

## Hydatid cyst of the gallbladder: A systematic review of the literature

Roberto Gómez, Yousef Allaoua, Rafael Colmenares, Sergio Gil, Pilar Roquero, José M Ramia

Roberto Gómez, Yousef Allaoua, Rafael Colmenares, Sergio Gil, Pilar Roquero, Faculty of Medicine, Universidad de Alcalá, 28805 Alcalá de Henares, Spain

José M Ramia, Servicio de Cirugía General y del Aparato Digestivo, Hospital Universitario de Guadalajara, 19002 Guadalajara, Spain

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Correspondence to: José M Ramia, MD, PhD, FACS, FRCS, Servicio de Cirugía General y del Aparato Digestivo, Hospital Universitario de Guadalajara, C/Donantes de Sangre s/n. 7ª planta, 19002 Guadalajara, Spain. [jose\\_ramia@hotmail.com](mailto:jose_ramia@hotmail.com)  
Telephone: +34-61-6292056  
Fax: +34-94-9209218

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### Abstract

#### AIM

To evaluate all the references about primary gallbladder hidatidosis looking for best treatment evidence.

#### METHODS

Search: 1966-2015 in MEDLINE, Cochrane Library, SciELO, and Tripdatabase. Key words: "gallbladder hydatid disease" and "gallbladder hydatid cyst". We found 124 papers in our searches but only 14 papers including 16 cases were about hydatid cyst of the gallbladder (GBHC).

#### RESULTS

Eight cases of GBHC were women and seven men. One not mentioned. Median age was 48.3 years. The most frequent clinical symptom was abdominal pain (94%) usually in the right upper quadrant. Ultrasound was performed in ten patients (62.5%) but in most cases a combination of several techniques was performed. The location of the cysts was intravesicular in five patients. Five patients presented GBHC and liver hydatid cysts. Two patients presented cholelithiasis and one choledocholithiasis. The most frequent surgical technique was cholecystectomy by laparotomy (81.25%). Simultaneous surgery of liver cysts was carried out in five cases. Eleven patients did not present postoperative complications, but one died. The mean hospital stay was seven days. No recurrence of GBHC was recorded.

#### CONCLUSION

In GBHC, the most frequent symptom is right hypocondrium pain (evidence level V). Best diagnostic methods are ultrasound and computed tomography (level V, grade D). Suggested treatment is open cholecystectomy and postoperative albendazole (level V, grade D) obtaining good clinical results and none relapses.

**Key words:** Hydatid cyst; Gallbladder; Cholecystectomy; Review; Hydatidosis

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**Core tip:** Systematic review of gallbladder hydatidosis has not previously done. We have performed a systematic search trying to define best diagnostic procedures and best therapeutical strategies.

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## INTRODUCTION

Hydatid disease is a zoonotic infection found all over the world, which is caused by the larval stage of parasites of the *Echinococcus species*. *Echinococcus granulosus* is the most frequent (95% of cases); other species such as *Echinococcus multilocularis* are rare (5%). Hydatid disease is endemic in cattle-raising regions like the Mediterranean countries, Africa, South America, Middle East, Australia and New Zealand<sup>[1,2]</sup>.

*Echinococcus granulosus* lives in the intestine of dogs and other wild canines, which are the definitive hosts. Humans are accidentally infected *via* the fecal-oral route. Larval embryos pass through the intestinal wall and reach the liver through the portal system. Subsequently, through the liver and lungs, parasites reach the arterial circulation and may spread through the rest of the organs<sup>[1-3]</sup>. The larvae can remain and develop into hydatid cyst anywhere in the body, but liver (70%) and lungs (20%) are the most commonly affected sites.

Primary hydatid cyst of the gallbladder (GBHC) is an exceptional location for hydatidosis, and its pathogenesis is not completely clear. While the literature on liver hydatid disease is abundant, references to the primary involvement of the gallbladder are limited to clinical cases and so it is difficult to reach meaningful conclusions<sup>[3-16]</sup>. In this paper we present a systematic review of the literature on GBHC published to date.

