

# Evaluation of clinical, diagnostic and treatment aspects in hydatid disease: analysis of an 8-year experience

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## Abstract

**Background & Objective:** *Echinococcosis* is still a common health problem. The aim of this study was to discuss our 8-year data in terms of diagnosis, treatment and follow-up of cystic *Echinococcosis*.

**Methods:** A total of 178 patients who had hydatid cyst were analyzed retrospectively from the hospital records. The diagnosis of hydatid cyst was based on clinical-serological and radiological findings. Treatment response was evaluated with clinical, radiological and serological findings.

**Results:** A total of 178 medical records were evaluated; the male:female ratio was 0.73 and mean age  $44.6 \pm 16.9$  years. The most common symptom was abdominal pain (94, 52.8%). The mean cyst size was  $9.5 \pm 3.9$  cm. Eosinophilia was significantly higher in patients with complicated cyst (35.3%) ( $p=0.002$ ). The average duration of hospitalization in surgical patients was shorter than non-surgical patients ( $p=0.026$ ). There was no significant correlation between the preference of scolical agent (hypertonic saline,  $H_2O_2$ , povidone iodine) and recurrence in patients who underwent surgery ( $p>0.05$ ). There was no significant difference between the patients who underwent radical and conservative surgery in terms of complication and recurrence ( $p=0.077$ ,  $p=0.557$ ). No significant difference was found between percutaneous and surgical treatment in terms of complication and recurrence ( $p=0.264$ ,  $p=0.276$ ).

**Conclusion:** Even though considerable progress has been made, uncertainties remain in the diagnosis and treatment of *Echinococcosis*. Hence, standardized diagnostic and treatment procedures should be established with well-designed studies.

**Keywords:** *Echinococcosis*, hydatid cyst, diagnosis, treatment.

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## Introduction

*Echinococcosis* is a zoonotic disease in areas where agriculture and livestock are common such as Mediterranean region, SouthWestern United States, Latin America, Middle East, China and Africa<sup>1,2</sup>. It is reported that the incidence in humans can reach 50 per 100,000 person-years and prevalence increases from 5% to 10% in endemic countries<sup>3</sup>. In addition, no cases have been reported in Antarctica until now, while New Zealand, Cyprus, Tasmania

and Iceland could be eliminated through effective control programs<sup>4</sup>.

Cystic *echinococcosis* (hydatid disease) is an infection caused by the cestode may cause hydatid unilocular cystic disease in humans<sup>3</sup>. The feces of tapeworm-infected definitive-host is responsible for the contamination of environment. Infecting eggs are taken by fecal-oral route in intermediate hosts<sup>2</sup>. The parasite eggs may remain infective for weeks because they are resistant to environmental conditions<sup>5-9</sup>. Therefore, it is possible to transmit without direct contact with infected-host. It has not been demonstrated transmission between humans yet<sup>7,10</sup>.

Hydatid disease affects both developing countries and people traveling to these endemic regions<sup>2,3</sup>. Therefore, it is widespread throughout the world and causes about \$3 billion dollars in financial costs including livestock losses and treatment each year<sup>11,12</sup>. The disease may be spontaneously limited or it may also be observed with complications<sup>1,13</sup>. Unfortunately, the diagnosis is usually

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incidental and particularly atypical settlements may escape from attention which leads to increase in morbidity and mortality<sup>2</sup>. Also, there are different opinions about treatment and follow-up and there is not yet a common consensus on this issue<sup>6,14</sup>. The aim of this study was to discuss our 8-year data in terms of diagnosis, treatment and follow-up of cystic *Echinococcosis* with the context of the literature.

## Methods

We conducted a retrospective study at the Katip Celebi University, Atatürk Training and Research Hospital, a 1055-bed tertiary referral care center in Izmir, Turkey. A total of 204 patients who had hydatid cyst between January 2009 and May 2016 were analyzed retrospectively from the hospital records. The study protocol was approved by our local ethics committee. Twenty-six of these patients were excluded from the study due to the absence of a definitive diagnosis or as they had a different diagnosis. One hundred seventy-eight patients were included in the study. The diagnosis of hydatid cyst was based on clinical-serological and radiological findings. The diagnosis of patients who underwent surgery was confirmed by pathological examination. The demographic data, symptoms, physical examination findings, laboratory values, diagnostic methods, cyst details (localization and size), complications, treatment, length of stay, follow-up, recurrence and all deaths were recorded. X-ray, ultrasonography (USG), computed tomography (CT) and magnetic resonance imaging (MRI) were performed before the treatment in terms of differential diagnosis and screening. In asymptomatic patients, diagnosis was considered as the result of imaging studies for other reasons.

