

Treatment of liver hydatidosis: How to treat an asymptomatic carrier?

Bernardo Frider, Edmundo Larrieu

Bernardo Frider, Department of Medicine-Hepatology, Arg-erich Hospital, University of Buenos Aires, Maimonides Uni-versity, Salguero 2601, 1425 Buenos Aires, Argentina

Edmundo Larrieu, Department of Zoonosis, Ministry of Health of Rio Negro Province, Laprida 240, 8500 Viedma, Argentina; University of La Pampa, Calle 5 y 116, 6360 General Pico, Argentina

Author contributions: Both authors contributed to the writing and correction of the manuscript.

Correspondence to: Bernardo Frider, MD, Professor, De-partment of Medicine-Hepatology, Argerich Hospital, Univer-sity of Buenos Aires, Maimonides University, Salguero 2601, 1425 Buenos Aires, Argentina. bernardo@frider.com.ar

Telephone: +54-11-48010502 Fax: +54-11-48010502

Received: April 19, 2010 Revised: May 23, 2010

Accepted: May 30, 2010

Published online: September 7, 2010

Abstract

Liver hydatidosis is the most common clinical presenta-tion of cystic echinococcosis (CE). Ultrasonographic mass surveys have demonstrated the true prevalence, includ-ing the asymptomatic characteristic of the majority of cases, providing new insight into the natural history of the disease. This raises the question of whether to treat or not to treat these patients, due to the high and un-suspected prevalence of CE. The high rate of liver/lung frequencies of cyst localization, the autopsy findings, and the involution of cysts demonstrated in long time follow-up of asymptomatic carriers contribute to this dis-cussion. The decision to treat an asymptomatic patient by surgery, albendazole, or puncture aspiration injection and reaspiration or to wait and watch, is based on con-flicting reports in the literature, the lack of complications in untreated patients over time, and the spontaneous disappearance and involution of cysts. All these points contribute to difficulties of individual clinical decisions. The patients should be informed of the reasons and the risks of watchful/waiting without treatment, the possibil-ity of complications, and the risks of the other options.

As more information on the natural history of liver hy-datidosis is acquired, selection of the best treatment will be come easier. Without this knowledge it would be very difficult to establish definitive rules of treatment. At pres-ent, it is possible to manage these patients over time and to wait for the best moment for treatment. Follow-up studies must be conducted to achieve this objective.

© 2010 Baishideng. All rights reserved.

Key words: Hydatid cyst; Liver; Hepatic cystic echino-coccosis; Albendazole; Liver ultrasonography; Puncture aspiration injection and reaspiration; Ultrasonography screening; Asymptomatic liver hydatidosis

Peer reviewers: Taku Aoki, MD, Division of Hepato-Biliary-Pancreatic and Transplantation Surgery, Department of Surgery, Graduate School of Medicine, University of Tokyo, 7-3-1 Hon-go, Bunkyo-ku, Tokyo, 113-8655, Japan; Giovanni Tarantino, MD, Professor, Department of Clinical and Experimental Medi-cine, Federico II University Medical School, VIA S. PANSINI, 5, Naples 80131, Italy

Frider B, Larrieu E. Treatment of liver hydatidosis: How to treat an asymptomatic carrier? *World J Gastroenterol* 2010; 16(33): 4123-4129 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v16/i33/4123.htm> DOI: <http://dx.doi.org/10.3748/wjg.v16.i33.4123>

INTRODUCTION

The liver is the most frequently affected organ by hydatid cysts, and asymptomatic liver hydatidosis is the most com-mon clinical presentation of cystic echinococcosis (CE). To date, its treatment is subject of controversy. Echino-coccus granulosus is the agent of hydatid disease, affect-ing humans, as well as domestic and wild animals. CE has spread to all continents becoming a major health prob-lem, particularly amongst populations that practice sheep husbandry. Humans become infected by the ingestion of

eggs contaminated with the feces of dogs. Most transmission occurs in rural areas, but numerous dogs live in urban areas and often have access to viscera disposed off carelessly from slaughterhouses or from animals slaughtered in private homes^[1,2].

NATURAL HISTORY OF CE

Background

New imaging techniques such as ultrasonography (US), computed tomography scan (CT), magnetic resonance (MR), and advances in immunology and molecular biology have had a major impact on the epidemiology, diagnosis, prognosis, management, and understanding of the natural history of diseases. The “imaging finding” in asymptomatic cases is a new clinical feature that appeared as a consequence of applying these technologies in asymptomatic or symptomatic individuals^[3]. Some examples of this “new asymptomatic pathology” are gallbladder stones, cysts and other benign liver tumors, and other asymptomatic or pre-symptomatic pathologies^[4,5]. These “imaging findings” replaced the “autopsy finding” and give a more accurate picture of the prevalence of asymptomatic diseases; they also avoid the known bias of necropsy. The application of US in CE allowed the detection of hydatid cysts in the liver in early asymptomatic stages and gives a better understanding of the natural history^[6-9].

Asymptomatic liver hydatidosis is defined as the presence of CE detected incidentally in patients who do not have symptoms or have symptoms that are not thought to be due to CE. The diagnosis is made during routine US or imaging techniques, such as CT or MR, for other abdominal conditions, or in specific situations for detecting CE, for example, examination of cohabitants of CE patients or mass screening in endemic areas.

