Treatment of Hydatid Liver Disease: What does the evidence say

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Cystic echinococcosis is a disease of animals and humans caused by the larval stage of *Echinococcus granulosus sensu lato* and has a substantial public health impact globally. The condition is considered a neglected tropical disease (NTD) and neglected zoonotic disease (NZD), and prioritized by the World Health Organization (WHO) ¹. Within the last 10 years, advancements have taken place in *Echinococcus* biology and genetics, including the delineation of new species within *E. granulosus sensu lato* (s.l.)^{2,3} and full sequencing of *E. granulosus sensu stricto*². Consequently, researchers are now provided with new tools to better understand parasite biology and host-parasite interactions, with the goal of opening new avenues for therapy². *Echinococcus granulosus sensu stricto* (s. s.) (G1-3) is responsible for the great majority of human CE worldwide (88.48%), has the most cosmopolitan distribution and is often associated with transmission via sheep as intermediate hosts⁴.

Clinical manifestations of human CE typically result from the growth of single or multiple cysts in the liver, lungs, and/or other organs that can eventually produce a mass effect and impair organ function. The diagnosis and clinical management of cystic echinococcosis have evolved over decades in the absence of a systematic approach^{11,12}. The first widely used ultrasound classification of hepatic cystic echinococcosis cysts has been proposed by Gharbi et al. in 1981⁵ and has been used in the following years as the basis for a number of other classifications. The heterogeneity of these classifications resulted in the impossibility to compare the observations and treatment protocols made by

investigators in various clinical and epidemiological settings, which were not reported in a uniform manner. To overcome this problem, in 2003, the WHO-IWGE issued a standardized classification of hepatic cystic echinococcosis cysts 'to facilitate both the uniform reporting of results from field epidemiological studies as well as in clinical studies conducted in different parts of the world, which could be easy to use in different settings and could reflect physiopathological mechanisms of cystic echinococcosis'⁶. WHO-IWGE classification introduced the grouping of cystic echinococcosis cysts into three clinical categories: active, transitional, and inactive, reflecting the current knowledge of the natural history of cystic echinococcosis (CE). Accordingly, unilocular cysts (CE1) and multiloculated cysts with daughter vesicles without solid matrix (CE2) were classified as active cysts; cysts with detached endocyst and multiloculated cysts with daughter vesicles in a solid matrix were classified in the transitional group (CE3); and cysts with solid content with (CE5) or without (CE4) calcifications were classified as inactive cysts⁶.

Treatment usually consists of either a watch-and-wait approach, albendazole administration, surgical, percutaneous or per-endoscopic intervention, depending on the stage, integrity, number, size, and location of cysts⁷. The clinical management of cystic echinococcosis performed by different centres is extremely heterogeneous. In the past, surgery has been the only treatment modality for cystic echinococcosis, but with the introduction of benzimidazoles from the mid-1970s^{8,9} and the development of percutaneous treatment in the mid-1980s¹⁰, new options became available and were widely used in the following decades. Furthermore, the so-called 'watch and-wait' approach to uncomplicated inactive cysts has also been introduced on the basis of the observation that a good

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proportion of cysts become spontaneously inactive without any treatment and such cysts are likely to remain stable over time¹¹. No 'one-size-fits-all' treatment for cystic echinococcosis exists because of the proteiform presentation and evolution of this infection. Moreover, in the vast majority of cases, active hepatic infection is an asymptomatic disease with a spontaneous benign evolution. However, the accumulated knowledge based on single-centre experiences and on the few clinical trials comparing at least some of these treatment modalities^{12,16} supports a stage-specific approach to hepatic cystic echinococcosis^{7,11}. The WHO-IWGE expert consensus for the diagnosis and treatment of echinococcosis in humans, issued in 2010, indicated several stage-specific options for the management of hepatic cystic echinococcosis, although it also acknowledged that the choice of treatment for individual patients depends on a number of variables, including not only cyst stage but also other characteristics of the cyst, the patient, and the centre where the patient is visited. Additional important advancements introduced with this document concern the agreement on the use of benzimidazoles. These should be used as a peri-operative adjuvant to prevent iatrogenic seeding leading to local or systemic/extrahepatic secondary echinococcosis. Furthermore, when used as the only treatment, they should be administered continuously, without the 2-week interruption between monthly cycles recommended previously. Moreover, the need for a long-term follow-up of cystic echinococcosis patients was also stated, although a

definite length in years could not be provided

Over the last decade, a structured cyst stage-specific approach to patient management has been recommended based on the WHO-International Working Group on Echinococcosis cyst classification scheme, which was officially adopted in 2010⁷. Globally, there has been a push for physicians to take a patient's clinical condition, technical capability of the healthcare facility, safety and effectiveness of the approach, and the cost of treatment into account when devising a treatment plan. Unfortunately prospective studies to guide evidence-based therapeutic strategies are lacking and the adoption of a stage-specific approach by physicians has been slow¹⁷. In addition, whatever treatment plan is selected, long-term follow-up should be mandatory in order to detect recurrences^{7,17}.