Albendazol (10 mg/kg/day) was used in medical treatment. Albendazole administration was carried out as two doses daily for 3 months. The hydatid cysts were classified according to the WHO Informal Working Group on *Echinococcosis* (WHO-IWGE) classification system by USG<sup>15</sup>. Percutaneous treatment of the hydatid cyst with the PAIR (Puncture, Aspiration, Injection, Re-aspiration) technique was used on appropriate indications. The procedure was performed under USG guidance by interventional radiology. Firstly, the cyst contents were drained, a hypertonic saline was instilled into the cyst and left into the cavity for 15 minutes, then re-aspirated after the separation of germinative membrane. Surgical procedure was performed according to the cyst location, cyst structure

and surgeon's preference. Hypertonic saline, povidone iodine or H<sub>2</sub>O<sub>2</sub> was used as scolicidal agent during surgery. Treatment response was evaluated with clinical, radiological and serological findings. Clinical recovery of patients with the collapse, calcification or absence of cyst was evaluated as treatment success. The acquisition of new cyst in same or different organs and same or larger cyst size after treatment was evaluated as recurrence.

Statistical analyses were performed using the SPSS software version 24. The variables were investigated using the Kolmogorov-Smirnov test. Descriptive analyses were presented using means and standard deviations for normally distributed variables. Student's t-test was used to compare these parameters. The Mann-Whitney U test was used to compare of non-parametric parameters. The Chi-square test or Fisher's exact test was used for the comparison of independent groups. P value <0.05 was considered statistically significant.

## Results

### Patients

A total of 178 medical records were evaluated; the male:female ratio was 0.73 (75 men, 103 women) and mean age 44.6±16.9 years (range 4-81 years) at the time of diagnosis. Of this patients, 88 (49.4%) lived in rural areas while 90 (50.6%) lived in urban areas. Six patients were under 18 years of age. The number of patients who were diagnosed as hydatid cyst was 53 in 2009, 23 in 2010, 11 in 2011, 34 in 2012, 19 in 2013, 15 in 2014, 10 in 2015 and 13 in 2016.

### Clinical findings

The most common symptom was abdominal pain (94, 52.8%). Other symptoms were nausea/vomiting (12, 6.7%), upper abdominal bloating (7, 3.9%) and jaundice (7, 3.9%). In extrahepatic *Echinococcal* cases, there were different symptoms according to cyst location. There was a chest pain in 1 (0.5%) patient with cardiac *Echinococcosis*, palpable mass in 2 (1.1%) patients with *Echinococcosis* of extremity, urinary incontinence in 1 (0.5%) patient with spinal *Echinococcosis*, headache in 1 (0.5%) patient with intracranial *Echinococcosis*. Seventy-three (41%) patients were asymptomatic and the diagnosis was made incidentally. On general physical examination, abdominal tenderness (18, 10.1%), palpable mass in the extremity (2, 1.1%) and hepatomegaly (1, 0.6%) were found. The physical examination was normal in the majority of patients (157, 88.2%).

### Laboratory findings

The initial laboratory profile revealed a mean leukocyte level of  $8528.3 \pm 3092.8$  K/uL, a mean erythrocyte sedimentation rate (ESR) of  $31.2 \pm 23$  mm/h. Leukocytosis was found in 12.9% of the patients. Eosinophilia was defined as at least 6% of the leukocyte value on differential count, detected in 20.5% of patients and mean count was  $5.4 \pm 8.7\%$ . Eosinophilia was significantly higher in patients with complicated cyst (rupture or fistula) (35.3%) ( $p=0.002$ ). The sensitivity of *Echinococcal* indirect hemagglutination test (IHAT) was 81.6% (40/49), indirect immunofluorescence test (IFAT) sensitivity was 73.7% (70/95) and enzyme-linked immunosorbent assay (ELISA) sensitivity was 87.5% (147/168). USG was used as diagnostic test for 166 patients with hepatic cystic *Echinococcosis* and had 100% sensitivity. Endoscopic retrograde cholangiopancreatography (ERCP) was performed in 3 patients who had cholestasis.

