

Changing Concepts in the Management of Liver Hydatid Disease

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Hydatid disease is a rare entity primarily affecting the population of developing countries. The parasite shuttles between the liver and lungs, but almost any organ can be invaded, forming cysts. Septation and calcification of the cysts with a high antibody titre in the patient's serum confirm the diagnosis, although more sophisticated tests have been applied recently. Surgery constitutes the primary treatment, with a variety of techniques based on the principles of eradication and elimination of recurrence by means of spillage avoidance. Minimally invasive techniques and percutaneous drainage of the cysts are now feasible because of progress in the field.

The aim of this review is to collect the experience from three different institutions and to provide practical guidelines for diagnostic and therapeutic strategies. (J GASTROINTEST SURG 2005;9:869–877)
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INTRODUCTION

Echinococcosis in humans is a parasitic tapeworm infection, caused by a larval stage (the metacestode) of *Echinococcus* species. The infection can be asymptomatic or severe, causing extensive organ damage and even death of the patient. The metacestodes of all four recognized *Echinococcus* species can infect humans. There are three known forms of echinococcosis in humans: 1) cystic echinococcosis (CE – Hydatid disease) caused by *Echinococcus granulosus*, 2) alveolar echinococcosis (AE) caused by *Echinococcus multilocularis*, and 3) polycystic echinococcosis (PE) caused by *Echinococcus vogeli* or *Echinococcus oligarthus*. The most common sites for cystic echinococcosis infection are the liver and lungs (60% and 30%, respectively), although hydatid cysts may develop, rarely, at other sites, including kidney, bones, brain, and pericardium. In theory, hydatid cysts may develop at any site within the human body. The prevalence

of echinococcosis varies considerably but is endemic in the Middle East and Africa.^{1–8}

In this review the current concepts in the management of cystic liver echinococcosis (liver hydatid disease) from the perspective of the hepatobiliary surgeon are presented.

MORPHOLOGIC CLASSIFICATION OF HYDATID LIVER CYSTS

Several ultrasound classifications of liver hydatid cysts based on the morphologic characteristics of the cyst have been proposed in the past. The ultrasound classification described by Gharbi et al. seems to be most widely accepted. The pathognomonic characteristics and signs of hydatid liver disease such as the presence of a detached laminated membrane from the pericyst, the presence of daughter cysts, and

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Table 1. Classification for hydatid cysts*

Type	Description
I	Pure (clear) fluid collection (the cyst is similar to the simple liver cysts)
II	Fluid collection with a detached membrane
III	Fluid collection with multiple septa and/or daughter cysts
IV	Hyperechoic cyst contents with high internal echoes
V	Cyst with reflecting calcified thick wall

*Adapted from el-On J, Khaleel E, Malsha Y. *Echinococcus granulosus*: A seroepidemiological survey in northern Israel using an enzyme-linked immunosorbent assay. *Trans R Soc Trop Med Hyg* 1997;91:529-536.

calcifications of the cyst wall have all been included in Gharbi's criteria (Table 1).⁹

The need to evaluate the functional state of the parasite, especially in field studies, has resulted in a new, modified ultrasound classification of liver hydatid cysts. Based on cyst characteristics described in the Gharbi classification, the World Health Organization (WHO) Informal Working Group on Echinococcosis¹⁰ proposed a new classification reflecting the functional state of the parasite that facilitates selection of treatment modalities (Table 2).

