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Review

Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans☆

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ABSTRACT

The earlier recommendations of the WHO-Informal Working Group on Echinococcosis (WHO-IWGE) for the treatment of human echinococcosis have had considerable impact in different settings worldwide, but the last major revision was published more than 10 years ago. Advances in classification and treatment of echinococcosis prompted experts from different continents to review the current literature, discuss recent achievements and provide a consensus on diagnosis, treatment and follow-up. Among the recognized species, two are of medical importance – *Echinococcus granulosus* and *Echinococcus multilocularis* – causing cystic echinococcosis (CE) and alveolar echinococcosis (AE), respectively.

For CE, consensus has been obtained on an image-based, stage-specific approach, which is helpful for choosing one of the following options: (1) percutaneous treatment, (2) surgery, (3) anti-infective drug treatment or (4) watch and wait. Clinical decision-making depends also on setting-specific aspects. The usage of an imaging-based classification system is highly recommended.

For AE, early diagnosis and radical (tumour-like) surgery followed by anti-infective prophylaxis with albendazole remains one of the key elements. However, most patients with AE are diagnosed at a later stage, when radical surgery (distance of larval to liver tissue of >2 cm) cannot be achieved. The backbone of AE treatment remains the continuous medical treatment with albendazole, and if necessary, individualized interventional measures. With this approach, the prognosis can be improved for the majority of patients with AE.

The consensus of experts under the aegis of the WHO-IWGE will help promote studies that provide missing evidence to be included in the next update.

Contents

☆ This document is an abridged version of a more detailed text that will be published online on the WHO website.

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1. Introduction

Human echinococcosis is a zoonosis caused by larval forms (metacestodes) of *Echinococcus* (*E.*) tapeworms found in the small intestine of carnivores. Among the recognized species, two are of medical importance – *E. granulosus* and *E. multilocularis* – causing cystic echinococcosis (CE) and alveolar echinococcosis (AE) in humans, respectively. This expert consensus is a follow-up to the Guidelines published in 1996 by the WHO-Informal Working Group on Echinococcosis (WHO-IWGE) (WHO-IWGE, 1996). Readers are referred for detailed information and scientific discussion to WHO reports (WHO/OIE, 2001) and published reviews (Junghanss et al., 2008; McManus et al., 2003; Craig et al., 2007). In endemic areas, the annual incidence of CE ranges from <1 to 200 per 100,000 inhabitants (WHO/OIE, 2001); that of AE ranges from 0.03 to 1.2 per 100,000 inhabitants (Schweiger et al., 2007) but may be significantly higher in certain endemic foci (WHO/OIE, 2001; Craig, 2003). Human CE remains highly endemic in pastoral communities, particularly in regions of South America, the Mediterranean littoral, Eastern Europe, the Near and Middle East, East Africa, Central Asia, China and Russia. The distribution of human AE cases is more restricted but is an important public health concern in parts of central and eastern Europe, the Near East, Russia, China and northern Japan (WHO/OIE, 2001). The estimated minimum global human burden of CE averages 285,000 disability-adjusted life years (DALYs) or an annual loss of US $194,000,000 (Budke, 2006). In untreated or inadequately treated AE, mortality is >90% within 10–15 years of diagnosis (Torgerson et al., 2008). The mortality rate from CE (about 2–4%) is lower than that from AE, but it may increase considerably if medical treatment and care are inadequate.

2. Methodology for the preparation of the document

The process was initiated by the subgroup "Standardization/Classification" of the WHO-IWGE (chaired by Peter Kern, Ulm, Germany and Enrico Brunetti, Pavia, Italy) and discussed in Chengdu, P.R.China, May 2006 and Athens, Greece, May 2007. An expert meeting of the WHO-IWGE aimed to reach a consensus on the clinical management of patients with CE and AE was organized at the Saline Royale d'Arc-et-Senans and in Besançon, France, by Prof. D.A. Vuitton, Prof. S. Bresson-Hadni, Prof. G. Mantion, WHO Collaborating Centre for Prevention and Treatment of Human Echinococcosis, Besançon, France and Prof. Hao Wen, Urumqi, P.R.China, Xinjiang/China Key Lab of Basic and Clinical Research on Echinococcosis, and was chaired by Prof. P. Craig, Salford, UK Coordinator, WHO-IWGE, and by Dr. F.-X. Meslin, Division of Emerging Diseases, World Health Organization, Geneva; Switzerland. Rapporteurs of the different subsections and nominees by the WHO supported the writing panel. A final consensus was achieved by e-mail in February 2009.

Papers covering the subject were obtained by a Medline search of the literature published in English on this subject.

Key words were "echinococcal cysts," "hydatid cysts," "hydatid disease," "cystic echinococcosis," "alveolar echinococcosis," "liver transplant," "hydatidosis," "hydatid," "surgery," "mebendazole," "albendazole," "praziquantel," "chemotherapy," "PAIR," "percutaneous treatment," "percutaneous drainage," and "ultrasound." Papers published from 1980 to 2008 were included. The authors' files were used as well. Levels of recommendations given in this document follow the "Guide to Practice Guidelines" of the Infectious Diseases Society of America (Kish, 2001; Table 1).

3. Cystic echinococcosis (CE)

3.1. Organ location

In primary CE, metacestodes – the larval forms of the parasite – may develop in almost any organ. Up to 80% patients have a single organ involved and a solitary cyst localized to the liver (4/5) or lungs (1/5). The liver/lung ratio may vary from 2 to 1 to 7 to 1 or more (Larrieu and Frider, 2001). *E. granulosus* germinal layer generates brood capsules and protoscoleces into a central cavity filled with a clear "hydatid" fluid; it is surrounded first by an acellular laminated layer, then by the host reaction. "Daughter" vesicles of variable size may be present inside or outside the "mother" cyst (Fig. 1).