### Imaging findings

The mean cyst size was  $9.5 \pm 3.9$  cm (range 3 to 20 cm) and 52 (29.2%) cysts were larger than 10 cm. According to the WHO-IWGE classification, 13.7% of the cysts were type CE1, 37.3% were type CE2, 23.5% were type CE3 and 25.5% were type CE4 and CE5. The most common site of cyst was liver (151, 84.8%). In 108 (60.7%) patients, cysts were located in the right lobe of the liver and 18 (10.1%) patients had bilateral multiple liver cysts. Cyst localizations were shown in Table 1. There were 29 (16.3%) patients with at least one complicated cyst. Complications of cyst were as follows; infected cyst (37.9%), biliary fistula (31%), compression of bile ducts (24.1%), ruptured cyst (20.7%), duodenal fistula (6.9%). There was no significant difference between complicated and non-complicated cysts in terms of age, gender, and cyst size ( $p=0.132$ ,  $p=0.518$ ,  $p=0.906$  respectively).

**Table 1.** Cyst localizations

Localizations	n	%
Liver	151	84.8%
Liver + lung	8	4.5%
Liver + spleen	2	1.1%
Liver + intraperitoneum	1	0.6%
Liver + intraperitoneum + retroperitoneum	1	0.6%
Liver + heart	1	0.6%
Liver + pelvic cavity + transverse colon	1	0.6%
Liver + lung + brain (right parietal lobe)	1	0.6%
<i>Isolated organ involvement</i>		
Spleen	4	2.2%
Kidney	2	1.1%
Heart	1	0.6%
Stomach	1	0.6%
Thigh	1	0.6%
Spinal (lumber)	1	0.6%
Psoas muscle (right)	1	0.6%
Cruris posterior	1	0.6%

### Surgical results

One hundred and two (56.7%) patients underwent surgery. Radical surgery was performed in 8 patients (4 pericystectomy and 4 segmental liver resection) while the other patients underwent conservative surgery (partial cystectomy and drainage). Of these patients who un-

derwent partial cystectomy, 7 of them were treated with capitonnage, 13 patients with omentopexy and 2 patients with intraflexion. There was no significant difference between the patients who underwent radical or conservative surgery in terms of complication and recurrence ( $p=0.077$ ,  $p=0.557$ ). There was no significant correlation

between the preference of scolicalid agent (hypertonic saline, H<sub>2</sub>O<sub>2</sub>, povidone iodine) and recurrence in patients who underwent surgery (p>0.05). The patients with extrahepatic hydatid cyst were also surgically treated including splenectomy (4), nephrectomy (2), ventriculotomy (1) and pericardiotomy (1), craniotomy and cyst extirpation (1). Patients with pulmonary hydatid disease were referred to the department of cardiothoracic surgery at another hospital. Surgical morbidity was 34.3%. The surgery-related complications were as follows; leakage of cyst fluid (17), hepatic injury (8), diaphragmatic laceration (4), eventration/evisceration (3), liver abscess (1), spleen abscess (1) and cyst rupture (1) (Table 2). The average duration of hospitalization in surgical patients (11.9±8.3 days) was shorter than non-surgical patients (80.6±30.3 days) (p=0.026). The mean hospital stay in patients without postoperative complications was 16 days, while in patients with complications was 26.2 days (p=0.715). Surgical mortality was 0.9% (n=1). One patient with hepatic hydatid cyst died 1 month after surgery from biliary fistula, liver abscess and peritonitis.

### Percutaneous treatment results

PAIR was used in 49 (27.5%) patients. Procedure-related complications were observed in 9 (18.4%) patients. The complications of PAIR were abscesses formation in the residual cavity (6), bile leakage (4), anaphylactic shock (1), cyst rupture (1), pleural effusion (1) and intracystic hemorrhage (1). No death occurred related to PAIR.