Ultrasonographic mass screening

In the early 1970s, it was thought that “with the use of new diagnostic techniques, it is likely that the prevalence rates in humans in endemic areas will increase because of the low sensitivity of serology in detecting CE in lungs”. “An example of this, being the tripling of the prevalence rate in Rio Negro, Argentina, when mass miniature radiography [miniature chest X-ray (MXR)] was used as a screening method”^[10]. This was also observed when “Control Programs” in Argentina introduced such detection with dd5 (double diffusion of arc five)^[11]. The use of US in mass screening of the abdomen demonstrated a similar phenomena as the use of MXR and dd5, increasing the prevalence rates in the liver by detecting 2-3 times more hydatid cysts than serology^[5,6,8]. Surveys developed in the early 1980s using portable US devices showed an unsuspected prevalence of hydatid cysts in asymptomatic populations^[1,6,8,11,12]. Thereafter, several surveys confirmed those findings and demonstrated the high sensitivity and specificity (near 100%) of US in the detection of CE. US is much more precise in detecting abdominal cysts than immunodiagnostic tests, as the latter exhibit relatively high rates of false-negative and false-positive results^[2,6,8,13-19].

Mass surveys using portable US scanners have been carried out in rural areas of Argentina^[6,8,20], Tunisia^[21,22], Libya^[23,24], Uruguay^[25,26], China^[27,28], Perú^[17,29,30], Turkey^[31], and Morocco^[32] amongst others and demonstrated asymptomatic characteristic in the majority of these cases^[6-9,16,33]. The unsuspected high prevalence of the disease in asymptomatic patients has a major influence on the decision to treat or not to treat such patients.

Liver/lung frequencies of cysts localization and autopsy findings

Frequencies of localization in liver and in lungs differ whether based on hospital communications, surgery, autopsies, or screening in asymptomatic cases with simultaneous examination of abdomen by US and lungs by chest X-ray^[6,7,9,12,33]. Cases of CE who underwent surgery represent only a small proportion of infected persons in any area. The Argentine National Register of Hydatidosis reported a liver/lung ratio of localization of 1.8/1 in 11 589 cases (1935 to 1963), based on hospital notifications (symptomatic cases)^[34]. In a Chilean investigation, of 63 436 hydatid cases from hospital registries, the ratio was 1.73/1. In 732 CE autopsies, the ratio was 4.27/1. In a review of 21 573 autopsies from the University of Buenos Aires Hospital, (Argentina, 1879-1985) the prevalence of CE was 1.6% (349 cases), 80% in the liver and 20% in lung with a 4/1 liver-to-lung ratio. The ratio in this study was 2.6/1 in complicated cases. The ratio in uncomplicated cases was 7/1^[35]. These results were similar to those found in a US and chest X-ray simultaneous screening performed in 1126 asymptomatic individuals: 71 (90.1%) in liver and seven (9.9%) in lung (ratio 9/1)^[34]. This has allowed the determination of the true frequency of liver/lung cyst localization in asymptomatic carriers (prevalence), based till then mostly on data from hospital notifications of surgical cases^[6,9,34,35]. Some reports showed predominantly pulmonary localization, with slower growth and less frequent complications with the G8 strain of CE compared to other genotypes^[36]; however, in Argentina, the G8 strain was not detected^[37]. The liver/lung ratio determination revealed the true prevalence of CE infestation and raised questions about its natural history, mainly in the liver. The growth of cysts depends on the evolutionary potential of the hexacanth embryo, the host tissue in which it is harbored, and its resistance. The lung, due to the elasticity of its tissue, offers limited resistance, resulting in fast cyst growth with early appearance of clinical symptoms. In the liver, the resistance of the surrounding tissue is strong and in many cases the growth of the cyst is slow or even null for several years, producing a high percentage of asymptomatic carriers^[32,35]. The great tolerance of the liver to CE is another point to consider when therapeutic modalities are proposed.

Long-term follow-up of asymptomatic cases

Follow-up of asymptomatic liver cyst carriers represents a useful contribution to the better understanding of the disease^[33]. The demonstration by US of the evolution of cysts over time, their spontaneous disappearance, and the

absence or slow growth of liver cysts through long-term longitudinal studies changed some concepts of the natural history of CE infection. Long-term follow-up showed that most asymptomatic liver hydatid patients remain symptom-free for years, regardless of the cyst size or type, with a low risk of developing complications; thus it is difficult to establish specific rules for their therapy, if any^[33]. A retrospective study was done in 42 asymptomatic liver CE cases that emigrated to Buenos Aires City (non endemic) from endemic provinces between 25 to 45 years ago, derived as “liver imaging findings”, at our Hepatology Unit (tertiary university hospital). In this population, cysts detected according to World Health Organization (WHO) classification were: type CE 4, 45.2% (19/42), CE 5 21.4% (9/42) CE 2 or CE 3, 33.3% (14/42) (unpublished data: Frider *et al.*). The fact that these asymptomatic carriers lived years outside endemic areas, the unsuspected high prevalence of CE detected by mass US and the rate of cyst localization in liver /lung poses questions about the natural history. These results also raised doubts about what treatment, if any, should be administered to those asymptomatic patients. Waiting and watching (wait & watch) is an option in the management of some types of cysts and could be the rule in the majority of them^[6,8,33]. There are few studies based on follow-up of asymptomatic individuals; thus, the decision to treat is difficult and is based on some cyst features that are an indirect method of evaluating the viability of cysts^[38,39].

