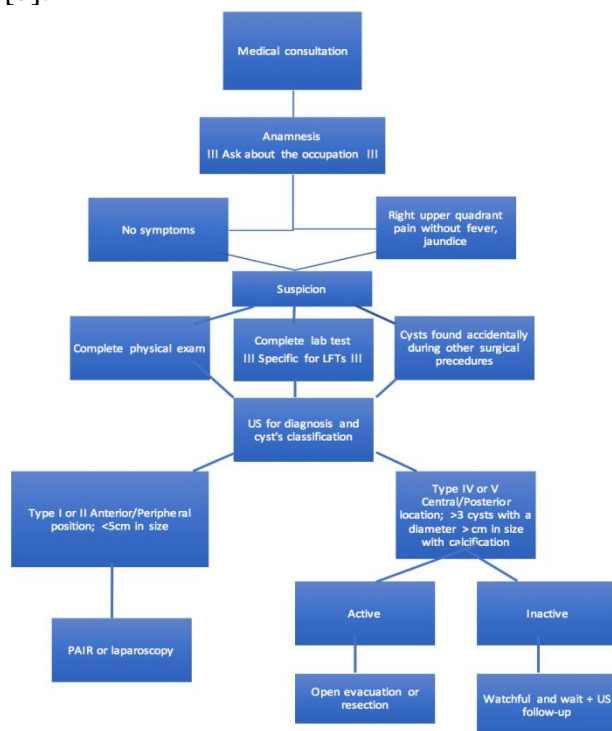
Over the course of time, this strategy of treatment for hepatic cyst echinococcosis has become more and more accepted for carefully selected patients. It includes either PAIR (puncture, aspiration, injection, and reabsorption) aimed to destroy the germinal cyst layer and the decompression by needle puncture accompanied with catheter drainage, whose goal is to evacuate the whole endocyst.

The use of catheter drainage is addressed in the treatment of giant, more than 10 cm, and unilocular cysts; the catheter remains in place until the daily output - less than 10 ml/day - is achieved.

The guidelines recommend PAIR in high-risk patients (such as those who refuse surgery or those in whom the medical treatment alone

failed) and in patients with infected cysts and with post-surgical cyst recurrence.

Concerning those cysts that measure more than 5 cm, classified as CE1 or CE3 by WHO, they are better approached by primary treatment with PAIR in association with Benzimidazole [7].



**Figure 1 - The therapeutic algorithm for patients affected by echinococcal infection (LFTs – liver function tests).**

In contrast, this technique is contraindicated in patients with comorbidities such as cysto-biliary fistulae [9], complicated cysts, not reachable/high-risk locations (superficial), CE2, CE4, CE5 and the inactive or calcified cysts.

If the patients are symptomatic, are pregnant or are children over three years of age, the use of PAIR is controversial although is an efficient and safe procedure in cases where percutaneous treatment is indicated [10].

It is estimated that more than 4000 PAIR interventions have already been performed over the last 20 years, thus proving the safety of this procedure [7].

In 2003, a meta-analysis of patients with all types of the disease, either complicated or uncomplicated, compared 769 patients treated by PAIR approach with some other 952 patients who diversely underwent surgical therapy. This study reported how the overall mortality rate was respectively 0.1% for PAIR and 0.7% for

open surgery, highlighting the safety of both treatment approaches [11].

### Watch and Wait

The idea of leaving certain cyst types untreated, monitoring them over time, is a logical consequence of two main findings: (a) A good proportion of cysts consolidate and calcify (i.e., become completely inactive) without any treatment; (b) Cysts that have reached this stage and behave quietly (i.e., do not compromise organ functions or cause discomfort) seem to remain like this or stabilize even further [12].

From March 1994 to October 2013, 38 patients with 47 hepatic cysts diagnosed as inactive - 26 belonging to the type CE4 and 21 to type CE5 - were followed with ultrasound and serology at 6-12 month intervals for a period of 2 years at “San Matteo” hospital of Pavia, Italy. In 97% of the cases, the cyst remained inactive during the entire observational period with no change from CE4 to CE5 recorded. These results significantly support the watch-and-wait approach for spontaneously inactivated CE4-CE5 cysts [13].

### Surgical Therapy

Before the 1980's the surgical therapy represented the only available strategy in the management of liver hydatidosis patients [7]. Surgery indications include: large CE2-CE3 cysts associated with a large amount of daughter cysts, superficial cysts with the risk of a spontaneous rupture, infected cysts, in the case of evolved biliary communication and those with a resulting mass effect on the nearby vital organs. Thus, when choosing operative therapy over other methods, one must take into account the cyst type, its size, the location and the presence of potential complications as well as the comorbidities and the compliance of each patient.