Table 1
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

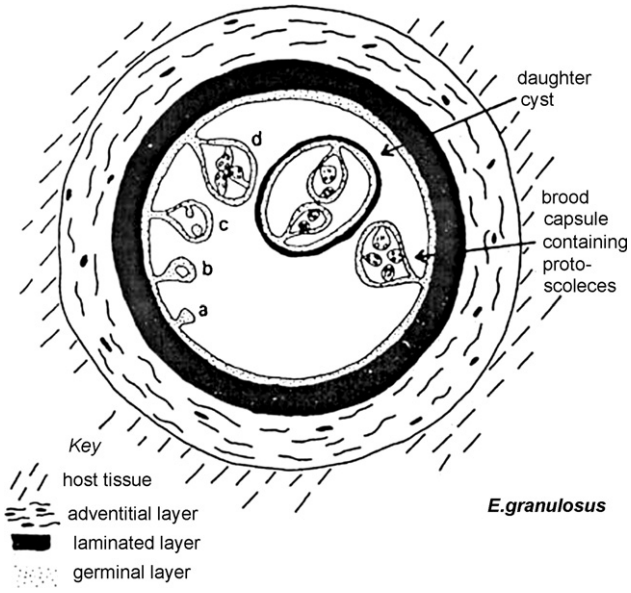


Fig. 1. Diagrammatic representation of structure of the echinococcal cyst.

3.2. Course of infection

Ultrasound (US) surveys have shown that cysts may grow 1–50 mm per year or persist without changes for years. They may also spontaneously rupture or collapse or disappear (Romig et al., 1986; Frider et al., 1999; Wang et al., 2006; Mufit et al., 1998). The sequence of cyst changes during the natural history is still unclear (Rogan et al., 2006). Liver cysts appear to grow at a lower rate than lung cysts (Larrieu and Frider, 2001). Clinical symptoms usually occur when the cyst compresses or ruptures into neighbouring structures.

3.3. Diagnosis

The diagnosis of CE is based on clinical findings, imaging techniques, and serology. Proof of the presence of protoscoleces may be given by microscopic examination of the fluid and histology.

3.3.1. Imaging

A. US examination and WHO classification

US examination is the basis of CE diagnosis in abdominal locations, at both the individual and population levels (Macpherson and Milner, 2003). US may visualize cysts in other organ locations, including lung when cysts are peripherally located (El Fortia et al., 2006).

In 1995, the WHO-IWGE developed a standardised classification that could be applied in all settings to replace the plethora of previous classifications and allow a natural grouping of the cysts into three relevant groups: active (CE1 and 2), transitional (CE3) and inactive (CE4 and 5) (WHO and Echinococcosis, 2003). WHO-IWGE classification is the basis for the present Guidelines (Fig. 2); it differs from Gharbi's classification introduced in 1981 (Gharbi et al., 1981) by adding a "cystic lesion" (CL) stage (undifferentiated), and by reversing the order of CE Types 2 and 3 (Fig. 3). CE3 transitional cysts may be differentiated into CE3a (with detached endocyst) and CE3b (predominantly solid with daughter vesicles) (Junghanss et al., 2008). CE1 and CE3a are early stages and CE4 and CE5 late stages.

B. Imaging techniques other than US

Conventional radiography is useful to diagnose thoracic and bone involvement.

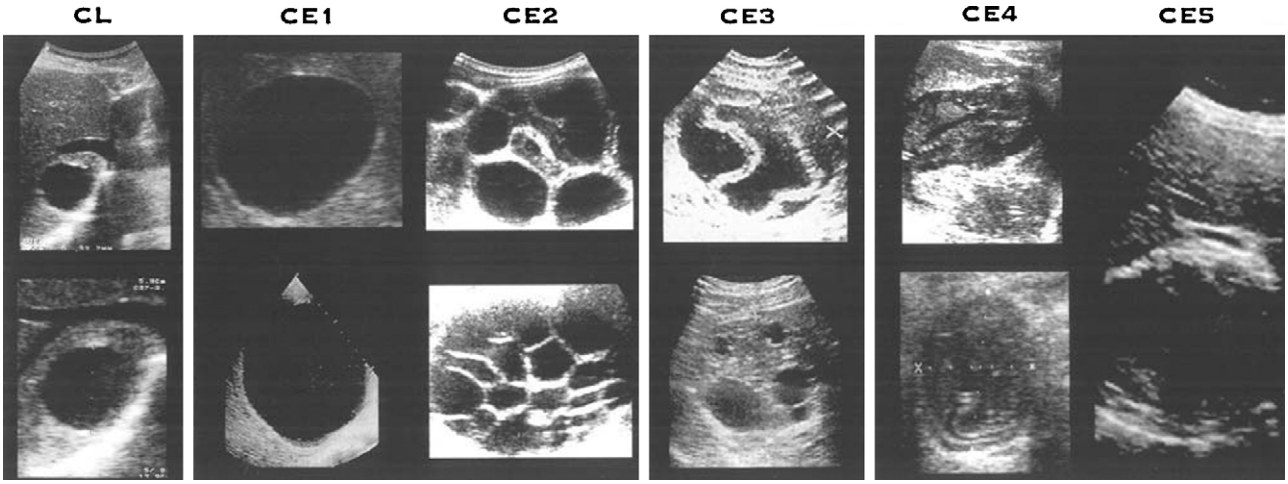


Fig. 2. WHO-IWGE standardized classification.

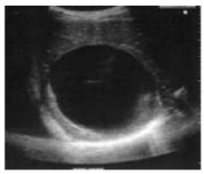
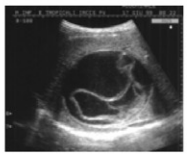
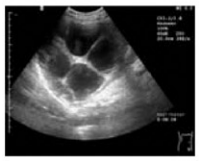
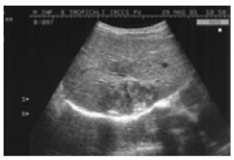
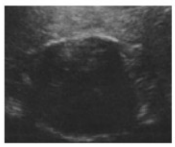
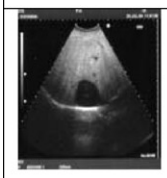
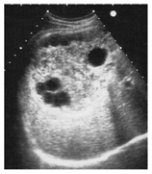
Gharbi	I	II	III	IV	V
					
WHO	CE1	CE3a	CE2	CE4	CE5
					
CL			CE3b		

Fig. 3. Comparison of Gharbi's and WHO-IWGE ultrasound classification. CL, as a potentially parasitic cyst, was not in Gharbi's. WHO CE3b had not been explicitly described by Gharbi. CE3b might be classified as Type III, although in the original Gharbi paper there was no distinction between multivesiculated (honeycomb-like) cysts and cysts with daughter cysts in solid matrix.