Classifications based on different stages of the natural evolution of hydatid cysts exist. Gharbi's and the WHO classification are the most commonly used^[40,41]. A longitudinal study in asymptomatic CE children without treatment showed that 11.4% (8 /70) of cysts disappear over a 44 mo of follow up and 25% (4/16) at 10 years^[42-44]. Hyaline cysts, CE1, are common in children and young men, and CE4 or CE5 are common in older people; nevertheless, different types of cysts could be observed in the same liver. A long-term follow-up of CE liver carriers showed that all CE1 cysts disappeared at 12 years and most cysts had evolutionary changes; however, the remarkable phenomenon was that three quarters of them persisted asymptotically^[33]. The evolution of cysts is a slow spontaneous involution that can be accelerated by local or systemic treatment^[33,38,39,43]. Calcification of the cyst wall or in the membranes, is better detected by CT than by US^[45]. Pancreatic calcifications in chronic pancreatitis are better demonstrated by CT than by US^[46]. This is a physical phenomenon of X-rays and the diagnosis of calcification of the cyst wall or its membranes is not an exception to this rule. A significant amount of calcium is needed to see calcifications with US, whereas small amounts of calcium can be detected in a high proportion by CT, not just in the inactive WHO types CE4 and CE5, but also in CE1, CE2, and CE3 cysts. The role of calcification for staging CE is controversial. Some authors affirm that cyst content solidification over time and the disappearing of inner cysts or septa predicts cyst inactivity more reliably than calcification^[33]. Although US is of an enormous benefit in CE, it is still a crude method for observing parasite tissues, and minimal alterations of hydatid membranes are

not seen by this method or by other imaging techniques. Degeneration of the germinal layer has been detected by electron microscopy, but is not picked up by US^[38]. CT or MR has the same difficulty, perhaps Positron Emission Tomography could detect more early lesions, but this methodology is costly for the majority of the endemic areas. Despite minimal alterations of the hydatid membrane not being detected by imaging methods, calcifications are an indirect sign that reflect disturbance of membranes or of the cyst wall^[38]. Some classifications like Gharbi's were done with older (1981) US devices, with which calcifications were more difficult to detect. There are two well-known pathological types of calcification, dystrophic and metastatic. Dystrophic calcification occurs in degenerated or necrotic tissue as a reaction to tissue damage. The different types of calcifications seen in CE, from sprinkled, eggshell-like to circular content^[45] are also signs of involution and aging of cysts. Nevertheless calcifications, except for totally calcified cysts (“rocky cysts”), do not always guarantee the absence of complications. Abscesses can develop in calcified type IV as in other cysts with partial calcifications. This emphasizes the need for follow-up of all types of cysts, calcifies or not. In spite of the caution needed in the definition of cyst viability by imaging alone (immunology and possibly molecular biology could aid in the diagnosis of CE), US invaluable in terms of diagnosis, prognosis and spontaneous or induced changes of CE in the liver^[16,33,39,42,43]. More studies with more cases and more years of follow-up are needed to gain a better understanding of the natural history CE in the liver.

TREATMENT OF CE

The widespread use of US and the detection of unsuspected cysts have given rise to a great deal of controversy regarding the optimal management of asymptomatic liver CE. The incomplete knowledge of the natural history also contributes to this controversy and to the choice of a definitive therapeutic strategy. The scarcity of trials with long-term follow-up of treated or untreated asymptomatic carriers has contributed to the absence of evidence-based clinical guidelines^[33,47]. Reviews and meta-analysis have tried to form conclusions as a palliative to this situation^[48-52]. The most significant challenge in the evaluation of patients with upper digestive symptoms who are found to have hydatid cysts, is whether the cyst is the cause of the symptoms or is an incidental finding. This difference is important, because upper digestive symptoms are common in the general population, and the presence of CE is not always related to these symptoms. This is a crucial issue in the definition of symptomatic or asymptomatic CE and in the subsequently choices for the management of the disease. For many years, surgery was the only treatment option. The possibility of detecting CE in the early stages before complications appear, and the use of precocious surgery led to mass screening with immunological tests and US in endemic areas^[8,12,24,53-56].

Apart from surgery, the current treatment options for CE include chemotherapy with benzimidazole

(BMZ) compounds, albendazole (ALZ) and Mebendazole (MBL)^[57-59], PAIR with injection of scolicides (alcohol, hypertonic sodium solution, *etc.*)^[59,60-62] laparoscopy, radiofrequency ablation (still very restricted), and also the watch/wait modality (no treatment at all, only observation)^[8,33,43,49]. Each of these therapeutic tools has limitations depending on the individual case. The evidence supporting any of these modalities from carefully designed clinical studies is insufficient and the choice of treatment options remains controversial^[33,49-52]. Surgery is still the mainstay of radical treatment in symptomatic or complicated cases, but chemotherapy and the PAIR method with concomitant chemotherapy offer new options. According to the WHO recommendations, surgery is indicated for large hepatic cysts with multiple daughter cysts, for single hepatic cysts situated superficially (risk of spontaneous or trauma rupture), for infected cysts, and for cysts communicating with the biliary tree and/or exerting pressure on adjacent vital organs. Curative surgery is not always possible, the risk of relapse and morbidity is considerable, particularly when the surgery is repeated. Surgery has progressed, with shorter treatment duration, decreased post-operative complication rates, and increased curative rates^[57,58]. Overall recurrence is seen in about 6% of cases and mortality in about 0.5% and 4%, depending on the type of surgery and medical facilities^[52,63-65]. PAIR or a laparoscopic surgical approach^[61,63] are emerging, but despite being minimally invasive techniques, morbidity, recurrence, and low mortality rates are reported. Surgery is contraindicated in patients in whom general contraindications for surgery apply, for example, pregnant women, inactive asymptomatic cysts, very small cysts, multiple cysts or cyst that are difficult to access^[52]. Cyst rupture can occur spontaneously, while surgical damage with spillage and widespread dissemination in the peritoneal cavity is possible^[62]. In addition to contraindications for surgery, in some highly endemic regions, long hospital waiting lists and a lack of adequate medical facilities and/or experienced staff exist^[48].