General indications for treatment: a stage-specific approach

The opinion of WHO-IWGE experts⁷ with regard to a stage-specific approach is summarized in Table 1. Radical surgery aims to remove cysts completely. Percutaneous treatments (PT) and antiparasitic treatment with benzimidazoles (BMZ) represent alternatives to surgery. Cyst type (according to US classification), size, location and presence/absence of complications are the basis for decision-making¹⁸. The present quality of evidence and strength of recommendation has been characterized as per . Infectious Diseases Society of America grading system in Table 2

Table 1. Suggested stage-specific approach to *uncomplicated* cystic echinococcosis of the liver^a.

WHO classification	Surgery	Percutaneous treatment	Drug therapy	Suggested	Resources setting
CE1				<5 cm ABZ	Optimal
				PAIR	Minimal
		✓	✓	>5 cm PAIR + ABZ	Optimal
				PAIR	Minimal
CE2			✓	Other PT + ABZ	Optimal
	✓	✓			
				Other PT	Minimal
CE3a				<5 cm ABZ	Optimal
		✓	✓	PAIR	Minimal
				>5 cm PAIR + ABZ	Optimal
				PAIR	Minimal
CE3b				Non-PAIR PT + ABZ	Optimal
	✓	✓	✓		
				Non-PAIR PT	Minimal
CE4				Watch and Wait	Optimal
CE5				Watch and Wait	Optimal

^aTable adapted from Brunetti et al(7)

Table 2. Infectious Diseases Society of America grading system (strength of recommendation and quality of evidence).

Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support recommendation against use
Quality of evidence	
I	Evidence from ≥ 1 properly randomized, controlled trial
II	Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies; from multiple time series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of committees

SURGERY

The most common technique is total or partial cystectomy. Although surgical techniques have improved, there is considerable controversy as to what is the most effective technique, the role of cyst aspiration and external drainage, hepatic and lung resection, management of the residual cavity in CE of the liver, cyst recurrence after surgery, and high rates of complications and mortality related to reoperation in recurrent disease (1924). An immediate cure is claimed for surgical treatment of liver cysts, but even with radical procedures, this is far from being achieved, with morbidity, mortality, and relapse rates of 32%, 8%, and 20%, respectively. Surgery should be carefully evaluated against other options before choosing this treatment. It is the first choice for complicated cysts. In the liver, it is indicated for: 1 removal of large CE2-CE3b cysts with multiple daughter vesicles, 2 single liver cysts, situated superficially, that may rupture spontaneously or as a result of trauma when PTs are not available, 3 infected cysts, again, when PTs are not available, 4 cysts communicating with the biliary tree (as alternative to PT) and 5 cysts exerting pressure on adjacent vital organs. Surgery can be performed as an open procedure, with either radical or conservative techniques, or laparoscopically. There are still controversies as to the safest and most effective technique, and in which cases it should be applied^{25,27}. As a rule, perioperative ABZ prophylaxis, from 1 wk prior to surgery until 4 wk postoperatively, is necessary to minimize the risk of secondary echinococcosis from seeding of protoscoleces in the abdominal cavity⁷.

Recurrence, both local and as secondary echinococcosis, is associated with spillage during removal of the cyst, incomplete removal of the endocyst, and possibly the presence of unnoticed exophytic cyst development^{28,29}. For the latter, intraoperative US has been shown to be an important tool to improve the quality of hepatic surgery³⁰.

Contraindications

Surgery is contraindicated in patients to whom general contraindications for surgery apply, inactive asymptomatic cysts, difficult to access cysts, and very small cysts

Strength of recommendation: B Quality of Evidence: III

Percutaneous treatment

This includes PAIR and its modifications. PAIR is a minimally invasive technique used in the treatment of cysts in the liver and other abdominal locations. Best results with PAIR+BMZ are achieved in $>5\text{cm}$ CE1 and CE3 acysts where it may be the first-line treatment. It is also indicated for inoperable patients and those who refuse surgery, in cases of relapse after surgery or failure to respond to BMZ alone^{12,14,16}. Communication with bile ducts should be assessed by analyzing cyst fluid for bilirubin or by injecting contrast medium into the cyst cavity before the "injection" step³¹. Giant ($>10\text{cm}$) cysts are best treated with continuous catheter drainage until the daily output falls below 10mL ³². In pregnant women with symptomatic cysts and in children aged <3 years, the risk of BMZ must be carefully assessed³³. Protoscolicides used in PAIR are mainly 20% NaCl and 95% ethanol. Transhepatic cyst puncture prevents peritoneal protoscoleces spillage.

Prophylaxis with ABZ 4 h before and 1 month after PAIR is mandatory³⁴. Percutaneous treatment procedures may be performed on an out-patient basis³⁵; our department routinely performs this procedure under day-care admission with most patients being discharged after a few hours of observation.