Computed tomography (*CT*), and *magnetic resonance* (*MR*) *imaging*, with one T2-weighted imaging sequence and if possible cholangiopancreatography (MRCP) are indicated in (1) subdiaphragmatic location, (2) disseminated disease, (3) extra-abdominal location, (4) in complicated cysts (abscess, cysto-biliary fistulae) and (5) pre-surgical evaluation. Whenever possible, MR imaging should be preferred to CT due to better visualization of liquid areas within the matrix (Hosch et al., 2008).

3.3.2. Direct assessment of E. granulosus and its viability

Microscope examination of protoscoleces after cyst fluid aspiration using vital staining gives evidence for the parasitic nature and viability of a cyst (WHO/OIE, 2001). Detection of parasitic antigens gives no indication of viability. Presence of calcification is not reliable as an indicator of non-viability: more frequent in CE4 and CE5, it may be observed at all stages (Hosch et al., 2007). MR spectroscopy has been evaluated to assess cyst viability in fluids taken surgically or percutaneously (Hosch et al., 2008). *In vivo* evaluation of cyst viability has already been performed using MR spectroscopy in cysts that do not move with respiration such as brain cysts (Seckin et al., 2008) and might become possible for other locations in the future (Hosch et al., 2008).

3.3.3. E. Granulosus serology

Sensitivity of serum antibody detection using indirect hemagglutination, ELISA, or latex agglutination, with hydatid cyst fluid antigens, ranges between 85 and 98% for liver cysts, 50–60% for lung cysts and 90–100% for multiple organ cysts (Siracusano and Bruschi, 2006; Ito and Craig, 2003; Siles-Lucas and Gottstein, 2001). Specificity of all tests is limited by cross-reactions due to other cestode infections (*E. multilocularis* and *Taenia solium*), some other helminth diseases, malignancies, liver cirrhosis and presence of anti-P1 antibodies. Confirmatory tests must be used (arc-5 test; Antigen B (AgB) 8 kDa/12 kDa subunits or EgAgB8/1 immunoblotting) in dubious cases (Siracusano and Bruschi, 2006; Ito and Craig, 2003). Immunoblotting may be used as a first-line test and is best for differential diagnosis (Akisu et al., 2006). Mass screening in populations at risk optimally deploys US and serology (Macpherson and Milner, 2003).

Detection of parasite-specific IgE or IgG4 has no significant diagnostic advantage. Both, as well as eosinophil count, are more elevated after rupture/leakage of cysts (Khabiri et al., 2006).

3.3.4. CE case definition

The International Classification of Diseases and Related Health Problems ICD10 (10th Revision Version for 2007; http://www.who.int/classifications/icd/en) subclassifies:

B67.0 E. granulosus, liver infection
B67.1 E. granulosus, lung infection
B67.2 E. granulosus, bone infection
B67.3 E. granulosus, other organs and multiple site infection
B67.4 E. granulosus, unspecified infection

ICD 9 codes are also listed as they are still used in many countries:

122.0 E. granulosus, liver infection
122.1 E. granulosus, lung infection
122.2 E. granulosus, thyroid infection
122.3 E. granulosus infection, other
122.4 E. granulosus, unspecified infection

A. Clinical criteria

At least one of the following three:

1. A slowly growing or static cystic mass(es) (signs and symptoms vary with cyst location, size, type and number) diagnosed by imaging techniques.
2. Anaphylactic reactions due to ruptured or leaking cysts.
3. Incidental finding of a cyst by imaging techniques in asymptomatic carriers or detected by screening strategies.

B. Diagnostic criteria

1. Typical organ lesion(s) detected by imaging techniques (e.g. US, CT-scan, plain film radiography, MR imaging).

2. Specific serum antibodies assessed by high-sensitivity serological tests, confirmed by a separate high specificity serological test.
3. Histopathology or parasitology compatible with cystic echinococcosis (e.g. direct visualization of the protoscolex or hooklets in cyst fluid).
4. Detection of pathognomonic macroscopic morphology of cyst(s) in surgical specimens.

C. Possible versus probable versus confirmed case

Possible case. Any patient with a clinical or epidemiological history, *and* imaging findings *or* serology positive for CE.

Probable case. Any patient with the combination of clinical history, epidemiological history, imaging findings *and* serology positive for CE on two tests.

Confirmed case. The above, plus either (1) demonstration of protoscoleces or their components, using direct microscopy or molecular biology, in the cyst contents aspirated by percutaneous puncture or at surgery, or (2) changes in US appearance, e. g. detachment of the endocyst in a CE1 cyst, thus moving to a CE3a stage, or solidification of a CE2 or CE3b, thus changing to a CE4 stage, after administration of ABZ (at least 3 months) or spontaneous.

3.4. Treatment

There is no "best" treatment option for CE and no clinical trial has compared all the different treatment modalities, including "Watch and Wait." Treatment indications are complex and are based on cyst characteristics, available medical/surgical expertise and equipment, and adherence of patients to long-term monitoring. Because treatment involves a variety of options and requires specific clinical experience, patients should be referred to recognized, reference and national/regional CE treatment centres, whenever available.

3.4.1. General indications for treatment: a stage-specific approach

The opinion of WHO-IWGE experts with regard to a stage-specific approach is summarized in Table 2. 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-making (Menezes da Silva, 2003). For complicated cysts and cysts with multiple locations, a staging system similar to that used for AE has been proposed (Kjossev and Losanoff, 2005), however it should be tested prospectively in larger series of patients and various settings before final validation.

3.4.2. Surgery for abdominal cysts

A. Indications

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.

B. Contraindications

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

C. Choice of surgical technique

Parasitic material should be removed as much as possible. However, the more radical the intervention, the higher the operative risk, but with the likelihood of fewer relapses, and vice versa (Aydin et al., 2008). Laparoscopic surgery is a technical option in selected cases but the risk of complications including spillage has never been fully evaluated (Baskaran and Patnaik, 2004).