Over the past 30 years, ALZ and MBL have increasingly been used to treat CE^[52,66]. Chemotherapy is important because completely curative surgery is not always possible, and PAIR also involves a 2% to 15% risk of relapse. The outcome of benzimidazole (BZM) therapy is related to the size and age of the parasite, calcification and fibrosis. "Recent" cysts and/or those with thin walls are more accessible to drugs than "old" cysts with thick or calcified walls^[48]. ALZ can be used on patients of any age, and is less limited by the patient's status than surgery or PAIR. ALZ showed better absorption and tissue distribution than MBZ^[58,59]. Close surveillance of signs of hepatotoxicity is mandatory in all patients receiving ALZ, and it is contraindicated in advanced chronic liver diseases. Chemotherapy cure can be expected in about 30% of patients and improvement in 30%-50%, after 12 mo of follow-up^[52,67]. Chemotherapy is indicated in inoperable liver or lung cysts, or cysts in more than two organs, in peritoneal localizations, in multiple small cysts deeply localized in the liver parenchyma, in patients with incomplete surgery or relapse, and to prevent spillage associated to surgery or

PAIR. Chemotherapy is contraindicated in large cysts that have a risk of rupture, especially in superficial or infected cysts, because of the possibility of hydatid abscess (two unpublished own cases) and in early pregnancy^[66,67]. Studies have shown the cysts' response to chemotherapy can be clearly demonstrated by US^[16,43,52,57,58,68]. Decreasing size, margins of the cyst wall, detachment of the inner membrane, the appearance of echogenic material (matrix) in the cyst cavity or the disappearing of cysts are sensitive and specific signs of a good response^[39,50]. In some series, a certain degree of response was observed in more than 75% of patients^[58,69]. Evaluations at up to 12 mo, showed about 30% cyst disappearance, 30%-50% cyst degeneration and/or a significant size reduction, but 20%-40% exhibited no changes. There is only one prospective, controlled, randomized, open study of ALZ in patients with liver CE in which parasite viability after treatment was assessed in all patients^[69]. In 65 asymptomatic children there were no statistical differences between ALZ-treated with and untreated at 29 mo of follow-up. However, four years after treatment, the differences were significant, 76% (treated) *vs* 38.5% (untreated)^[43]. Interestingly, in the same population, the non treated group (watch/wait) comprised 14 (87.6%) who were CE 1 or CE2 and two (12.6%) who were CE4 and CE5, but at 10 years follow-up three (18.8%) were CE1 or CE2 and eight (50.1%) were CE4 or CE 5, reflecting a degree of involution. In the treated ALZ group, two (8%) were CE1 or CE2 and 17 (68%) were CE4 or CE5, with no significant differences between the two groups^[44].

PAIR was introduced in 1986, is widely used and indications and contraindications are well-described elsewhere. PAIR seems to have greater clinical efficacy, and lower rates of complications and disease recurrence compared to surgery^[52,60]. A randomized study comparing drainage with ALZ to ALZ alone or to drainage alone, showed that a maximum size reduction was observed in cysts treated with combination of PAIR and ALZ^[70]. A subsequent study demonstrated that PAIR combined with ALZ is an effective and safe alternative to surgery for the treatment of uncomplicated liver cysts and requires a shorter hospital stay^[71]. Surgery should be reserved for patients with secondary bacterial infection or for those with difficult-to-manage cyst-biliary communication or obstruction^[72-74]. Another unresolved point is for how long is it necessary to treat patients with ALZ? Treatment for three months is generally used and some cysts show a rapid response, others show non response during treatment or months after stopping the drug. In these cases long-term use of ALZ can be useful and should be investigated. In some disseminated CE cases, the use of ALZ for years resulted in a cure of the disease with a disappearance of the majority of cysts^[75]. The adherence of patients, the strict control of possible toxicity (liver enzymes and granulocytes), and imaging are essential for this extended treatment. The continuous and long-term use of ALZ in the treatment of alveolar echinococcosis (AE) is safe and well-tolerated, with good results and without significant adverse events^[76]. The results of long-term use in AE allowed the longer use

of ALZ in CE. Some other presentations of ALZ, such as an emulsion can offer better results^[77]. Future advances in chemotherapy might be achieved by identifying drugs with higher efficiency. Today, ALZ should be considered as the primary choice of treatment for patients who are not candidates for surgery (inoperable), recurrent cases, those with peritoneal involvement or with multiple cysts in several organs, those who refuse surgery or PAIR, and, perhaps, for asymptomatic carriers^[72].