Surgery is usually contraindicated in patients who are not fit enough for surgery and when the cyst is asymptomatic, poorly located and very small.

### Scolicidal Agents

These agents are strongly recommended for the inactivation of the protoscoleces and the

prevention of the dangerous spillage during the surgical intervention. Formalin, Cetrinide, and Chlorhexidine are commonly used, but their safety and efficacy have not been established yet [7].

The World Health Organization (WHO) suggests the use of 20% hypertonic saline solution in contact with the germinal cystic layer, at least 15 mins before the evacuation of the cyst. However, its usage must be avoided in cases of presence of biliary cyst fistulas due to their high risk in inducing sclerosing cholangitis after they penetrate the biliary tract. Major attention deserves the potential development of hypernatremia in hypertonic saline solution overuse [14].

An in vitro studied conducted in Ankara in 1998, examined *E. Granulosus* protoscoleces obtained from local slaughtered sheep's liver containing cysts [15]. The protoscoleces were separated by the cysts via aseptic techniques; the material is settled in a sterile bottle and the supernatant removed. The scolical agents tested were: 10% Poly-vinyl-pirrolidone-Iodine (Betadine®), 3% Hydrogen Peroxide, 95% Ethyl Alcohol, 1.5% Cetrinide-0.15% Chlorhexidine (10% Savlon®) and 20% Saline, and their further dilutions. The first concentration used was the one available commercially while the second and the third were respectively 50% and 10% of the original solutions diluted with sterile distilled water for simulating the agent's behavior within the cyst contents. None of the other scolical agents were as effective as the Savlon® in diluted and undiluted forms [15]. However, the pre-evacuation injection of this solution into the cyst should be avoided as the pressure inside the cyst is already high and could provoke a protoscolex spillage.

#### *Open Cyst Evacuation*

It is considered one of the safest approaches as well as a conservative surgical therapy and it is the surgical gold standard when the cysts location is peripheral, or it is close to the liver's surface.

The abdominal approach is the best in the case of an anterior location, while the lateral flank approach is indicated in cases in which the cyst is present in the segments 6 and 7.

The operated area must be lined with hypertonic saline solution-soaked gauzes in the case of spillage. The cavity of the cyst is opened with the subsequent aspiration of the cystic contents by a large suction device with a high negative pressure. Once the cyst is open, the following procedures can be performed: daughter cyst removal and active cyst lining resection with clearance of the residual debris. At this point, the cyst can be irrigated by using scolical agent except when the cyst fluid is bile strained or there is a cyst communication with the bile ducts on preoperative endoscopic retrograde cholangiopancreatography. In this case, absorbable sutures interrupt the biliary connection and the cyst cavity is filled with omentum. If the fistula cannot be closed, an external drainage with a close suction drain is recommended [7].

#### *Laparoscopic Cyst Evacuation*

It is adopted in selected patients with hydatid liver cyst located peripherally and it is considered to be the best surgical procedure in anteriorly located cysts without thick calcified walls and, by later approach, the one found in the hepatic segments 6 and 7 [7].

A retrospective study of 22 patients with echinococcal cysts, treated with a laparoscopic approach between June 2009 and June 2013, was conducted in the Hospital of Xinjiang Medical University. The results demonstrated how a total cystectomy in liver cyst hydatidosis appears to be safe and effective in selected patients with unique, small-sized, superficially located cysts [16]. The procedure is achieved using a 11 mm trocar slightly above the cyst and through which 10% Povidone-Iodine-soaked sponges are placed – acting as a scolical agent. At this point, the cyst is punctured with a 14-gauge needle and it is aspirated – leading to the endocyst's shrinking away from the wall and eventually falling to the bottom of the cyst. Then, the 11 mm trocar is replaced by a bigger 18mm trocar that allows the aspiration of the germinal membrane. The laparoscope is inserted directly into the cyst for the identification of any potential residual daughter cysts or biliary fistulae. Here, just as it was described in the open cyst evacuation, the cavity is irrigated using 20% hypertonic saline solution. The final step is the excision of the cystic wall with