Total removal of the cyst is usually described as "pericystectomy." "Closed total pericystectomy" removes the cyst without opening it, and "open total pericystectomy" sterilizes the metacestode with protoscolicidal agents, evacuates the contents of the cyst, then removes the pericystic tissue. A cleavage plane between the inner layer of the host's reaction facing towards the parasite and the outer layer, or adventitia, described by Peng and co-workers, limits the damage to liver parenchyma when dissecting around the cyst and allows safer removal of the cyst (Peng et al., 2002). Based

Table 2
Suggested stage-specific approach to *uncomplicated* cystic echinococcosis of the liver.

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*[a]
CE5				*Watch and Wait*	*Optimal*[a]

[a] "Minimal" may not be applicable here because in low resources, remote endemic areas, it may be impossible or too expensive to travel to the nearest hospital just to get a diagnosis.

on these anatomical considerations, such an operation should be more adequately named "total cystectomy."

Partial cystectomy, in which the cyst content is sterilized and removed after opening, with the pericyst partially resected, is especially suited for endemic areas where the operations are performed by general surgeons. No special equipment is required and liver tissue is neither entered nor resected. However, the risk of secondary echinococcosis from protoscolex dissemination is higher than with total pericystectomy or total cystectomy.

D. Prevention of protoscolex spillage; choice of protoscolicides

Any effort made to avoid fluid spillage is recommended, including protection of peritoneal tissues and organs with protoscolicide-soaked surgical drapes and injection of protoscolicide into the cyst before opening. At present, 20% hypertonic saline is recommended (WHO/OIE, 2001). Saline should be in contact with the germinal layer for at least 15 min, and its use avoided when communication between the cyst and the bile ducts is found, to avoid the risk of chemically-induced sclerosing cholangitis. A series of compounds are protoscolicidal in vitro, including ivermectin, praziquantel (PZQ) and BMZ. However, they should be further studied in humans for efficacy and safety (Hokelek et al.,2002; Bygott and Chiodini, 2009; Dziri et al., 2009).

Peri-operative BMZ may reduce cyst pressure and decrease the risk of secondary CE. The length of administration usually ranges between 1 day before and 1 month after surgery but has never been formally evaluated. A recent paper comparing different peri-operative ABZ regimens concluded that ABZ is an effective adjuvant therapy in surgical treatment of liver CE (Arif et al., 2008), but the question of what is the best timing remains unanswered. Adjunctive PZQ might be helpful, but this needs confirmation (Cobo et al., 1998).

E. Management of cysto-biliary fistulas

Cyst diameter is a factor associated with a high risk of biliary-cyst communication in clinically asymptomatic patients. With a cyst diameter of 7.5 cm as a cut-off point, a 79%, likelihood to find a cysto-biliary fistula was calculated (Aydin et al., 2008). Thus, surgeons operating on cysts larger than 7.5 cm should be prepared to deal with this complication. Sphincterotomy alone is not an adequate treatment (Aydin et al., 2008). Biliary communication can be detected, located and classified intra-operatively by using dye or radio-opaque markers. During surgery, most communications can be managed with suture. However, biliary-intestinal anastomosis or liver resection are sometimes necessary. If post-operative bile leakage occurs, patience is advised. Operative management should be avoided whenever possible. The chances of spontaneous closure of fistulae from cysts with a calcified wall are small.

F. Benefits

Surgery may cure the patient completely but does not totally prevent recurrence. Given the dearth of clinical trials, the level of evidence is low for the surgical treatment of complicated liver CE and disseminated CE (Dziri et al., 2004). Standardized terminology and procedures should be agreed upon by surgeons for the techniques to be compared.

G. Risks

The risks include those associated with any surgical intervention, anaphylactic reactions, and secondary CE owing to spillage of viable parasite material. Operative mortality varies from 0.5% to 4%, but may be higher if surgical and medical facilities are inadequate (WHO/OIE, 2001; Junghanss et al., 2008).

H. Medical requirements

The medical staff must have experience in treating CE and the surgical ward must be adequately equipped.

Strength of recommendation: B Quality of Evidence: III

3.4.3. PERCUTANEOUS TREATMENTS (PTs)

PTs can broadly be divided into: (1) those aiming at the destruction of the germinal layer (PAIR) and (2) those aiming at the evacuation of the entire endocyst (also known as Modified Catheterization Techniques).

PAIR (Puncture, aspiration, injection, re-aspiration)

A. Indications

PAIR is a minimally invasive technique used in the treatment of cysts in the liver and other abdominal locations (WHO-IWGE, 2003a,b). It is indicated for inoperable patients and those who refuse surgery, in cases of relapse after surgery or failure to respond to BMZ alone. Best results with PAIR + BMZ are achieved in >5 cm CE1 and CE3a cysts where it may be the first-line treatment (Khuroo et al., 1993). In pregnant women with symptomatic cysts and in children aged <3 years, the risk of BMZ must be carefully assessed (Ustunsoz et al., 2008).

B. Contraindications

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

C. Principle and technique

PAIR includes: (1) percutaneous puncture of cysts using US guidance, (2) aspiration of cyst fluid, (3) injection of protoscolicide for 10–15 min and (4) re-aspiration of the fluid (WHO-IWGE, 2003a,b). Safety assessment lies on data from more than 4000 PAIRs over a period of more than 20 years. CE2 and CE3b cysts treated by PAIR tend to relapse (Junghanss et al., 2008). 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" step (WHO-IWGE, 2003a,b). Giant (>10 cm) cysts are best treated with continuous catheter drainage until the daily output falls below 10 mL (Men et al., 2006).

D. Choice of protoscolicides; prevention of protoscolex spillage

Protoscolicides used in PAIR are mainly 20% NaCl and 95% ethanol. Transhepatic cyst puncture prevents peritoneal protoscolex spillage. Prophylaxis with ABZ 4 h before and 1 month after PAIR is mandatory (WHO-IWGE, 2003a,b; Morris and Taylor, 1988).

E. Benefits

PAIR confirms the diagnosis and removes parasitic material. It is minimally invasive, less risky and usually less expensive than surgery (Smego et al., 2003).

F. Risks

Risks include those associated with any liver PTs, biliary fistulae after intracystic decompression, sclerosing cholangitis should the scolecidal agent reach the biliary vessels persistence of exophytic daughter vesicles, anaphylactic reactions, and secondary echinococcosis. Specific complications are no more frequent after PAIR than after surgery (Ustunsoz et al., 1999).

G. Medical requirements

PAIR should only be performed by experienced physicians with drugs and resuscitation equipment to manage anaphylactic shock at hand and a surgical back-up team.