CONCLUSION

The great tolerance of the liver and the asymptomatic character of CE infestation is an established fact. This tolerance raises the questions of “to treat or not to treat” these asymptomatic patients^[6,8,33,43,44]. The debate to whether a particular asymptomatic patient should undergo treatment or only enter in a watch/wait option is based on conflicting reports. These are: the lack of complications in untreated patients over years, the beneficial effect of existing therapies, the difficulties of accurately predicting prognosis and the possibility of developing severe complications, even mortality, because of the growth of cysts^[6,8,9,33,43,52,65,73]. Large cysts are more likely to develop such complications when they are located superficially^[52,74]. Surgery and PAIR are not innocuous and mortality, morbidity and relapse are possible^[78]. All these points demonstrate the difficulties of individual clinical decisions. The patients should be informed of the reasons and the risks of no treatment (watch/wait) and also about the risks of the other options. The long-term response and the good tolerance of ALZ in children have raised expectations about this treatment in the early stage of infestation. The current conditions surrounding asymptomatic liver hydatidosis are still confusing and we can not draw definite conclusions about the treatment of these carriers. Due to the scarcity of controlled and follow up studies of this neglected illness, treatment decisions are difficult to take. We are sure that further investigations are essential to determine the proper treatment in these cases. We emphasize the urgent need for more comparative studies between treatment or watch and wait, with close follow up. We feel that the treatment of liver hydatidosis has been performed without a clear discrimination between symptomatic or asymptomatic patients, especially in some surgery papers. An increase of follow-up studies is also the way to continue the path opened by the use of US initiated in the early 1980s, with the access to medical control of an enormous number of asymptomatic CE carriers. The knowledge of the natural history of hydatidosis is ongoing and a better understanding of this history will allow us to select the best therapeutic option to be administered at the right moment.

REFERENCES

- 1 **Larrieu PE**, Lester R, Rodríguez Jauregui J, Odriozzola M, Medina M, Aguero AM. [Epidemiology of human hydatidosis in the Province of Río Negro, Argentina] *Acta Gastroenterol Latinoam* 1986; **16**: 93-108
- 2 **Eckert J**, Deplazes P. Biological, epidemiological, and clinical aspects of echinococcosis, a zoonosis of increasing concern. *Clin Microbiol Rev* 2004; **17**: 107-135
- 3 **Gandolfi L**, Fukuda M. Current Trends in Digestive Ultrasonography. *Front Gastrointest Res* (Karger, Preface) 1997; **24**: IX-X
- 4 **Ren FY**, Piao XX, Jin AL. Efficacy of ultrasonography and alpha-fetoprotein on early detection of hepatocellular carcinoma. *World J Gastroenterol* 2006; **12**: 4656-4659
- 5 **Jang HJ**, Yu H, Kim TK. Imaging of focal liver lesions. *Semin Roentgenol* 2009; **44**: 266-282
- 6 **Frider B**, Losada CA, Larrieu E, de Zavaleta O. Asymptomatic abdominal hydatidosis detected by ultrasonography. *Acta Radiol* 1988; **29**: 431-434
- 7 **Caremani M**, Maestrini R, Occhini U, Sassoli S, Accorsi A, Giorgio A, Filice C. Echographic epidemiology of cystic hydatid disease in Italy. *Eur J Epidemiol* 1993; **9**: 401-404
- 8 **Frider B**, Larrieu E, Vargas F, Odriozzola M, Lester R. [An echographic, serologic and radiologic register of human hydatidosis. Contributions to a control program] *Acta Gastroenterol Latinoam* 1985; **15**: 199-211
- 9 **Larrieu EJ**, Frider B. Human cystic echinococcosis: contributions to the natural history of the disease. *Ann Trop Med Parasitol* 2001; **95**: 679-687
- 10 **Soulsby EJJL**. Archives of the XIII Congress of Hidatidology. Madrid (Spain) 1985; 18
- 11 **Larrieu EJ**, Varela-Díaz VM, Medina M, Coltorti EA, Coniglio R. [Human hydatidosis: contribution of immunodiagnosis for the detection, notification and registration of cases in the Province of Río Negro, Argentina] *Bol Chil Parasitol* 1983; **38**: 3-9
- 12 **Varela-Díaz VM**, Coltorti EA, de Zavaleta O, Pérez-Caviglia H, Zabert EI, Guarnera EA. Immunodiagnosis of human hydatid disease: applications and contributions to a control program in Argentina. *Am J Trop Med Hyg* 1983; **32**: 1079-1087
- 13 **Del Carpio M**, Moguilansky S, Costa M, Panomarenko H, Bianchi G, Bendersky S, Lazcano M, Frider B, Larrieu E. Diagnosis of human hydatidosis. Predictive value of a rural ultrasonographic survey in an apparently healthy population. *Medicina (B Aires)* 2000; **60**: 466-468
- 14 **MacPherson CN**, Romig T, Zeyhle E, Rees PH, Were JB. Portable ultrasound scanner versus serology in screening for hydatid cysts in a nomadic population. *Lancet* 1987; **2**: 259-261
- 15 **Macpherson CN**, Spoerry A, Zeyhle E, Romig T, Gorfe M. Pastoralists and hydatid disease: an ultrasound scanning prevalence survey in east Africa. *Trans R Soc Trop Med Hyg* 1989; **83**: 243-247
- 16 **Macpherson CN**, Bartholomot B, Frider B. Application of ultrasound in diagnosis, treatment, epidemiology, public health and control of Echinococcus granulosus and E. multilocularis. *Parasitology* 2003; **127** Suppl: S21-S35
- 17 **Gavidia CM**, Gonzalez AE, Zhang W, McManus DP, Lopera L, Ninaquispe B, Garcia HH, Rodríguez S, Verastegui M, Calderon C, Pan WK, Gilman RH. Diagnosis of cystic echinococcosis, central Peruvian Highlands. *Emerg Infect Dis* 2008; **14**: 260-266
- 18 **Frider B**, Ledesma C, Odriozzola M, Larrieu E. [Echographic specificity in the early diagnosis of human hydatidosis] *Acta Gastroenterol Latinoam* 1990; **20**: 13-15
- 19 **Mlika N**, Larouzé B, Gaubet C, Braham B, Allegue M, Dazza MC, Dridi M, Gharbi S, Gaumer B, Bchir A. Echotomographic and serologic screening for hydatidosis in a Tunisian village. *Am J Trop Med Hyg* 1986; **35**: 815-817
- 20 **Frider B**, Larrieu E, Odriozzola M, Vargas F. Catastro ecográfico de hidatidosis humana. Estudio comparativo con doble difusión cinco. Aportes a un programa de control. *Rev Iber Parasitol* 1986; **46**: 257-266
- 21 **Bchir A**, Larouze B, Soltani M, Hamdi A, Bouhaouala H, Ducic S, Bouden L, Ganouni A, Achour H, Gaubet C. Echotomographic and serological population-based study of hydatidosis in central Tunisia. *Acta Trop* 1991; **49**: 149-153