DIAGNOSIS

In the majority of cases definitive diagnosis of the disease can be established by a combination of imaging techniques (Figs. 1, 2, and 3) and either serological or immunoassay techniques. At least two tests are required to confirm the diagnosis. Immunofluorescence assay, indirect hemagglutination, immunoelectrophoresis, or coelectrocytotoxicity with antigen 5 identification confirm the diagnosis in 80% to 96% of patients with liver hydatidosis. The tests are less sensitive when the cysts are not in the liver. Special techniques such as ELISA have a high specificity and accuracy independent of disease stage and site of the cyst.^{11,12}

Table 2. WHO classification

Type of cyst	Status	Ultrasound features	Remarks
CL	Active	Signs not pathognomonic, unilocular, no cyst wall	Usually early stage, not fertile; differential diagnosis necessary
CE 1	Active	Cyst wall, hydatid sand	Usually fertile
CE 2	Active	Multivesicular, cyst wall, "rosette-like"	Usually fertile
CE 3	Transitional	Detachment of laminated membrane, "water-lily sign," less round—decreased intracystic pressure	Starting to degenerate, may produce daughter cysts
CE 4	Inactive	Heterogenous hypo- or hyper-echogenic degenerative contents; no daughter cysts	Usually no living protoscoleces; differential diagnosis necessary
CE 5	Inactive	Thick calcified wall, calcification partial to complete; not pathognomonic but highly suggestive of diagnosis	Usually no living protoscoleces

MEDICAL TREATMENT

Thirty years after the first attempts to establish effective medical treatment, surgery is still the gold standard for achieving complete cure of liver hydatid disease.

Chemotherapy with benzimidazole compounds (albendazole and mebendazole) is currently indicated for: (1) inoperable primary liver hydatidosis, (2) multiple cysts in two or more organs, (3) multiple small liver cysts, (4) cysts deep in liver parenchyma, (5) prevention and management of secondary hydatidosis, (6) management of recurrent hydatidosis, (7) unilocular cysts in unfit elderly patients, (8) use in combination with surgery and interventional procedures, (9) pulmonary echinococcosis, and (10) long-term administration for cystic echinococcosis at specific sites (bone, brain, eye, etc.).

The effectiveness of preoperative chemotherapy in preventing secondary echinococcosis and recurrence needs further investigation. Chemotherapy is routinely administered prior to interventional procedures, and in some centers it is used preoperatively. It is still unclear whether preoperative chemotherapy is beneficial and many centers do not administer it.

Chemotherapy is contraindicated in the following: (1) large cysts, (2) cysts with multiple septa divisions (honeycomb-like cysts), (3) cysts that are prone to rupture (superficial), (4) infected cysts, (5) inactive cysts, (6) calcified cysts, (7) severe chronic hepatic disease, (8) bone marrow depression, and (9) early pregnancy.^{13,14}

Mebendazole (MBZ) is a broad-spectrum antihelminthic drug with poor intestinal absorption that is active against intestinal nematodes. Albendazole (ABZ) has better intestinal absorption, better tissue distribution, and achieves considerably higher cyst fluid concentrations. It undergoes a rapid first-pass metabolism in the liver to albendazole sulfoxide, the antiscotolecoidal agent flubendazole. The MBZ fluorinated analog does not penetrate the cyst, and therefore the drug is not an alternative for treatment.¹⁵⁻¹⁷

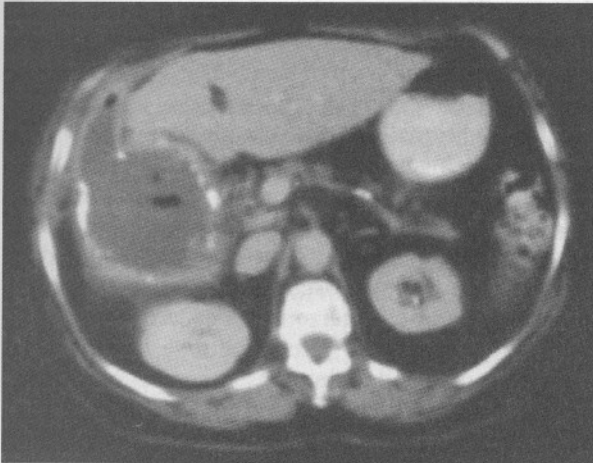


Fig. 1. CT image of hydatid cyst with air-fluid level suggesting infection with abscess formation.