OTHER PERCUTANEOUS TREATMENTS

These are reserved to cysts that are difficult to drain or tend to relapse after PAIR (CE2 and CE3b). These procedures aim to remove the entire endocyst and daughter cysts from the cyst cavity. Large-bore catheters (Haddad et al., 2000; Schipper et al., 2002) and cutting devices together with an aspiration apparatus have been successfully employed (Saremi and McNamara, 1995). Among more than 1000 patients, rates of short- and medium-term success are satisfactory with minimal complications (Vuitton et al., 2002; Wang et al., 1994). These techniques have also been successfully employed for CE2 cysts located outside the abdomen (Akhan et al., 2007). However, long-term evaluation is still not available, therefore caution is advised before drawing reliable conclusions.

Strength of recommendation: B Quality of Evidence: III

3.4.4. Antiparasitic drug treatment

A. Indications

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 (Dogru et al., 2005; Vutova et al., 1999). BMZ should be used to prevent recurrence following surgery or PAIR (Arif et al., 2008).

B. Contraindications

BMZ are contraindicated in 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. Therefore, the risk of fetal exposure from the recommended therapeutic dose is probably very small. 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 fetus (Bradley and Horton, 2001).

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.

C. Drugs: benzimidazoles

Albendazole (ABZ) is currently the drug of choice to treat CE, either alone or together with PT (Franchi et al., 1999). Given orally, at a dosage of 10–15 mg/kg/day, in two divided doses, with a fat-rich meal to increase its bioavailability, it should be administered continuously, without the monthly treatment interruptions recommended in the 1980s (Franchi et al., 1999). Treatment interruptions were felt to be required because of the limited long-term toxicity data available in the early days of use (Junghanss et al., 2008). However, optimal dosage and optimal duration have never been formally assessed. Alternatively, mebendazole (MBZ), the first BMZ tested successfully against *Echinococcus*, may be used at a dosage of 40–50 mg/kg body weight daily, in three divided doses with fat-rich meals, if ABZ is not available or not tolerated (WHO-IWGE, 1996; Franchi et al., 1999).

D. Other drugs

PZQ 40 mg/kg once a week in combination with ABZ seems more effective in killing protoscoleces than ABZ alone (Cobo et al., 1998). The usefulness of PZQ in avoiding secondary echinococcosis needs further study.

E. Benefits

BMZ can be used in patients of any age. However, there is little experience with children under-6 years old; it is less limited by the patient's status than surgery. Standard dosage-ABZ for 3–6 months produces an average of 30% cure. The number of patients with clinical or US improvement increases with longer durations of treatment while the proportion of patients with cure does not significantly change (Vutova et al., 1999; Franchi et al., 1999). ABZ is more effective in young patients and for small CE1 and CE3a cysts. BMZ are less effective for CE2 and CE3b (Vutova et al., 1999; Franchi et al., 1999). The importance of cyst stage and size in determining response to treatment was recently confirmed by a systematic review in which data relative to 1159 liver and peritoneal cysts were analyzed (Stojkovic et al., 2009).

Randomized controlled trials that compare standardized benzimidazole therapy on responsive cyst stages with the other treatment modalities are needed to draw reliable conclusions.

F. Risks

Adverse effects of BMZ include hepatotoxicity, severe leucopenia, thrombocytopenia and alopecia (Junghanss et al., 2008). Increase in aminotransferase levels may be due to drug-related efficacy or to real drug-related toxicity. Risks include embryotoxicity and teratogenicity, which have been observed in laboratory animals (Bradley and Horton, 2001).

G. Medical requirements

Hospitalization is not necessary but regular follow-up is required. Costs of BMZ and repeated examinations may be prohibitive in countries with limited resources.

H. Pharmacovigilance

Recommandations for pharmacovigilance are given below under "Monitoring of CE patients" and 4.4.2 F.

Strength of recommendation: B Quality of Evidence: III

3.4.5. 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 hold (Junghanss et al., 2008).

This approach deserves formal evaluation.

Strength of recommendation: B Quality of Evidence: III

3.4.6. Management of cysts in extra-hepatic sites and specific situations

Because of the lower frequency of CE in extra-hepatic sites, the strength of recommendation is even lower than for treatment of hepatic CE.

A. Lung

The presentation of pulmonary CE varies widely, making a uniform treatment recommendation impossible. BMZ used alone showed good efficacy on small, uncomplicated lung cysts. BMZ should be avoided pre-operatively in larger lung cysts. Surgery aims at removing the parasite and treating associated pathology. It should be as conservative as possible. Radical procedures are required for extended parenchymal involvement, severe pulmonary suppuration, and complications (Isitmangil et al., 2002).

B. Bone

Bone involvement accounts for 0.5–2% of the total number of cases and is potentially the most debilitating form of CE. The most effective treatment is radical resection of the affected bone (Zlitni et al., 2001). Multiple recurrences with the need for repeated surgical procedures, in addition to the presence of serious complications such as spinal involvement, fistulae, acute and chronic osteomyelitis, have an extremely poor prognosis. When the hip is involved, broad resections should be carried out, with the implantation of a prosthetic hip absolutely contraindicated. CE in bone is less sensitive to ABZ than cysts at other sites and high dosage and long-term administration (years) are indicated.

C. Heart

Cardiac involvement accounts for 0.5–2% of total cases with 10% of cases showing various symptoms. Surgery is the treatment of choice (Thameur et al., 2001). Venous filters are used to prevent dissemination. If complete removal of the cysts is possible, the prognosis is good, with a low rate of recurrence.

D. Disseminated disease

When cysts are widespread, usually after cyst rupture, spontaneously or during surgery, a surgical approach is often impractical (Chawla et al., 2003). If the cysts are very large or located in or near vital organs the treatment should be combined surgery and ABZ, despite its palliative nature. However, medical treatment alone with ABZ, maintained for an indefinite length of time, is the only option available in most cases, with an acceptable response (reduction in the number and/or size of lesions) (Chawla et al., 2003). Discontinuation is often associated with recurrence.