### Watch-and-wait approach

The 'watch-and wait' approach was applied to 12 (6.7%) patients who had uncomplicated inactive cysts (10 hepatic and 2 splenic cysts). The diameter of the cyst ranged between 2 and 10 cm (6.2±2.8 cm). The IFAT test was negative in all of these patients, whereas the IHA test was positive in 2 patients. Mean follow-up was 33 months (range 6-84 months). In follow-up, no reactivation or complication was observed serologically and radiologically.

### Follow-up findings

The median follow-up was 19.1±24.9 months (range 0-168 months). Seven of the patients (3.9%) were lost to follow-up before the treatment. The treatment of 171 patients who were followed up is shown in Table 2.

**Table 2.** Recurrence and complication rates according to the use of chemotherapy (albendazole)

Treatment	%, n	Mean cyst size (cm)	Complication (% ,n)	p	Recurrence (% ,n)	p
Watch and wait	7% (12/171)	6.2±0.8	-		-	
Chemotherapy	5.3% (9/171)	7.1±1.1	-		-	
PAIR	7% (12/171)	11±1.2	25% (3/12)	0.557	58.3% (7/12)	0.190
Chemotherapy + PAIR	21.6% (37/171)	8.4±0.6	16.2% (6/37)		27% (10/37)	
Surgery	37.4% (64/171)	10.6±0.5	26.6% (17/64)	0.821	37.5% (24/64)	0.295
Chemotherapy + Surgery	22.2% (38/171)	10.1±0.6	28.9% (11/38)		23.7% (9/38)	
PAIR (Total)	27.5% (49/178)	9.1±3.6	18.4% (9/49)	0.076	34.7% (17/49)	0.806
Surgery (Total)	56.7% (102/178)	10.4±3.9	27.5% (28/102)		32.4% (33/102)	

\* One patient with liver and spleen cysts underwent PAIR+surgery (splenectomy)

There were 89 (50%) patients followed longer than 12 months and recurrence was found in 40/89 (44.9%) of these patients. A total recurrence rate was 28.6% (n=51) from the time of initial diagnosis. All recurrences occurred in the liver, additionally in 2 cases in the peritoneum and in 1 case in the small intestine. The IFAT was performed in 16 of 51 patients with recurrence and was

found positive in all of these patients. USG and CT were used in detecting recurrence of hydatid disease. No significant difference was found between PAIR and surgical treatment in terms of complication and recurrence ( $p=0.264$ ,  $p=0.276$ ). The mean duration of albendazole treatment in patients with recurrence was shown in Table 3.

**Table 3.** Duration of treatments according to the type of treatment and recurrence

		Recurrence (+)			Recurrence (-)		
		Surgery	PAIR	p	Surgery	PAIR	p
Duration of Treatment s(days) (mean±SD)	Pre-operative treatment	9.3±27.7	30.3±50.8	0.327	15.4±25.8	16.1±12.7	0.16
	Post-operative treatment	11.2±22.1	65±48.6	0.005	27.8±44	65.7±72.8	0.018
	Total	10.6±32.3	63.5±74.9	0.008	28.6±49.5	72.7±70.5	0.002

\* Kolmogorov-Smirnov Z test was performed at the beginning of the analysis. We found that our data was not show normal distribution because the p value was smaller than 0.05. Therefore we used Mann Whitney U test which is non-parametric counterpart of the t-test. The mean and standard deviation (mean±SD) are given in the table and the p values belong to the Mann Whitney U test.

## Discussion

The worldwide incidence and prevalence of *Echinococcus* has decreased significantly as a result of disease control programs in recent years<sup>16</sup>. Nevertheless, *Echinococcus* is still a common health problem in developing countries, especially in rural areas<sup>2</sup>. Community-based studies have shown that the prevalence of disease is between 1% and 10% in endemic regions<sup>17</sup>. It has been reported that prevalence is higher in women and in middle age group as shown in our study<sup>3,17,18</sup>. It may be caused by gender roles such as closer contact with dogs, tending gardens, feeding or milking livestock in endemic areas and slow growth of the cyst hydatid.