The benzimidazole carbamates have a direct effect on the cumulus oophorus and on the wall of the cyst. Younger cysts and cysts with thin walls show a better response. Chemotherapy with ABZ or MBZ may lead to liver enzyme elevation (10%–20% of patients), bone marrow suppression, pancytopenia, agranulocytosis, and alopecia. These adverse effects are reversible once the treatment is stopped.^{18–20}

The indicated dosage of ABZ is 10 to 15 mg/kg/day postprandially in two divided doses. The manufacturer suggests a therapeutic cycle of 4 weeks of treatment followed by a 2-week pause. The usual dosage scheme is 3 to 6 or more cycles for liver hydatid disease. For cystic echinococcosis of other

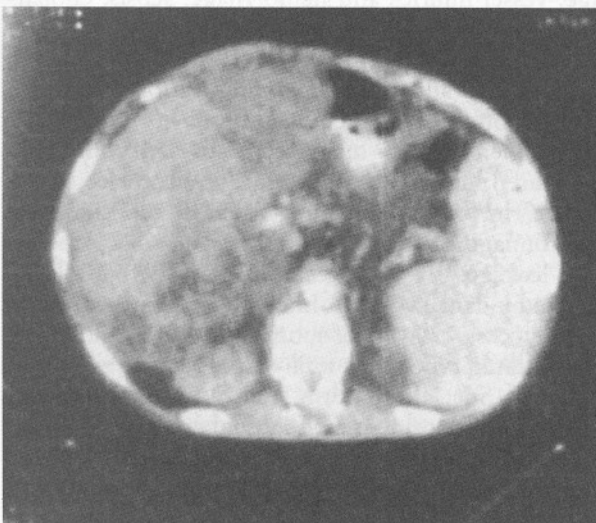


Fig. 2. Multiple daughter cysts invading both right and left liver lobes.



Fig. 3. Multiple daughter cysts in the right liver lobe with extension to the abdominal wall.

organs, duration of therapy is much longer. Recent data have shown equal or improved efficacy of continuous treatment for 3 to 6 months or longer without an increase in adverse effects.²¹ Cyclic ABZ treatment seems to be no longer advisable. The equivalent dosage for MBZ chemotherapy is 40 to 50 mg/kg/day in 3 divided doses, for 3 to 6 months. Serum drug levels may vary widely in individual patients, and therefore correlation with oral doses and drug efficacy is inconsistent.

ABZ, the most efficient agent used so far, may induce apparent cure, as indicated by cyst shrinkage or disappearance in 20% to 30% of patients.²² Some authors have reported degeneration of cysts in up to 50.6% of patients treated with MBZ and 80% of patients treated with ABZ. The interpretation of these studies is difficult because of lack of standardization and interference with the natural history of the disease.²³

A prospective, controlled, randomized trial has demonstrated the efficiency of preoperative ABZ administration. Following 1 and 3 months preoperative administration, 72% and 92% of cysts were found at surgery to be nonviable, versus 50% of cysts in the control group, which were treated by surgery alone.²⁴

According to the WHO guidelines, preoperative administration should begin between 1 month and 4 days before surgery for ABZ and 3 months before surgery for MBZ.²⁵

The expected results of adequate chemotherapy are: (1) 10% to 30% cyst disappearance (cure), (2) 50% to 70% degeneration or significant size decrease, and (3) 20% to 30% with no morphologic changes (treatment failure). The rate of relapse after chemotherapy is high (3%–30%), but fortunately relapses are sensitive to retreatment in up to 90% of patients.²⁶

Praziquantel, a synthetic isoquinoline-pyrazine derivative, has been used in combination with ABZ. Combined chemotherapy seems to be more effective than ABZ alone.²⁷⁻²⁹

Coordinated, prospective trials are necessary to establish the value of chemotherapy in hydatid disease. All the available data suggest that conservative management of hydatid disease yields poor results, and in the majority of patients the therapy fails or the disease recurs.³⁰

SURGICAL TREATMENT

There are many surgical procedures for the management of liver hydatid cysts. Much controversy exists regarding the most appropriate surgical technique, which should effectively eliminate the parasite as well have a low morbidity and mortality rate and a negligible recurrence rate.