3.5. Strength of recommendation: B Quality of Evidence: III

3.5.1. Monitoring of CE patients

Follow-up visits, including US examination should be done every 3–6 months initially and every year once the situation is stable. Leukocyte counts and aminotransferase measurements are necessary at monthly intervals to detect adverse reactions. Oral drug doses can be adapted to individual patients in order to achieve adequate serum levels but only a few laboratories have the capability to determine ABZ sulfoxide or MBZ plasma drug levels (WHO-IWGE, 1996) (see also section on AE).

One of the major problems of CE is the frequency of relapses. Serological markers to assess relapses have been widely studied, but while the persistence of raised antibody levels or a further increase may be suggestive of residual disease or recurrence, this may happen even when cysts have been successfully removed with surgery (Galitza et al., 2006). This may be confusing even to experienced clinicians. New antigens seem to be promising in improving the performance of serology in post-treatment monitoring (Ben Nouir et al., 2008).

4. Alveolar echinococcosis

4.1. Organ location

Initially, metacestodes of *E. multilocularis* develop almost exclusively in the liver, predominantly in the right lobe, from foci of a few millimeters to areas of 15–20 cm or more in diameter, sometimes with central necrosis (WHO-IWGE, 1996; WHO/OIE, 2001). *E. multilocularis* does not form cysts as *E. granulosus* does. From the liver, the larva spreads to other organs by infiltration or metastasis formation. Primary extra-hepatic locations of *E. multilocularis* are rare (Kern et al., 2003).

4.2. Course of infection

AE is characterized by an initial asymptomatic incubation period of 5–15 years and a subsequent chronic course. The symptoms are primarily cholestatic jaundice (1/3 cases) and/or abdominal pain (1/3 cases). In 1/3 of patients, AE is found incidentally on investigation of various symptoms such as: fatigue and weight loss, hepatomegaly and abnormal US or routine laboratory findings (WHO-IWGE, 1996; WHO/OIE, 2001). Mortality is high in non-treated patients but in Europe treatment has changed average life expectancy at diagnosis from 3 years in the 1970s to 20 years in 2005 (Torgerson et al., 2008). Under the influence of the host's defense mechanisms, the larva can degenerate and die; calcified dead lesions can be identified during mass screening programmes (Rausch et al., 1987; Bresson-Hadni et al., 1994; Gottstein et al., 2001; Romig et al., 1999).

4.3. Diagnosis

Diagnosis of alveolar echinococcosis is based on clinical findings and epidemiological data, imaging techniques, histopathology and/or nucleic acid detection, and serology.

4.3.1. Imaging

A. Ultrasound examination

As for CE, US examination is the basis of AE diagnosis in abdominal locations, at the individual and population levels, but needs an experienced examiner (Bartholomot et al., 2002; Romig et al., 1999). Typical findings (70% of cases) include (1) juxtaposition of hyper- and hypoechogenic areas in a pseudo-tumour with irregular limits and scattered calcification and (2) pseudo-cystic appearances due to a large area of central necrosis surrounded by an irregular hyperechogenic ring. Less typical features (30% of cases) include (1) haemangioma-like hyperechogenic nodules as the initial lesion and (2) a small calcified lesion due either to a dead or a small-sized developing parasite (Bresson-Hadni et al., 2000, 2006). US

with colour Doppler provides information on biliary and vascular involvement.

B. Imaging techniques other than US

CT gives an anatomical and morphological characterization of lesions and best depicts the characteristic pattern of calcification (WHO/OIE, 2001). In cases of diagnostic uncertainty, MR imaging may show the multivesicular morphology of the lesions, thereby supporting the diagnosis (Bresson-Hadni et al., 2006) and is the best technique to study extension to adjacent structures. For pre-operative evaluation, MRCP has replaced percutaneous cholangiography to study the relationship between the AE lesion and the biliary tree (Bresson-Hadni et al., 2006). Initial radiological examination to exclude pulmonary and cerebral AE is recommended.

4.3.2. Direct assessment of E. multilocularis and its viability

Histopathological examination shows the parasitic vesicles delineated by a Periodic-Acid-Schiff (PAS)+ laminated layer. The periparasitic granuloma is composed of epithelioid cells lining the parasitic vesicles, macrophages, fibroblasts and myofibroblasts, giant multinucleated cells, and various cells of the nonspecific immune response, usually surrounded by lymphocytes. Also present are collagen and other extracellular matrix protein deposits (Yamasaki et al., 2007).

Polymerase chain reaction (PCR) can detect *Echinococcus*-specific nucleic acids in tissue specimens resected or biopsied from patients and RT-PCR may assess viability (Ito and Craig, 2003; Yamasaki et al., 2007). However, a negative result on a thin needle aspiration sample does not rule out disease and a negative finding using RT-PCR does not indicate complete inactivity of a lesion (Yamasaki et al., 2007).

[^{18}F]Fluoro-Deoxyglucose-Positron-Emission-Tomography (FDG-PET) scanning indirectly demarcates areas of parasitic activity. If combined with CT (PET/CT), or MRI (PET/MRI), it may show active lesions at a time when clinical symptoms are absent and recurring disease not yet detectable by conventional imaging (Reuter et al., 2004; Stumpe et al., 2007). However, lack of detectable metabolic activity does not mean parasite death, but indicates suppressed periparasitic inflammatory activity (Stumpe et al., 2007). Delayed PET image acquisition (3 h after FDG injection) improves the assessment of primary and metastatic liver lesions (Bresson-Hadni et al., 2006).

4.3.3. WHO classification of AE

The WHO-IWGE PNM classification system, based on imaging findings, has been established as the international benchmark for standardized evaluation of diagnostic and therapeutic measures (WHO/OIE, 2001; Kern et al., 2006). It denotes the extension of the parasitic mass in the liver (P), the involvement of neighbouring organs (N), and metastases (M) (Table 3). PNM classification should improve the quality control of current treatment strategies in single centres and uniform evaluation of multicentre studies.