Puncture of echinococcal cysts had long been discouraged because of the risk of anaphylactic shock and spillage of the fluid; however, as experience with US-guided interventional techniques has increased since the early 1980s, a growing number of articles have reported its safety in treating abdominal, especially liver, echinococcal cysts. In a recent systematic analysis on percutaneous aspiration of echinococcal cysts with 5943 punctures in 5517 hepatic and non-hepatic echinococcal cysts., only 2 cases of lethal anaphylaxis (0.04%) and 99 reversible anaphylactic reactions (1.8%) were reported, and incidence no greater than sporadic drug related anaphylaxis³⁶.

Contraindications

PAIR is contraindicated for CE2 and CE3b, for CE4 and CE5, and for lung cysts. Biliary fistulae contraindicate protoscolicide use.

Strength of recommendation: B Quality of Evidence: III

Antiparasitic drug treatment

While both albendazole and MBZ have been proven effective against the larval stage of *E. granulosus*, ABZ is the current treatment of choice due to better absorption³⁷. ABZ is administered orally at a dose of 10-15 mg/kg per day continuously without interruptions, generally for 3-6 mo. However, the optimal dose and duration of treatment with ABZ have not been formally assessed. In multiple series, reported outcome rates for hepatic cysts are: 28.5%-58% cure/marked improvement, 10%-51% partial response, 13%-37% no change, and 4%-33% worsened. Relapse rates range from 9%-25%, and, although responsive to subsequent treatments, cysts tend to relapse multiple times³⁸. BMZ are indicated for inoperable patients with liver or lung CE; patients with multiple cysts in two or more organs, or peritoneal cysts. Small (<5 cm) CE1 and CE3a cysts in the liver and lung respond favourably to BMZ alone^{39,40}. BMZ should be used to prevent recurrence following surgery or PAIR⁴¹. A recent study has shown enhanced efficacy of ABZ when co-administered with Metformin when used in experimental mice for both

primary and prevention of secondary hydatidosis⁴².

Contraindications

BMZ are contraindicated in cases with hypersensitivity to the drug, cysts at risk of rupture and in early pregnancy. ABZ has been proven teratogenic in rats and rabbits. Physiological exposure to ABZ and its principal metabolite, ABZ sulfoxide, in early human pregnancy is substantially lower (perhaps 10/100 times) than in the animal species in which teratogenic or embryotoxic effects have been recorded. Despite the fact that no abnormal birth outcome has been observed following ABZ administration during pregnancy, treatment of gravid or potentially gravid females should be avoided, unless the benefit of treatment significantly outweighs the potential risk to the developing fetus⁴³.

BMZ must be used with caution in patients with chronic hepatic disease and avoided in those with bone-marrow depression. Inactive or calcified asymptomatic cysts should not be treated unless they are complicated.

BMZ alone are not effective in large cysts (over 10 cm), as their effect is extremely slow in cysts with large volumes of fluid.

Strength of recommendation: B Quality of Evidence: III

Watch and Wait approach

Some cysts do not require any treatment if uncomplicated, namely, CE4 and CE5 (CL cysts should not be treated, until their parasitic nature has been proven). Long-term follow-up of patients with US imaging has increased clinicians' confidence that in selected cases, i.e. when inactive cysts are not complicated, treatment can be put on hold¹¹. Analysis of long-term follow-up data from a prospective CE patient cohort of 223 patients which included included 30 patients with 46 inactive cysts who never received medical treatment and were managed with the wait and watch approach. No relapse was seen in this subset of patients during 18 months of follow-up. In contrast cysts which reach inactivity through treatment with benzimidazoles behaved differently, showing a relapse rate of 50% shown in the Kaplan-Meier analysis⁴⁴.

Strength of recommendation: B Quality of Evidence: III

Clinical Decision-making on Hepatic CE

CE can be very difficult to treat and even more difficult to cure for a number of reasons. The disease is complex and dynamic, with an evolving phase and quietly growing cysts,

followed by an involution process during which the parasite is gradually dying, leaving behind a solidified, often calcified cyst or a scar.

Each successive active cyst stage carries its own risks for serious and even life-threatening complications. This variation during the CE disease process leads to a wide range of treatment modalities with an equally wide range of technological and training backgrounds necessary for implementation and delivery. As a result of all of these issues, no “one size fits all” management approach is available, and a stage-specific approach currently appears to be the best way to manage this condition.

Control program implementation for CE has historically relied on a combination of local education regarding slaughter and hygiene practices and dog population management and/or deworming initiatives using praziquantel¹. The development of vaccines targeting sheep intermediate hosts has now added a new tool to combat CE in highly impacted populations. The EG 95 vaccine has been tested in a number of countries, including China and Argentina with promising results^{45,46}. Control program evaluation relies on surveillance for the pathogen in domestic dogs and ruminants, which is costly and labor-intensive. Overall, the prevalence of human CE has been reduced in areas where long-term intensive control programs have been put in place. However, in most resource-poor areas, CE control remains a challenge⁹. Researchers are working to better understand the ecology of wildlife definitive (e.g., foxes and other wild canids) and intermediate (e.g., small mammals) hosts, to predict risks for human infection and improve anthelmintic baiting practices in rural and urban areas⁴⁵.

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