## MATERIALS AND METHODS

### Search strategy

We introduced the following keywords in the MEDLINE (PubMed), Tripdatabase, SciELO and Cochrane Library databases: "gallbladder hydatid disease (GHD)" and "gallbladder hydatid cyst (GHC)" without restrictions on publication date or author until 31 December 2015<sup>[17]</sup>. The first selection of papers was made after reading title and abstract, and in case of doubt, after reading the full text. A flowchart is shown in Figure 1.

Our results were as follows: (1) zero results in SciELO; (2) 2 results for both searches (GHD and GHC) in the Cochrane Library: Neither met the inclusion criteria; (3) 21 results for GHD and 17 for GHC in Tripdatabase. After

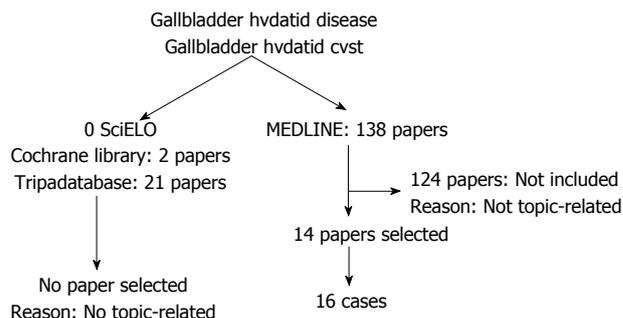


Figure 1 Search flowchart.

review, none were found to be related to the topic; and (4) 137 results for GHD and 138 for GHC in MEDLINE. Since the overlap between search results was 99%, we used the latter search with 138 results; of them, only 14 (10.14%) met the selection criteria for this study.

These 14 papers included 16 clinical cases covering a wide range of clinical, diagnostic and therapeutic aspects of GBHC. These characteristics are summarized in Tables 1-4.

In the next step, to assess the quality of the selected studies we used the rating scale described by Manterola *et al*<sup>[18]</sup>, which assesses each publication individually depending on the type of study, the size of the sample and whether it is justified, and the methodology used. A mean score of all the selected studies is produced ranging from 6 to 36 points, with a quality cut-off score of 18 points. The mean score in our review was 10.3; however, due to the rarity of GBHC and the few studies of this issue published, we selected all the papers available.

We also carried out a qualitative analysis of the selected papers and their conclusions, based on the classical levels of evidence and grades of recommendation proposed in Cook *et al*<sup>[19]</sup> and Sackett<sup>[20]</sup>.

## RESULTS

Eight cases of GBHC were women and seven men. The sex of one patient was not specified. Median age was 48.3 years (range: 27-76). The most frequent clinical manifestation was abdominal pain (15/16) (94%) (Table 1), in the right upper quadrant in 13 patients) (81.25%), in the epigastrium in four (25%), (three of whom combined upper quadrant pain in right hypochondrium and epigastric pain), and finally diffuse abdominal pain in two (12.5%). In one case, no data on abdominal pain were included (6.25%). Three patients presented vomiting and two had nausea; no information on nausea or vomiting was reported in the rest of patients. Three patients had fever, four were fever-free, and no data on fever were available for the remaining nine patients. Four patients had jaundice, five did not, and no data were available in seven cases. As regards past medical history, two patients had been previously diagnosed with hydatid disease and one had had hepatitis.

On physical examination (Table 1), four patients presented abdominal tenderness, three hepatomegaly,