4.3.4. E. Multilocularis serology

As for CE, immunodiagnosis represents a valuable diagnostic tool to confirm the nature (and species) of the etiological agent (WHO-IWGE, 1996; WHO/OIE, 2001; Ito and Craig, 2003). The use of purified and/or recombinant, or *in vitro*-produced *E. multilocularis* antigens (Em2, Em2+, Em18; for complete list, see WHO-IWGE, 1996; Ito and Craig, 2003) has a high diagnostic sensitivity of 90–100%, with a specificity of 95–100%. Most of the purified antigens allow discrimination between AE and CE in 80–95% of cases. Immunoblotting tests may be used for confirmation or as a first-line investigation if easily available. For AE screening, a combined approach using US and serology discriminates different infection status among seropositive individuals: (1) patients with active hepatic lesions, (2) individuals presenting with fully calcified lesions and (3) individuals presenting with no detectable lesion at all. The latter two variants refer to persons exposed to infection but in whom the parasite has not become established or does not progress (Vuitton et al., 2006).

Table 3
PNM classification of alveolar echinococcosis.

P	Hepatic localisation of the parasite
PX	Primary tumour cannot be assessed
P0	No detectable tumour in the liver
P1	Peripheral lesions without proximal vascular and/or biliar involvement
P2	Central lesions with proximal vascular and/or biliar involvement of one lobe[a]
P3	Central lesions with hilar vascular or biliar involvement of both lobes and/or with involvement of two hepatic veins
P4	Any liver lesion with extension along the vessels[b] and the biliary tree
N	Extra-hepatic involvement of neighbouring organs [diaphragm, lung, pleura, pericardium, heart, gastric and duodenal wall, adrenal glands, peritoneum, retroperitoneum, parietal wall (muscles, skin, bone), pancreas, regional lymph nodes, liver ligaments, kidney]
NX	Not evaluable
N0	No regional involvement
N1	Regional involvement of contiguous organs or tissues
M	The absence or presence of distant metastasis [lung, distant lymph nodes, spleen, CNS, orbital, bone, skin, muscle, kidney, distant peritoneum and retroperitoneum]
MX	Not completely evaluated
M0	No metastasis[c]
M1	Metastasis

[a] For classification, the plane projecting between the bed of the gall bladder and the inferior vena cava divides the liver in two lobes.
[b] Vessels mean inferior vena cava, portal vein and arteries.
[c] Chest X-ray and cerebral CT negative.

4.3.5. AE case definition

The International Classification of Diseases and Related Health Problems ICD10 (10th Revision Version for 2007; http://www.who.int/classifications/icd/en) subclassifies:

B67.5 E. multilocularis, liver infection
B67.6 E. multilocularis, other organs and multiple site infection
B67.7 E. multilocularis, unspecified infection

ICD 9 codes are also listed as they are still used in many countries:

122.5 E. multilocularis, liver infection
122.6 E. multilocularis infection, other
122.7 E. multilocularis infection, unspecified

A. Clinical criteria

At least the following: a slowly growing tumour (signs and symptoms vary with tumour location, size and type (solid, partly multivesicular, with central necrosis)), diagnosed by imaging techniques.

B. Diagnostic criteria

At least one of the following four:

1. Typical organ lesions detected by imaging techniques (e.g. abdominal US, CT, MR).

2. Detection of *Echinococcus* spp. specific serum antibodies by high-sensitivity serological tests and confirmed by a high specificity serological test.
3. Histopathology compatible with AE.
4. Detection of *E. multilocularis* nucleic acid sequence(s) in a clinical specimen.

C. Possible versus probable versus confirmed case

Possible case. Any patient with clinical and epidemiological history and imaging findings or serology positive for AE.

Probable case. Any patient with clinical and epidemiological history, and imaging findings and serology positive for AE with two tests.

Confirmed case. The above, plus (1) histopathology compatible with AE and/or (2) detection of *E. multilocularis* nucleic acid sequence(s) in a clinical specimen.

4.4. Treatment

Treatment should be planned in a multidisciplinary discussion, taking all elements of available pre-treatment imaging into account. In addition to chemotherapy, early diagnosis, improved surgery, and medical care of the patients have contributed to the success of treatment and to the increase in patients' survival time during the past 3 decades (Bresson-Hadni et al., 2000; Kadry et al., 2005; Buttenschoen et al., 2009a; Torgerson et al., 2008). Patients should be referred to recognised national/regional AE treatment centres whenever available, or treated under the guidance of such centres.

4.4.1. General indications for treatment

The following principles should be followed: (1) BMZ are mandatory in all patients, temporarily after complete resection of the lesions, and for life in all other cases, (2) interventional procedures should be preferred to palliative surgery whenever possible and (3) radical surgery is the first choice in all cases suitable for total resection of the lesion(s). A consensus view of a number of experts on a stage-specific approach is summarized in Table 4.

4.4.2. Antiparasitic drug treatment

A. Indications

Long-term BMZ treatment for several years is mandatory in all inoperable AE patients and following surgical resection of the parasite lesions. Since residual parasite tissue may remain undetected at radical surgery, including liver transplantation (LT), BMZ should be given for at least 2 years and these patients monitored for a minimum of 10 years for possible recurrence (Reuter et al., 2000). Pre-surgical BMZ administration is not recommended except in the case of LT.

B. Contraindications

In view of the severity of AE, there are only a few contraindications for medical treatment and they are mostly due to life-threatening side effects. In some instances (e.g. pregnant women) certain precautions are necessary (see Contraindications in Section 3).

C. Drugs: BMZ

ABZ is given orally at a dosage of 10–l5 mg/kg/day, in 2 divided doses, with fat-rich meals. In practice, a daily dose of 800 mg is given to adults, divided in two doses. Continuous ABZ treatment of AE is well tolerated and has been used for more than 20 years in some patients. Intermittent treatment should no longer be used. Occasionally, ABZ has been given in higher doses of 20 mg/kg/day for up to 4.5 years. Alternatively, if ABZ is not available or not well tolerated, MBZ may be given at daily doses of 40–50 mg/kg/day split into three divided doses with fat-rich meals. For details on the pharmacology of BMZ, see (WHO-IWGE, 1996).

Strength of recommendation: B Quality of Evidence: III

D. Other drugs

Based on experimental data, PZQ has no place in the treatment of human AE (Marchiondo et al., 1994).

Table 4
Stage-specific approach to alveolar echinococcosis.