The most common locations of the *Echinococcus* are liver (68-75%) and lung (15-22%)<sup>17-19</sup>. The right lobe of the liver is affected more common than the left lobe<sup>3</sup>. More rarely, hydatid disease can occur anywhere in the body (5-10%), such as spleen, kidney, heart, bones, muscles, skin, abdominal or pelvic cavity, brain and ovaries<sup>6,19</sup>. Although cysts are usually solitary in a single organ (about 80%), the incidence of multiple cysts or multiple organ involvement ranges from 10-15% depending on the parasite genotype and geographic region<sup>3,6,11</sup>. In our study, the hepatic hydatid cysts were usually solitary (84.8%)

and were detected in the right lobe (60.7%). Two or more organ involvement was detected in 8.6% of patients. In endemic areas, hydatid cyst should be kept in mind when a cystic lesion is detected anywhere in the body. If the lesion is hydatid cyst, the liver and lung must be screened for primary involvement.

There are usually no symptoms in intact and small cysts, however symptoms may appear in growing cysts which compress the surrounding tissue (biliary tract, bronchus, major vessels, intestine) or in complicated cysts such as rupture, infection or anaphylaxis<sup>3,20,21</sup>. The most common symptom is upper abdominal pain for hepatic *Echinococcus* and cough for pulmonary *Echinococcus*<sup>17</sup>. Atypical localizations in hydatid disease may present with different symptoms depending on which organ is involved<sup>2</sup>. In this study, abdominal pain was the most common complaint as expected in hepatic *Echinococcus*, while different clinical manifestations such as mass, urinary incontinence and headache were detected in hydatid disease with atypical localization. None of our pulmonary hydatid disease patients had any symptoms and were detected by screening. This may be due to the fact that cough is ignored by patients with pulmonary hydatidosis and they are not seek-

ing medical care for minor symptoms. In endemic areas, persistent abdominal pain and dry cough should be questioned in terms of hydatid disease because symptoms are usually minor in *Echinococcosis*. These complaints should be investigated in terms of hydatid disease if symptoms do not resolve with symptomatic treatment. In addition, it is appropriate to evaluate the cystic lesions detected in endemic regions in terms of hydatid cysts, because clinical findings may be different in atypical presentation.

The diagnosis of disease is mainly based on imaging results; epidemiological data, clinical findings and serological tests are also helpful in confirming the diagnosis<sup>3,21</sup>. The combination of imaging techniques with serological markers reveals a much higher detection rate in diagnosis of *Echinococcosis*, therefore patients with symptoms should be evaluated with these two methods<sup>21</sup>. Although many new serological methods are mentioned in the literature, there is a limited number of serological tests commonly used in endemic regions including IHAT, ELISA and IFAT<sup>3,6,18,21-23</sup>. Routine laboratory tests are usually non-specific<sup>3</sup>. Eosinophilia has been reported in 20-34% of patients and may be associated with fluid leakage from cyst<sup>20</sup>. Eosinophilia is an important laboratory finding especially in complicated cysts as indicated in our study. Additionally, highest sensitivity was obtained by ELISA in our study. We conclude that ELISA may be more useful in routine screening and follow-up of patients.

USG, radiography, CT and MRI are usually used for diagnosis. Chest X-ray is often preferred for pulmonary *echinococcosis* screening and plain radiographs can also be used to detect calcified cysts which occur in the muscle or bone<sup>21</sup>. USG is the primary diagnostic procedure, for hepatic or extrahepatic *echinococcal* cysts, also helpful in the follow-up period and sensitivity ranges from 93-98%<sup>15,24</sup>. However, USG has lower sensitivity to detect smaller cysts<sup>21</sup>. The World Health Organization Informal Working Group on *Echinococcosis* (WHO-IWGE) published an international classification system in 2003 based on ultrasonographic imaging by modifying the Gharbi classification<sup>15</sup>. According to this classification, the cysts are divided into 6 stages in 3 different clinical groups. Class CE1 and CE2 cysts are active (viable), CE3 (CE3a and CE3b) is transitional group which contains degenerative cyst, CE4 and CE5 are inactive group. Class CE3 cysts are divided into two groups; CE3a cysts responds to medical/percutaneous

treatment while CE3b cysts are usually unresponsive. CT or MRI can be used if USG is not appropriate in terms of anatomic location. We concluded that USG sensitivity was 100% because the patients with symptomatic and large cysts referred to the hospital for diagnosis. In patients with small cysts, we often think that the diagnosis is frequently overlooked. We think that the use of X-ray and USG is more cost-effective for scanning, especially in case of suspicious cysts, -CT and MRI should be applied in selected cases in terms of differential diagnosis.