Table 1 Clinical data

Ref.	Sex	Age	Abdominal pain	Nausea and vomiting	Fever	Jaundice	Abdominal exploration	Past medical history
Noomene <i>et al</i> <sup>[3]</sup> , 2013	Male	48	Diffuse		No (36.7 °C)	Yes	Painful palpation in right hypocondrium	
Ertem <i>et al</i> <sup>[4]</sup> , 2012	Male	32	Right hyponcondrium and epigastrium	Nausea	No	No	Painful palpation in right hypocondrium	
Krasniqi <i>et al</i> <sup>[5]</sup> , 2010	Female	39	Right hypocondrium (18 mo)	Nausea		No	Painful palpation in right hypocondrium	
Murtaza <i>et al</i> <sup>[6]</sup> , 2008	Female	32	Right hyponcondrium and epigastrium (3 mo)		No	No	Hepatomegaly	Liver hydatid surgery 8 yr ago
Sabat <i>et al</i> <sup>[7]</sup> , 2008	Female	35	Right hyponcondrium and epigastrium		Yes	Yes		
Wani <i>et al</i> <sup>[8]</sup> , 2005	Female	51	Right hyponcondrium		Yes (38 °C-39.5 °C)		Abdominal distension	
Pitiakoudis <i>et al</i> <sup>[9]</sup> , 2006	Male	60	Right hyponcondrium (10 d)	Vomiting				
Safioleas <i>et al</i> <sup>[10]</sup> , 2004	Female	65	Right hyponcondrium and epigastrium	Vomiting				
Safioleas <i>et al</i> <sup>[10]</sup> , 2004	Female	51	Right hyponcondrium (6 mo)				Normal	
Safioleas <i>et al</i> <sup>[10]</sup> , 2004	Male	63	Right hyponcondrium and epigastrium				Normal	
Kumar <i>et al</i> <sup>[11]</sup> , 2004	Female	27	Diffuse					Relapsed liver hydatid cyst
Raza <i>et al</i> <sup>[12]</sup> , 2003	Male	27	Right hyponcondrium (4 mo)		No	No	Hepatomegaly	
Kapoor <i>et al</i> <sup>[13]</sup> , 2000	Male	53	Right hyponcondrium (2 mo)		Yes (high fever, 10 d)	Yes	Abdominal distension, ascitis, gallbladder mass	
Cangiotti <i>et al</i> <sup>[14]</sup> , 1994	Male							
Rigas <i>et al</i> <sup>[15]</sup> , 1979	Female	65	Right hyponcondrium	Vomiting		No	Normal	
Barón Urbano <i>et al</i> <sup>[16]</sup> , 1978	-	76	Right hyponcondrium			Sí	Hepatomegaly, rubi spots in thorax and abdomen	Hepatitis

Table 2 Radiological and analytical studies

Ref.	Alkaline phosphatase (UI/L)	Bilirubin (mg/dL)	Ultrasound	CT	MRI	Cysts inside gallbladder	Cholelithiasis	Cholelithiasis	Serology <i>E. granulosus</i>
Noomene <i>et al</i> <sup>[3]</sup> , 2013	220	7.1	Yes	Yes	Cholangio MRI			Yes	Positive
Ertem <i>et al</i> <sup>[4]</sup> , 2012			Yes	Yes	Yes	Yes	No	No	Negative
Krasniqi <i>et al</i> <sup>[5]</sup> , 2010			Yes	Yes				No	
Murtaza <i>et al</i> <sup>[6]</sup> , 2008	140	10.2	Yes	Yes					
Sabat <i>et al</i> <sup>[7]</sup> , 2008			Yes	Yes					
Wani <i>et al</i> <sup>[8]</sup> , 2005			Yes	Yes			Yes		
Pitiakoudis <i>et al</i> <sup>[9]</sup> , 2006		0.9	Yes	Yes	Yes	Yes			
Safioleas <i>et al</i> <sup>[10]</sup> , 2004							Dude	Dude	
Safioleas <i>et al</i> <sup>[10]</sup> , 2004			Yes						
Safioleas <i>et al</i> <sup>[10]</sup> , 2004				Yes		Yes			Positive
Kumar <i>et al</i> <sup>[11]</sup> , 2004				Yes		Yes			
Raza <i>et al</i> <sup>[12]</sup> , 2003			Yes				Yes		
Kapoor <i>et al</i> <sup>[13]</sup> , 2000	465	5.6	Yes			Yes			Positive
Cangiotti <i>et al</i> <sup>[14]</sup> , 1994									
Rigas <i>et al</i> <sup>[15]</sup> , 1979				Yes				No	
Barón Urbano <i>et al</i> <sup>[16]</sup> , 1978	266	8.8							