- 22 **Bchir A**, Larouze B, Bouhaoula H, Bouden L, Jemmali M. Echotomographic evidence for a highly endemic focus of hydatidosis in central Tunisia. *Lancet* 1987; **2**: 684
- 23 **Shambesh MA**, Craig PS, Macpherson CN, Rogan MT, Gusbi AM, Echtuish EF. An extensive ultrasound and serologic study to investigate the prevalence of human cystic echinococcosis in northern Libya. *Am J Trop Med Hyg* 1999; **60**: 462-468
- 24 **Shambesh MK**, Macpherson CN, Beesley WN, Gusbi A, Elsonosi T. Prevalence of human hydatid disease in north-western Libya: a cross-sectional ultrasound study. *Ann Trop Med Parasitol* 1992; **86**: 381-386
- 25 **Sato H**, Kamiya H, Grauert MR, Stern D, Altamirano Z, Perdomo R, Carmona C, Carbó A, Alvarez C, Monti J, Sakai H, Oku Y, Kamiya M. Comparison of serodiagnostic tests and ultrasonography for cystic hydatidosis in an epidemiological study of rural Uruguay. *J Parasitol* 1996; **82**: 852-854
- 26 **Cohen H**, Paolillo E, Bonifacino R, Botta B, Parada L, Cabrera P, Snowden K, Gasser R, Tessier R, Dibarboure L, Wen H, Allan JC, Soto de Alfaro H, Rogan MT, Craig PS. Human cystic echinococcosis in a Uruguayan community: a sonographic, serologic, and epidemiologic study. *Am J Trop Med Hyg* 1998; **59**: 620-627
- 27 **Wang Y**, He T, Wen X, Li T, Waili TT, Zhang W, Zhou H, Zheng H, Wen H, Davaadorj N, Gambolt L, Mukhar T, Rogan MT, Craig PS. Human cystic echinococcosis in two Mongolian communities in Hobukesar (China) and Bulgan (Mongolia). *Trans R Soc Trop Med Hyg* 2005; **99**: 692-698
- 28 **Chai JJ**. Epidemiological studies on cystic echinococcosis in China--a review. *Biomed Environ Sci* 1995; **8**: 122-136
- 29 **Moro PL**, Gilman RH, Verastegui M, Bern C, Silva B, Bonilla JJ. Human hydatidosis in the central Andes of Peru: evolution of the disease over 3 years. *Clin Infect Dis* 1999; **29**: 807-812
- 30 **Moro PL**, Garcia HH, Gonzales AE, Bonilla JJ, Verastegui M, Gilman RH. Screening for cystic echinococcosis in an endemic region of Peru using portable ultrasonography and the enzyme-linked immunoelectrotransfer blot (EITB) assay. *Parasitol Res* 2005; **96**: 242-246
- 31 **Altıntaş N**. Cystic and alveolar echinococcosis in Turkey. *Ann Trop Med Parasitol* 1998; **92**: 637-642
- 32 **Macpherson CN**, Kachani M, Lyagoubi M, Berrada M, Shepherd M, Fields PF, El Hasnaoui M. Cystic echinococcosis in the Berber of the Mid Atlas mountains, Morocco: new insights into the natural history of the disease in humans. *Ann Trop Med Parasitol* 2004; **98**: 481-490
- 33 **Frider B**, Larrieu E, Odriozola M. Long-term outcome of asymptomatic liver hydatidosis. *J Hepatol* 1999; **30**: 228-231
- 34 **Frider B**, Larrieu E, Corti OL. Frecuencia de las localizaciones hepática y pulmonar del quiste hidatídico en pacientes sintomáticos y en portadores asintomáticos de áreas endémicas. *Rev Ibérica Parasitol* 1988; **48**: 149-153
- 35 **Frider B**, Cravero A, Koch OR. Hidatidosis Hepática. Aportes de la Ultrasonografía y de la Autopsia al conocimiento de su historia natural. (Abstract). Congreso Extraordinario del V Centenario del Encuentro entre España y América, XVII Congreso de la asociación Española para el Estudio del Hígado. Madrid (España), 1992
- 36 **McManus DP**, Thompson RC. Molecular epidemiology of cystic echinococcosis. *Parasitology* 2003; **127** Suppl: S37-S51
- 37 **Kamenetzky L**, Gutierrez AM, Canova SG, Haag KL, Guarnera EA, Parra A, García GE, Rosenzvit MC. Several strains of Echinococcus granulosus infect livestock and humans in Argentina. *Infect Genet Evol* 2002; **2**: 129-136
- 38 **Rogan MT**, Hai WY, Richardson R, Zeyhle E, Craig PS. Hydatid cysts: does every picture tell a story? *Trends Parasitol* 2006; **22**: 431-438
- 39 **Caremani M**, Benci A, Maestrini R, Accorsi A, Caremani D, Lapini L. Ultrasound imaging in cystic echinococcosis. Proposal of a new sonographic classification. *Acta Trop* 1997; **67**: 91-105