The recommended methods for treatment of cystic *Echinococcosis* are surgery, percutaneous procedures, anti-infective drug treatment and observation (watch and wait)<sup>25</sup>. It is unclear which method is superior because of a lack of randomized controlled trials comparing these methods<sup>21,22</sup>. Although surgery is indicated as the main treatment for hydatid disease, it becomes an alternative method due to the successful outcome of less invasive approaches<sup>6,22</sup>. Therefore, surgery is especially applied to multivesicular cysts (CE2 and CE3b) which are not suitable for percutaneous interventions, cysts larger than 10 cm and complicated cysts<sup>21,22,26</sup>. PAIR is recommended for all CE1 and CE3a cysts that >5cm combined with medical treatment or <5 cm which unresponsive to medical treatment<sup>5,6,21,22,25</sup>. We showed that PAIR or surgical choice did not cause a significant difference in the development of complication or recurrence. Therefore, choosing less invasive procedure for the appropriate indication may be a more rational approach.

Benzimidazoles (albendazole, mebendazole) are used in medical treatment of *Echinococcosis*<sup>21,22,24,25</sup>. In recent years, albendazole is preferred because it is reported to be more effective than mebendazole<sup>6,19-21</sup>. Apart from albendazole, it has also been reported that different antiparasitic drugs such as praziquantel, nitazoxanide and ivermectin are used alone or in combination for the treatment of *Echinococcosis*<sup>19,21,22,24</sup>. However, for each stage of cysts, randomized controlled trials should be performed comparing the results of treatment with benzimidazole to different options<sup>19,21,24</sup>.

Spillage of the cyst fluid into the abdominal cavity during surgery or PAIR may cause secondary (recurrent) *Echinococcosis*<sup>21,22</sup>. Although duration of prophylaxis is not clearly defined by controlled studies, medical prophylaxis is generally recommended for 1 day-1 month before surgery

and 1 month-2 months after surgery to prevent recurrence<sup>25,26</sup>. Albendazole administration is recommended for 4 hours before puncture and 1 months after puncture to prevent PAIR related recurrence or anaphylaxis<sup>22,25,27</sup>. The data presented in our study with very wide standard deviation suggest that some patients have received more than 30 days; others have received less than 30 days. The considerable variability in albendazole administration may be due to the application of different treatment protocols in different clinics. This could also explain the recurrence rate, higher than those found in other studies<sup>28</sup>. We conclude that the use of peroperative albendazole, which has been shown in some studies that reduce complications and recurrence, should be routinely used in all interventional procedures.

Routine USG scan is recommended every 3 to 6 months in the first 2 years, and then once a year at least 3 to 5 years in terms of recurrence<sup>6,25,27</sup>. Since serologic tests alone cannot distinguish recurrent or residual disease, it is recommended that serologic tests should be combined with imaging methods in the follow-up of patients<sup>6</sup>. Further prospective studies are required to make decision about the duration of prophylaxis.

### Conclusion

Even though considerable progress has been made, uncertainties remain in the diagnosis and treatment of *Echinococcosis*. Imaging methods may not be easily accessible in resource poor settings even though they are essential for diagnosis, furthermore imaging techniques may not recognize early-stage cysts. Therefore new serodiagnostic tests that can be widely used and has high sensitivity and specificity should be defined. The stage-specific approach recommended by WHO-IWGE should be used more widely in clinical practice since it is also a guide for the treatment option in *Echinococcosis*<sup>21</sup>. Clinical trial data that systematically assesses current treatments is not available and there is no ideal treatment option. Hence, standardized diagnostic and treatment procedures should be established with well-designed studies. In addition, new strategies must be determined in order to eliminate the disease in collaboration with policy makers and veterinarians.

### Conflict of interest

The authors declare that there is no conflict of interest.

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