Indications for surgery in patients with liver hydatidosis are: (1) large cysts with multiple daughter cysts, (2) single liver cysts situated superficially that may rupture, (3) infected cysts, (4) cysts communicating with the biliary tree, (5) cysts exerting pressure on adjacent vital organs, and (6) cysts in the lung, brain, bones, kidneys, and other organs.

In addition to overall high-risk factors for surgery such as extreme age, pregnancy, and concomitant severe disease, specific contraindications for surgery in liver hydatidosis are: (1) multiple cysts, (2) cysts difficult to access, (3) dead cysts, (4) cysts partially or totally calcified, and (5) very small cysts.

Surgical procedures can be divided into three groups: classic open surgical procedures, laparoscopic procedures, and interventional (minimally invasive) procedures.³¹

Open Surgical Procedures

The classic open surgical procedures can be subdivided into two groups: (1) conservative, tissue-sparing techniques, limited to removing the parasite, with part or most of the pericyst left in situ, and (2) radical procedures that remove the entire pericyst, with or without entering the cyst itself. The choice of surgical technique depends on the size, site, and type of the cyst(s), the existence of complications, and the surgeon's expertise.³²

The most common conservative, tissue-sparing, techniques are: simple drainage, marsupialization (external drainage—an historical procedure), partial cystopericystectomy (partial resection of the pericyst), and near-total pericystectomy. All of these procedures have some common goals: (1) safe and complete exposure of the cyst, (2) safe decompression of

the cyst, (3) safe evacuation of the cyst contents, (4) sterilization of the cyst, (5) management of cyst-bile duct communications, if present, and (6) management of the remaining cyst cavity.³³

The traditional surgical simple drainage of the cysts is still in use by many surgeons. In this procedure, the abdomen is carefully packed with pads around the cysts to reduce the risk of peritoneal soilage and contamination, the cysts are aspirated by a closed system, and antisclecolidal agents (e.g. alcohol, chlorhexidine, hypertonic saline, etc.) are infused in the emptied cavity. After repetitive infusions the cyst is unroofed and drained. The recurrence rate following this procedure ranges from 10% to 30%.^{34,35} Evaluation of the cyst contents is important. Bile staining implies a communication with the biliary tree and should warn against the injection of antisclecolidal agents because of the definite risk of sclerosing cholangitis.

Marsupialization was commonly used several decades ago, especially for infected cysts, and it is practically not used anymore due to the high complication rate. In this procedure, following evacuation and sterilization of the cyst, the cavity is drained externally by suturing the opening on the pericyst to the abdominal wall.³⁶ The management of such patients is prolonged, with suppuration and frequent bleeding from the cyst. The procedure is ideal for infected cysts but convalescence is slow and drainage may persist for months.

Although these techniques are simple, easy, and quick, they are operator dependent and are often accompanied by a high rate of postoperative complications, such as persistence of residual cavity, disease soilage in biliary tract or intraperitoneal, bile leakage, vessel injuries and hemorrhage, sepsis, cholangitis and anaphylactic shock. For that reason several technical improvements have been proposed, such as interrupting all external communications from the cyst and obliterating the remaining cavity with omentum (omentoplasty) or muscle flaps. The omentum is sutured into place and a drain is also placed fixed to the rim of the opening. Other surgeons suggest capitonnage of the remaining cyst's wall to reduce bile leakage.^{37,38} This technique involves infolding the redundant cyst wall into the depths of the cyst with successive layers of sutures. Capitonnage is contraindicated when the wall of the cyst is rigid and calcified. Special attention is also required to avoid deep suture placement with subsequent bleeding from hepatic vein injury.³³

In partial cystopericystectomy, the parasitic foci is eliminated and the surrounding pericyst is removed. Dr. Milicevic, the corresponding author of this study, suggests entailed excision of the exuberant

part of the cyst that protrudes from the liver, especially in small and young hydatid cysts with elastic and thin pericysts.³⁹