- 40 **Gharbi HA**, Hassine W, Brauner MW, Dupuch K. Ultrasound examination of the hydatid liver. *Radiology* 1981; **139**: 459-463
- 41 International classification of ultrasound images in cystic echinococcosis for application in clinical and field epidemiological settings. *Acta Trop* 2003; **85**: 253-261
- 42 **Romig T**, Zeyhle E, Macpherson CN, Rees PH, Were JB. Cyst growth and spontaneous cure in hydatid disease. *Lancet* 1986; **1**: 861
- 43 **Larrieu E**, Del Carpio M, Salvitti JC, Mercapide C, Sustercic J, Panomarenko H, Costa M, Bigatti R, Labanchi J, Herrero E, Cantoni G, Perez A, Odriozola M. Ultrasonographic diagnosis and medical treatment of human cystic echinococcosis in asymptomatic school age carriers: 5 years of follow-up. *Acta Trop* 2004; **91**: 5-13
- 44 **Larrieu E**, Del Carpio M, Mercapide CH, Salvitti JC, Sustercic J, Panomarenko H. Programa de diagnóstico ultrasonográfico y tratamiento con albendazol de la equinococcosis quística en portadores asintomáticos: 10 años de seguimiento de casos. XXIII Congreso Mundial de Hidatidosis, Colonia (Uruguay), 2009: 151
- 45 **Hosch W**, Stojkovic M, Jänisch T, Kauffmann GW, Junghans T. The role of calcification for staging cystic echinococcosis (CE). *Eur Radiol* 2007; **17**: 2538-2545
- 46 **Bolondi L**, Li Bassi S, Gaiani S, Barbara L. Sonography of chronic pancreatitis. *Radiol Clin North Am* 1989; **27**: 815-833
- 47 **Kern P**. Medical treatment of echinococcosis under the guidance of Good Clinical Practice (GCP/ICH). *Parasitol Int* 2006; **55** Suppl: S273-S282
- 48 **Teggi A**, Lastilla MG, De Rosa F. Therapy of human hydatid disease with mebendazole and albendazole. *Antimicrob Agents Chemother* 1993; **37**: 1679-1684
- 49 **Junghans T**, da Silva AM, Horton J, Chiodini PL, Brunetti E. Clinical management of cystic echinococcosis: state of the art, problems, and perspectives. *Am J Trop Med Hyg* 2008; **79**: 301-311
- 50 **Stojkovic M**, Zwahlen M, Teggi A, Vutova K, Cretu CM, Virdone R, Nicolaidou P, Cobanoglu N, Junghans T. Treatment response of cystic echinococcosis to benzimidazoles: a systematic review. *PLoS Negl Trop Dis* 2009; **3**: e524
- 51 **Brunetti E**, Junghans T. Update on cystic hydatid disease. *Curr Opin Infect Dis* 2009; **22**: 497-502
- 52 **Brunetti E**, Kern P, Vuitton DA. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. *Acta Trop* 2010; **114**: 1-16
- 53 **Varela-Díaz VM**, Coltorti EA, Ricardes MI, Prezioso U, Schantz PM, Garcia R. Evaluation of immunodiagnostic techniques for the detection of human hydatid cyst carriers in field studies. *Am J Trop Med Hyg* 1976; **25**: 617-622
- 54 **Varela-Díaz VM**, Guarnera EA, Coltorti EA, Angiorama E, Conesa H, Hernández A, Cavallo C, Morrone R, Garcia R. Significance of hydatid immunodiagnostic surveys to health care and estimation of prevalence in the Argentine Province of Chubut. *Tropenmed Parasitol* 1983; **34**: 98-104
- 55 **Guarnera E**, Larrieu E, Coltorti E, Perez A, Cantoni G, Alvarez J, Nelsy G. [Community participation and appropriate technology in the early diagnosis of human hydatidosis] *Rev Inst Med Trop Sao Paulo* 1993; **35**: 491-494
- 56 **Larrieu E**, Frider B, del Carpio M, Salvitti JC, Mercapide C, Pereyra R, Costa M, Odriozola M, Pérez A, Cantoni G, Sustercic J. [Asymptomatic carriers of hydatidosis: epidemiology, diagnosis, and treatment] *Rev Panam Salud Publica* 2000; **8**: 250-256
- 57 **Bezzi M**, Teggi A, De Rosa F, Capozzi A, Tucci G, Bonifacino A, Angelini L. Abdominal hydatid disease: US findings during medical treatment. *Radiology* 1987; **162**: 91-95
- 58 **Horton RJ**. Albendazole in treatment of human cystic echinococcosis: 12 years of experience. *Acta Trop* 1997; **64**: 79-93
- 59 **Capan M**, Keltner S, Thalhammer F, Winkler S, Jäger W, Zeitlinger M, Ramharter M. Intra-cystic drug concentration of albendazole sulphoxide in patients with Echinococcus