CT: Computed tomography; MRI: magnetic resonance imaging; *E. granulosus*: *Echinococcus granulosus*.

two abdominal distension, and one a palpable mass. Serological information was available in only five cases (Table 2). Levels of alkaline phosphatase and bilirubin were high in four patients, normal in one, and no information was recorded for the other eleven. In the cases in which they were specified, alkaline phosphatase levels were between 140 and 465 IU/L and bilirubin between 5.6 and 10.2 mg/dL. *Echinococcus* serology was performed in four cases, being positive in three and negative in one.

Image diagnostic methods are described in Table 2. Abdominal ultrasound (US) was performed in ten patients (62.5%), abdominal computed tomography (CT) in nine (56.25%), and magnetic resonance imaging (MRI) in three (18.75%). In most cases a combination of several techniques was performed: US + CT + MRI in three cases, US + TC in three others; so four cases underwent US alone and three CT alone. The location of the cysts was intravesicular in five patients. Five patients presented

**Table 3 Therapeutical strategies**

Ref.	Preoperative albendazole	Treatment	Liver hydatidosis	Intraoperative treatment cyst	Intraoperative findings
Noomene <i>et al</i> <sup>[3]</sup> , 2013	No	ERCP + Stent Laparoscopy cholecystectomy	No	No	Biliary sludge and stones in ampulla seen in ERCP
Ertem <i>et al</i> <sup>[4]</sup> , 2012	No	Cholecystectomy by laparotomy	No	No	Galbladder cyst with inflammatory changes
Krasniqi <i>et al</i> <sup>[5]</sup> , 2010	No	Cholecystectomy by laparotomy	Yes Cystopericystectomy	No	Calcified primary gallbladder cyst
Murtaza <i>et al</i> <sup>[6]</sup> , 2008	Yes (2 wk)	Subtotal Cholecystectomy by laparotomy	No	Yes	Biliary communication into the cyst closed with sutures
Sabat <i>et al</i> <sup>[7]</sup> , 2008	No	Cholecystectomy by laparotomy	No	Yes (aspiration + hypertonic solution cleaning)	-
Wani <i>et al</i> <sup>[8]</sup> , 2005	No	Cholecystectomy by laparotomy	No	No	-
Pitiakoudis <i>et al</i> <sup>[9]</sup> , 2006	No	Cholecystectomy by laparotomy	No	Yes	-
Safioleas <i>et al</i> <sup>[10]</sup> , 2004	No	Cholecystectomy by laparotomy	No	No	5 cm × 4 cm cyst
Safioleas <i>et al</i> <sup>[10]</sup> , 2004	No	Cholecystectomy by laparotomy	No	No	3 cm × 4 cm cyst
Safioleas <i>et al</i> <sup>[10]</sup> , 2004	No	Cholecystectomy by laparotomy	No	No	5 cm × 4 cm cyst
Kumar <i>et al</i> <sup>[11]</sup> , 2004	No	Cholecystectomy by laparotomy	Yes Cysts segment IV and VIII. Cystopericystectomy segment IV + PAIR segment VII	Yes (aspiration + hypertonic solution cleaning) segment VII cyst	Cyst invading segment IV. Communication between cyst and gallbladder
Raza <i>et al</i> <sup>[12]</sup> , 2003	No	Cholecystectomy by laparotomy	Yes Right Lobe Enucleation	No	In gallbladder: Stones and daughter vesicles
Kapoor <i>et al</i> <sup>[13]</sup> , 2000	No	NO. ERCP + Stent	No	No	-
Cangiotti <i>et al</i> <sup>[14]</sup> , 1994	No	Cholecystectomy by laparotomy	SI. Right lobe. Cystopericystectomy	No	-
Rigas <i>et al</i> <sup>[15]</sup> , 1979	No	Cholecystectomy by laparotomy	No	No	-
Barón Urbano <i>et al</i> <sup>[16]</sup> , 1978	No	Cholecystectomy by laparotomy	Yes Segment IV. Done by thoracotomy	-	Enlarged liver. Cholangitis. Daughter vesicles in cystic conduct lumen

ERCP: Endoscopic retrograde cholangiopancreatography.