Subtotal pericystectomy (*fere totalis*) is an alternative to partial cystopericystectomy. In partial cystopericystectomy, small pericystic areas close to vascular and biliary vessels are not resected because of a high risk of severe complications.⁴⁰ The modification proposed by Burgeon et al. includes inner membrane excision with preservation of the outer layer to protect liver parenchyma, biliary ducts, and blood vessels, minimizing postoperative complications such as biliary leaking and hemorrhage.⁴¹

In radical operations the parasitic content and the entire pericystic membrane is removed. In this subcategory, the main procedures are total pericystectomy and liver resection.

Total pericystectomy, first described in the 1930s, can be performed either with the "open" or the "closed-cyst" method. In the open technique, the cyst is opened, the contained material is removed, antiscolicoidal substances are infused, and then the pericyst is removed. In the closed-cyst method, en block pericystectomy is performed with no other manipulations. During the pericyst's removal, afferent blood and biliary vessels are ligated in order to prevent hemorrhage or postoperative bile leakage. This procedure, although technically more demanding, causes cavity disappearance and prevents relapse of the disease and secondary inflammatory complications.^{42,43} There is no doubt that a radical operation in the hands of experts in dedicated centers gives superior results. The operation has the advantage of identifying exogenous daughter cysts adjacent to the main cyst but is to be avoided for cysts impinging on the major hepatic veins, the inferior vena cava, and close to the liver hilum. Closed cystopericystectomy creates no residual adventitia, eliminates the need for antiscolicoidal agents, and avoids biliary fistula, but bleeding can be profuse due to the adjacent vessels in the liver parenchyma.^{33,38} Open cystopericystectomy is preferred when the cyst wall is thin and impending rupture is expected and when major vascular structures have been encountered during the closed procedure.⁴⁴

Many authors suggest liver resection for echinococcosis. Although this method seems to be the most complete treatment for hydatid disease, the high postoperative morbidity and mortality rate, and the unknown ability of the remaining liver to regenerate suggest a more skeptical use of this technique. For that reason, liver resection is indicated when other more conservative surgical therapies have failed to eliminate the disease, cysts have destroyed an entire

lobe or segment, thus compressing the healthy parenchyma interrupting the bile ducts, or when external cyst-biliary fistula draining zones need to be formatted. In such cases typical left or right hepatectomy or segmentectomy can be performed.^{45,46}

In the modern era of radiofrequency (RF) thermal ablation, Brunetti et al. suggest a novel technique for liver hydatid cyst treatment. The RF electrodes were inserted through liver parenchyma into the echinococcal cysts. The cysts were destroyed with a pattern similar to those of hepatic metastases. Histologic examination in the material that was removed with suction showed no live parasites or eggs, and in their small series no recurrence was observed, while no complications have been reported perioperatively. This modification may present a new alternative in liver hydatid cyst treatment, especially in deep cysts, in multiple cysts, or in complicated cases that require severe and multiple operations.⁴⁷ RF total cystopericystectomy and RF liver resection are the most recently applied modification. Tissue-desiccating necrosis is limited only to the narrow resection surface layer of the liver parenchyma, providing excellent hemo-, bile and lymphostasis as well as a safe margin, considering exogenous vesiculation as a potential cause of local recidivism.

Management of Bile Duct Communication

Preoperative detection and assessment of cyst-bile duct communication is essential. Large cysts occupying several liver segments and episodes of cholangitis are highly suggestive of cyst-bile duct communications, and a search for the fistula should be meticulous. The direction of the bile duct can be determined by gentle exploration with a thin curved probe. Terminal biliary branches can be sutured with or without T-tube drainage. In some patients with bile-stained hydatid debris, no communication is detected and no additional procedure is done. Bile duct exploration, choledochoscopy, and T-tube drainage is usually done in order to secure and decompress a tenuous closure of a large bile duct in a rigid pericyst. A Roux-en-Y intracystic hepaticojejunostomy may be necessary for large cysts in which major ducts are disrupted, the jejunum being sutured to the duct within the cyst cavity. Choledochoduodenostomy or Roux-en-Y hepaticojejunostomy are performed for massive penetration of hydatid debris and daughter cysts into the common bile duct.⁴⁸ Indications for sphincteroplasty are very infrequent and include obstruction of the papilla by calcified hydatid debris or sclerosis.⁴⁹