- granulosus cysts. *Am J Trop Med Hyg* 2009; **81**: 712-713
- 60 **Filice C**, Pirola F, Brunetti E, Dughetti S, Strosselli M, Foglieni CS. A new therapeutic approach for hydatid liver cysts. Aspiration and alcohol injection under sonographic guidance. *Gastroenterology* 1990; **98**: 1366-1368
- 61 **Filice C**, Brunetti E. Use of PAIR in human cystic echinococcosis. *Acta Trop* 1997; **64**: 95-107
- 62 **Siracusano A**, Teggi A, Ortona E. Human cystic echinococcosis: old problems and new perspectives. *Interdiscip Perspect Infect Dis* 2009; **2009**: 474368
- 63 **Xu M**. Progress in surgical treatment of hydatid diseases in China. A clinical analysis of 22,005 surgical cases. *Chin Med J (Engl)* 1995; **108**, **4**: 295-299
- 64 **Secchi MA**, Pettinari R, Mercapide C, Bracco R, Castilla C, Cassone E, Sisco P, Andriani O, Rossi L, Grondona J, Quadrelli L, Cabral R, Rodríguez León N, Ledesma C. Surgical management of liver hydatidosis: a multicentre series of 1412 patients. *Liver Int* 2010; **30**, **1**: 85-93
- 65 **Yagci G**, Ustunsoz B, Kaymakcioglu N, Bozlar U, Gorgulu S, Simsek A, Akdeniz A, Cetiner S, Tufan T. Results of surgical, laparoscopic, and percutaneous treatment for hydatid disease of the liver: 10 years experience with 355 patients. *World J Surg* 2005; **29**: 1670-1679
- 66 **Saimot AG**. Medical treatment of liver hydatidosis. *World J Surg* 2001; **25**: 15-20
- 67 **Guidelines for treatment of cystic and alveolar echinococcosis in humans**. WHO Informal Working Group on Echinococcosis. *Bull World Health Organ* 1996; **74**: 231-242
- 68 **Caremani M**, Benci A, Maestrini R, Rossi G, Menchetti D. Abdominal cystic hydatid disease (CHD): classification of sonographic appearance and response to treatment. *J Clin Ultrasound* 1996; **24**: 491-500
- 69 **Gil-Grande LA**, Rodriguez-Caabeiro F, Prieto JG, Sánchez-Ruano JJ, Brasa C, Aguilar L, García-Hoz F, Casado N, Bárceña R, Alvarez AI. Randomised controlled trial of efficacy of albendazole in intra-abdominal hydatid disease. *Lancet* 1993; **342**: 1269-1272
- 70 **Khuroo MS**, Dar MY, Yattoo GN, Zargar SA, Javaid G, Khan BA, Boda MI. Percutaneous drainage versus albendazole therapy in hepatic hydatidosis: a prospective, randomized study. *Gastroenterology* 1993; **104**: 1452-1459
- 71 **Khuroo MS**, Wani NA, Javid G, Khan BA, Yattoo GN, Shah AH, Jeelani SG. Percutaneous drainage compared with surgery for hepatic hydatid cysts. *N Engl J Med* 1997; **337**: 881-887
- 72 **Smego RA Jr**, Sebanego P. Treatment options for hepatic cystic echinococcosis. *Int J Infect Dis* 2005; **9**: 69-76
- 73 **Manterola C**, Vial M, Sanhueza A, Contreras J. Intrahepatic rupture of hepatic echinococcosis, a risk factor for developing postoperative morbidity: a cohort study. *World J Surg* 2010; **34**: 581-586
- 74 **Al-Bahrani AZ**, Al-Maiyah M, Ammori BJ, Al-Bahrani ZR. Factors predictive of frank intrahepatic rupture in patients with hepatic hydatid cysts. *Hepatogastroenterology* 2007; **54**: 214-217
- 75 **Frider B**, Castano G, Viudez PC, Sookoian S, Fontana D. Long-term treatment with albendazole in a case of multiple hydatid cyst of liver, lung, mediastinum, kidney and spleen. XIX International Congress of Hidatidology, Bariloche (Argentina), 1999
- 76 **Liu YH**, Wang XG, Gao JS, Qingyao Y, Horton J. Continuous albendazole therapy in alveolar echinococcosis: long-term follow-up observation of 20 cases. *Trans R Soc Trop Med Hyg* 2009; **103**: 768-778
- 77 **Chai JJ**, Menghebat, Jiao W, Sun DY, Liang B, Shi JC, Fu C, Li X, Mao YD, Wang XL, Dolikun, Guliber, Wang YC, Gao FH, Xiao SH. [Efficacy of albendazole emulsion in treatment of 212 patients with cystic echinococcosis] *Zhongguo Jishengchongxue Yu Jishengchongbing Zazhi* 2001; **19**: 129-134
- 78 **Nasseri Moghaddam S**, Abrishami A, Malekzadeh R. Percutaneous needle aspiration, injection, and reaspiration with or without benzimidazole coverage for uncomplicated hepatic hydatid cysts. *Cochrane Database Syst Rev* 2006; CD003623

S- Editor Wang JL L- Editor Stewart GJ E- Editor Ma WH