GBHC and liver hydatid cysts. Two patients presented cholelithiasis and one choledocholithiasis.

The data on therapeutic management are displayed in Table 3. One patient received preoperative albendazole for two weeks, but no data on the other fifteen were available. The most frequent surgical technique was cholecystectomy by laparotomy (81.25%), performed in 13 patients; laparoscopic cholecystectomy was performed in two cases (12.5%), in one of them a previous endoscopic retrograde cholangiopancreatography (ERCP) was done and received a biliary stent; in the last patient, cholecystectomy was not performed, only ERCP and biliary stenting (6.25%). Cholecystectomies were total in 14 cases (93.3%) and subtotal in the patient treated preoperatively with albendazole (6.7%). Simultaneous surgery of liver hydatid cysts was carried out in five cases: Cystopericystectomy in three cases, enucleation in one, and in the other the surgical technique was not specified except for the fact that access was made by thoracotomy. Eleven patients did not present postoperative complications: One presented fever, atelectasis

and pleural effusion, and another multiple organ failure and death. No data regarding postoperative outcome were recorded in three cases. The pathological examination (Table 4) was performed in nine patients. In three, the presence of *Echinococcus granulosus* was confirmed microscopically.

The mean hospital stay was seven days (range: 1-12 d). Seven patients were treated postoperatively with varying doses of albendazole. In nine cases follow-up after the postoperative period was recorded, for a mean period of 38 mo (range: 1-120 mo); no recurrence of GBHC was recorded.

## DISCUSSION

Hydatidosis is a disease caused by the larva of the genus *Echinococcus*, within which *Echinococcus granulosus* is the most common species. Although cases have been diagnosed all over the world as a result of increased intercontinental migration, areas in which the incidence is significantly higher include the Mediterranean Sea,

**Table 4 Pathology, postoperative course and follow-up**

Ref.	Pathologic study	Stay	Postoperative treatment	Morbidity	Follow-up
Noomene <i>et al</i> <sup>[3]</sup> , 2013	Cysts in gallbladder. Chronic inflammation	1	Albendazole 400 mg/d	No	
Ertem <i>et al</i> <sup>[4]</sup> , 2012	Cyst in gallbladder	4		No	6 mo
Krasniqi <i>et al</i> <sup>[5]</sup> , 2010	Calcified cyst 7 cm × 5 cm located in gallbladder mucosa	7	Albendazole 400 mg/d, 42 d	No	5 yr
Murtaza <i>et al</i> <sup>[6]</sup> , 2008				No	2 mo
Sabat <i>et al</i> <sup>[7]</sup> , 2008			Albendazole 10 mg/kg, 9 mo	No	
Wani <i>et al</i> <sup>[8]</sup> , 2005					
Pitiakoudis <i>et al</i> <sup>[9]</sup> , 2006	Echinococcus in gallbladder	12	Albendazole 800 mg/d, 4 mo	No	2 yr
Safioleas <i>et al</i> <sup>[10]</sup> , 2004	Echinococcus in gallbladder			No	10 yr
Safioleas <i>et al</i> <sup>[10]</sup> , 2004	Cyst with wall of 5 mm. Daughter vesicles	7		No	6 yr
Safioleas <i>et al</i> <sup>[10]</sup> , 2004	Calcified cyst with daughter vesicles	10	Albendazole 2 mo	Yes: Fever, atelectasis and pleural effusion	4 yr
Kumar <i>et al</i> <sup>[11]</sup> , 2004			Albendazole	No	1 yr
Raza <i>et al</i> <sup>[12]</sup> , 2003			Albendazole 10 mg/kg per day	No	1 mo
Kapoor <i>et al</i> <sup>[13]</sup> , 2000	Postmortem: Cholangitis, chronic liver obstruction			Yes: Sepsis, Multiorgan failure. Death	
Cangiotti <i>et al</i> <sup>[14]</sup> , 1994					
Rigas <i>et al</i> <sup>[15]</sup> , 1979	Cyst 5 cm × 4 cm with membranes. <i>Echinococcus</i> in gallbladder	9		No	
Barón <i>et al</i> <sup>[16]</sup> , 1978					