Laparoscopic Treatment

Laparoscopic treatment of liver echinococcosis has been increasingly popular during the last few decades because of the significant progress in laparoscopic surgery, although no randomized clinical trials comparing laparoscopic with conventional open surgical treatment of hydatid disease have been reported. Laparoscopic treatment includes partial or total pericystectomy and cyst drainage with omentoplasty. A major disadvantage of laparoscopy is the lack of precautionary measures to prevent spillage under the high intraabdominal pressures caused by pneumoperitoneum. Some authors suggest that pneumoperitoneum is beneficial in preventing spillage,⁵⁰ while others suggest a decrease in intraabdominal pressure.⁵¹ The most difficult part of the laparoscopic procedure is the initial cyst puncture and aspiration of the cyst fluid.⁵² Pre- and intraoperative use of antisclecolidal factors seems to be of great importance because it ensures the inactivation and clearance of the parasites, while some authors avoid them because of the potential risk of sclerosing cholangitis.^{53,54} Seven et al. suggest that intraoperative spillage can be avoided by fixing the cyst in the abdominal wall with a special umbrella trocar and suction with a specific suction device.⁵⁵ Bickel et al. suggest a combination of filling the right subdiaphragmatic suprahepatic space with antisclecolidal fluid (cetrimide) and Trendelenburg position for decreasing the risk of spillage, although this approach cannot prevent a sudden jet of fluids escaping the cyst.⁵⁰ In their study, they propose a new technique with a transparent cannula and vacuum for complete fluid evacuation. The tip of the device is adhered firmly to the cyst wall to prevent spillage in the peritoneal cavity.

The indications for laparoscopic excision of liver echinococcosis has changed through the years. In the past, patients with cysts with a diameter greater than 15 cm and those with recurrent disease were excluded from laparoscopic treatment. Nowadays, the only excluding criteria for laparoscopic intervention are deep intraparenchymal cysts or posterior cysts situated close to the vena cava, more than 3 cysts, and cysts with thick and calcified walls.^{56,57}

Conversion to open laparotomy may occur because of unsafe exposure, unsatisfactory access, intraoperative bleeding, or intrabiliary rupture of the cyst. Cholecystectomy, irrigation, and T-tube drainage is indicated in these patients, although open laparotomy prolongs significantly hospitalization. A more conservative approach is laparoscopic removal of the cysts and endoscopic sphincterotomy for intrabiliary rupture or external biliary fistulas.^{58,59}

Postoperative morbidity in laparoscopic studies ranges from 8% to 25%,^{50,60} while in open series varies from 12% to 63%.^{43,46} The treatment-related death after laparoscopy is almost zero, while in open series it ranges from 0% to 3%.^{39,43,46} Major complications (in the form of allergic reactions) seem to be more common in laparoscopic interventions due to peritoneal spillage during debridement and removal of cysts content.⁵⁰ The rate of short-term recurrence varies from 0% to 9% after laparoscopy,^{50,55} while in open series it is even higher (0% to 30%).^{39,43,46} These favorable results of laparoscopic treatment of liver hydatid disease may be related to not only the advantages of minimally invasive surgery but also the selection criteria for the patients.^{61,62}

The well-known advantages and the superiority of laparoscopy are strengthened in the light of the need for a much larger upper abdominal incision for open hydatid surgery and the prolonged hospitalization. Mean hospitalization time ranges between laparoscopic (3–12 days) and open series (9–20 days), and a significant statistical difference seems to exist.^{50,56,62}

Criticisms that may be made of the existing studies are that the patients were not randomized into laparoscopic and open intervention, the total number of patients is relatively small, and patients with contraindications for laparoscopic treatment were handled with open surgery.