subsequent omentoplasty or, if needed, a closed suction drainage. The laparoscopic approach includes several advantages such as: decreasing hospitalization duration, decreased hospital costs, earlier return to productive activity, short operative time (less than 90 mins) and low complication rates, with conversion to an open procedure in less than 5% of the cases [17]. Despite the innovations of this technique, it has not been accepted worldwide due to difficulties caused by its relative inability to avoid/control potential peritoneal spillage in cases of increased intra-abdominal pressures from the pneumoperitoneum, the limited manipulation area and the difficulty in aspirating the thick cyst contents. To minimize the risk of cyst spillage, there are techniques such as: the insertion of iodine-soaked sponges, the fixation of the cyst to the abdominal wall, the cyst lavage by a scolical agent (or scolical "pool" around the liver), the operation with patient in reverse Trendelenburg position and the innovative three-dimensional (3D) reconstruction for liver resection [7]. The 3D reconstruction demonstrated the ability to provide comprehensive and precise anatomical information for the liver and thus improves the chance of success as well as reducing the risk of hepatectomy in patients with hepatic and alveolar echinococcosis [18].

#### *Pericystectomy*

The pericystectomy with perioperative Albendazole therapy offers very high curative, is safe and simple [19], as reported in a study conducted in Nepal on 33 patients operated for cystic echinococcosis in liver, lungs, retroperitoneum, and mesentery, over a period of 8 years.

This procedure includes complete resection of the cyst wall either closed, not penetrating the cyst cavity, or opened, using the protoscolical agents to sterilize the cystic contents and remove the pericyst's tissue. It can be achieved by an electrocautery or a dissector, depending on either approaching the outside of the pericyst or directly along the cyst wall and it is best done along the peripheral part of the liver. The main advantage of this procedure is the decreased risk of cystic content spillage into the peritoneal cavity (the reason why it is preferred over the open cyst evacuation), when

a closed pericystectomy is performed, the avoidance of complete removal of the adventitia and of the need for scolecidal agents. On the other hand, it has an increased bleeding risk and risk of bile duct damage in cyst wall proximity, that needs a hepatic parenchymal transection [7].

#### *Liver Resection*

It is the most radical approach, and can be achieved by a non-anatomical wedge resection or with a formal hemihepatectomy, which is now a procedure associated with a low morbidity and mortality. This treatment strategy is indicated in complicated cysts accompanied by large biliary fistulae, small cysts with peripheral localization and can be considered at the presence of multiple cysts located in proximity of major structures such as portal or hepatic veins and bile ducts. In high-risk for recurrence patients, where the disease is refractory to the conservative management, liver resection represents an optimal therapeutic option [7]. 130 hepatic resections in patients with echinococcosis were studied at the Institute of gastroenterology of Tajikistan. Among these patients, 59 (45.3%) underwent a major hepatic resection and 71 (54.6%) underwent a minor hepatic resection that - in most of the cases - was a non-anatomical with margins of 1.5-2 cm from the cyst wall. Postoperative complications were experienced only in 23 patients (17.6%).

The results of this study allowed further specification for indications and contraindications of liver resection in echinococcosis, recommending an increasing use of this approach in specialized surgical departments [20].

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#### **Evolution and Follow-up**

Because of the endemic etiology of the hydatid disease and its high potential for reinfestation, the long-term follow-up with serologic tests and imaging studies represent the gold standard for the post-operative patient management. The guidelines given by the World Health Organization suggest constant follow-up consultations including US imaging and complete hematological tests, complete blood count as well as Liver Function Tests

(LFTs) every 3-6 months immediately after the surgical procedure and then yearly once the patients clinical picture is declared stable [7].

Serology with recombinant antigen B could provide limited information about the effectiveness of Albendazole in CE cases. Indeed, post-treatment positive specific IgG antibody seroconversion, in initially seronegative CE1 type patients, was considered a good indication for positive therapeutic efficacy of Albendazole [21].

## Conclusions

Nowadays, surgery still remains the gold standard curative treatment modality besides the systemic chemotherapy. Other treatment's strategies include: the Puncture, Aspiration, Injection and Reabsorption (PAIR) and the watch and wait method, demonstrated to play an important role in hydatid cyst management. Recent innovations brought by the new management therapies, in patients with echinococcal cyst disease of the liver, have been accompanied by the data of decreasing morbidity and mortality of the disease. Patients with liver hydatid disease should be treated in a tertiary unit where a team consisting of an expert hepatobiliary surgeon, an experienced physician and an interventional radiologist are all available.

## Authors contribution

Gianmarco Lotito wrote the first draft of the manuscript, Ionut Negoii, and Mircea Beuran reviewed the manuscript; all authors approved the final version of the manuscript.

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