Africa, South America, Middle East, Australia and New Zealand. Hydatid disease is prevalent in pastoral areas where cattle and dogs are in close contact. Dogs are the definitive hosts; they excrete eggs in their feces, and humans become intermediate hosts through accidental fecal-oral infection<sup>[2,21]</sup>.

The reviews of Dziri *et al*<sup>[21,22]</sup> and Gomez I Gavara *et al*<sup>[1]</sup> concluded that many questions about liver hydatidosis still lack evidence-based answers. In 2016, PAIR or surgery, systematic or selective preoperative ERCP, the best surgical approach (conservative or radical), type of technique (laparoscopic or laparotomy), and the use of albendazole all remain topics for debate<sup>[1,21,22]</sup>.

GBHC is an extremely rare entity, even in places where hydatid disease is endemic. Primary involvement is even less common. It is essential to differentiate primary GBHC from secondary invasion of the gallbladder caused by daughter vesicles of primary liver hydatid disease. GBHC can be located within the vesicle or on its outer surface. GBHC pathogenesis is not very well documented; one of the most accepted hypotheses is infestation through the bile duct, although this explanation is unconvincing in cases of superficial cysts, and also often requires prior hepatic involvement. Larval spread through the lymphatic system after intestinal absorption is possible and may explain the intraluminal cysts. Other routes, such as contamination of gallbladder after surgery for hepatic hydatid cyst, should also be considered<sup>[3]</sup>.

In this evidence-based systematic review we have attempted to answer questions about the symptoms, diagnosis and treatment of GBHC. The main limitation is the lack of published series; all the reviewed papers are clinical cases, and so we are unable to reach an acceptable level of evidence. The most common symptom in GBHC is pain in the right upper quadrant<sup>[4-10,12-16]</sup>. Suspicion of GBHC is established by ultrasound and/or CT<sup>[3-13,15]</sup>. The involvement of the gallbladder is usually an incidental

finding in patients being examined for liver hydatid cysts<sup>[4-6,8,10-12,14-16]</sup>. The most common therapeutic approach is cholecystectomy by laparotomy and postoperative albendazole<sup>[4-12,14-16]</sup>. Few cases present postoperative complications, and the recurrence of hydatid disease is practically zero<sup>[3-12,15]</sup>.

In conclusion, three main conclusions can be drawn regarding the clinical diagnosis and treatment of GBHC: (1) the most common clinical finding is right upper quadrant pain with a very low level of evidence (level V, grade D recommendation); (2) the most useful diagnostic methods are diagnostic ultrasound and CT with a very low level of evidence (level V, grade D recommendation); and (3) the recommended treatment is cholecystectomy by laparotomy plus albendazole in the postoperative period. This strategy achieves good results: There is no postoperative recurrence in the subsequent months of follow-up, with a very low level of evidence (level V, grade D recommendation). To our knowledge, this is the first literature review that focuses on the clinical, diagnostic and therapeutic aspects of GBHC. The lack of published cases on the topic and the fact that all the papers included deal with clinical cases impeded us from achieving a higher level of evidence in the results. More studies are needed, especially randomized controlled trials, in order to reach meaningful conclusions.

## COMMENTS

### Background

Primary gallbladder hidatidosis is an unfrequent disease. No systematic reviews have been done before.

### Research frontiers

Obtaining best clinical evidence to treat primary gallbladder hydatidosis.

### Applications

Future cases and publications will have a systematic review to treat these

patients.

**Peer-review**

Hydatid disease of the gallbladder is very rare, from this point of view this systematic review has some interest.

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