Percutaneous Drainage

Until recently percutaneous treatment of hydatid liver cyst was contraindicated because of the fear of dissemination, peritoneal spillage, and anaphylactic shock. Since 1989, only a few sporadic, mainly unintentional, percutaneous aspirations followed by drainage of hydatid cysts have been reported.⁶³

Nowadays both of these complications are extremely rare and should not be considered as absolute contraindications.⁶⁴ The development of fine needles and catheters, the advances in imaging techniques, and the introduction of the intercostal intrahepatic approach minimizes the risk of anaphylactic shock or spillage.⁶⁵

Percutaneous aspiration can be performed either by ultrasound- or CT-guided control. The initial puncture can be established either by a freehand technique with ultrasound guidance or by a needle-guiding device mounted on a probe. After insertion the cyst's content is aspirated, a sample is derived, contrast is injected in order to opacify the cyst, and an antisclecolidal drug is infused followed by a Betadine infusion. The catheter remains clamped for 30 minutes, and after a second Betadine infusion the

catheter remains for drainage. In addition to Betadine, other antiscolicidal agents have been used successfully.^{66,67}

Percutaneous treatment is indicated for type I and II cysts, some groups of type III that do not involve nondrainable solid material, subtypes of type IV, suspected fluid collections, and infected hydatid cysts. In addition, percutaneous treatment should be considered in patients at high surgical risk, pregnant patients, and patients with multiple or disseminated cysts.

Percutaneous procedures are contraindicated in some subgroups of type III and IV (hydatid cysts with heterogeneous echo pattern) and in liver cysts that have ruptured into the biliary system or peritoneum.²⁵ It is generally accepted that hydatid cysts of type V do not need any intervention but can be managed with regular follow-up instead.⁶⁸

Treatment failure is defined as recurrence in the same location or complications related with the intervention. For uncomplicated hydatid cysts of type I and II, percutaneous treatment seems to be the optimal treatment. Recurrence ranges between 0% and 4% among several series with a low morbidity rate.^{69,70} The overall complication rates in percutaneous drainage varies from 15% to 40%. Major complications such as anaphylactic shock range from 0.1% to 0.2%, and minor complications (urticaria, itching, hypotension, fever, infection, fistula, rupture in biliary system) varied from 10% to 30%.⁷¹

The overall mortality is 0.9% to 2.5% among several studies and associated with perioperative complications, patient's age, and infection of the remaining cyst cavity.⁷²

Percutaneous drainage is gaining wide acceptance because of its low morbidity and easy applicability, but selection of the patients is of paramount importance.⁷³

A meta-analysis of percutaneous drainage of liver hydatid cyst showed no significant complications and immediate relief of the symptoms, and no recurrence was observed during 33 months of follow-up.⁷⁴

We suggest that percutaneous treatment has an important role in the treatment of hydatid liver cysts with results proved by several series with long-term follow-up. Therefore, we believe that in indicated cases percutaneous drainage is a very effective and reliable interventional minimally invasive procedure associated with low mortality and morbidity.⁷⁵ Surgeons should play a key role in the management of patients with hydatid disease and cooperate with the radiologists using these novel techniques.

CONCLUSION

What are the perspectives in the beginning of the third millennium? The answer can be obtained with

the determination of the disease-associated problems. Although several therapeutic procedures have been proposed, no randomized clinical trials for their comparison have been organized. Randomized clinical trials may define the therapeutic strategy to combine both low morbidity and radical elimination of recurrences. Encouraging results have been achieved recently by minimally invasive approaches. Current data suggests that laparoscopic and percutaneous drainage are feasible and in certain cases render open techniques unnecessary or obsolete. More sensitive diagnostic methods should be developed. The radical elimination of the disease can be achieved with improvements in agriculture, educational, social, and economic factors of the endemic regions and vaccine development.

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