WHO classification	Surgery	Interventional treatment	Drug therapy	Suggested	Resources setting
P1N0M0				Radical resection (R0) BMZ for 2 years PET/CT controls	*Optimal*
	√		√	Radical resection (R0) BMZ for 3 months	*Minimal*
P2N0M0			√	Radical resection (R0) BMZ for 2 years	*Optimal*
	√			Radical resection (R0) BMZ for 3 months	*Minimal*
P3N0M0			√	BMZ continuously PET/CT/MRI scan initially and in 2 years intervals	*Optimal*
				BMZ continuously	*Minimal*
P3N1M0		√	√	BMZ continuously + PET/CT/MRI scan initially and in 2 years intervals Surgery, if indicated	*Optimal* *Minimal*
P4N0M0		√	√	BMZ continuously + PET/CT/MRI scan initially and in 2 years intervals Surgery, if indicated	*Optimal* *Minimal*
P4N1M1		√	√	BMZ continuously + PET/CT/MRI scan initially and in 2 years intervals Surgery, if indicated	*Optimal* *Minimal*

Conventional and liposomal amphothericin B have been used as a salvage treatment in a few patients who did not tolerate BMZ (Reuter et al., 2003).

Nitazoxanide had no efficacy in a recent pilot trial (Kern et al., 2008).

New ABZ formulations such as liposomes and nanoparticles seem to improve ABZ bioavailability. Randomized, controlled trials are necessary to draw definitive conclusions on efficacy and side-effects of these new formulations.

E. Benefits

Controlled, but non-randomized studies showed that long-term BMZ improved the 10-year survival rate in non-radically operated AE patients compared to untreated historical control patients from 6–25% to 80–83%, respectively, and prevented recurrences after radical surgery (Ammann and Eckert, 1996; Torgerson et al., 2008).

F. Risks

The same risks for BMZ described in Section 3 exist for their use in AE. Although no systematic evaluation has been performed, long-term administration does not seem to increase such risks or to generate resistance.

G. Medical requirements

Hospitalization is not needed but regular medical and laboratory checks for adverse reactions and efficacy are necessary. The costs of anthelmintics and repeated medical examinations are high. Reference centres should be used to monitor drug levels and specific antibodies, and for specialised imaging techniques (such as PET/CT or MR scans).

C. Pharmacovigilance

Examinations for adverse reactions are necessary initially every 2 weeks (first 3 months), then monthly (first year), then every 3 months. As BMZ administration is crucial in all cases of AE, if an increase above 5 times the upper limit of normal (ULN) of aminotransferases is observed, the following steps are recommended: (1) check for other causes of the increase (other medication, viral hepatitis, AE-related biliary obstruction or liver abscess), (2) monitor drug levels, (3) if ABZ sulfoxide plasma levels are higher than the recommended range of concentrations (1–3 μmol/L, 4 h after morning drug intake), decrease ABZ dosage and shift to the alternative BMZ (MBZ if ABZ and vice versa) and (4) if an increase over 5 × ULN persists, consult a reference centre. Decrease of leukocyte count under 1.0 × 109/L indicates BMZ toxicity and warrants treatment withdrawal.

4.4.3. Surgery

Radical resection is the primary goal. Excision of the entire parasitic lesion should follow the rules of tumour surgery, classified according to the quality of resection: R0: no residue; R1: microscopic residue; R2: macroscopic residue. Non-radical liver surgery, previously regarded as beneficial for reducing the parasitic mass, does not appear currently to offer advantages over conservative treatment (Kadry et al., 2005; Buttenschoen et al., 2009). Lesions not confined to the liver are not a contraindication to surgery *per se*, but curative procedures have to meet the criteria for R0-resections as well. Lesions in other organs (e.g. brain) should be managed either by surgery or by alternative measures. Irrespective of the type of procedure, concomitant BMZ treatment is mandatory for at least 2 years. No staging system can judge "resectability" but the WHO-IWGE PNM classification (Kern et al., 2006) gives a rough estimation and enables comparison of results from different groups. Each case should be discussed in an interdisciplinary context.

A. Indications

Whenever possible complete resection of AE lesions should be performed. The potential for resection and whether there is disease dissemination must be assessed carefully by pre-operative imaging techniques. LT should be reserved for patients with very advanced forms of the disease as salvage therapy.

B. Contraindications

In principle, radical surgery should be avoided when R0-resection is not achievable. Palliative surgery is almost always contraindicated; the few exceptions should be discussed thoroughly. LT is contraindicated in the presence of extra-hepatic locations and if immunosuppressive drugs and/or BMZ are contraindicated.

C. Choice of surgical technique

Radical surgery is the treatment of choice (R0-resection). As the parasite's growth resembles a malignant tumour, procedures and techniques recommended in oncological surgery, with a 2 cm safety margin are logical (Marchiondo et al., 1994; Sato et al., 1997; Uchino et al., 1993). Post-operative BMZ and long-term follow-up are mandatory in all cases (Table 4).

Palliative surgery should be avoided whenever possible. However, the diversity of AE manifestations sometimes results in individual solutions. R1- or even R2-resections might be necessary to effectively deal with a septic focus if R0-resection is impossible and/or if percutaneous or endoscopic drainage, which should be attempted first, is not effective (Buttenschoen et al., 2009b). Palliative resection combined with BMZ has proven to be effective in treating skin lesions.

Strength of recommendation: B Quality of Evidence: III

D. Liver transplantation

LT has been performed in approximately 60 patients in the world, with inoperable lesions and/or chronic liver failure (Koch et al., 2003). Immunosuppression favours re-growth of larval remnants and formation or increase in size of metastases (Vuitton et al., 2006). The conditions to qualify a patient for LT are: (1) severe liver insufficiency (secondary biliary cirrhosis or Budd-Chiari syndrome) or recurrent life-threatening cholangitis, (2) inability to perform radical liver resection and (3) absence of extra-hepatic AE locations: cases with residual AE in lung or abdominal cavity should be regarded as exceptional indications, balancing all the pros and cons (Scheuring et al., 2003).

E. Benefits

Radical surgery may cure the patient. Palliative surgery has very little benefit, except in rare selected cases. In highly selected cases, LT may save AE patients' lives. In a study by Bresson-Hadni et al., 5-year survival was 71% and 5-year survival without recurrence was 58%, which is better than in LT for hepatocellular carcinoma (Bresson-Hadni et al., 2003). Long-term survival (over 15 years) is possible in patients with residual or recurrent lesions under BMZ treatment.

F. Risks

The risks include those associated with any surgical intervention and specifically possible damage to major vessels along with the immunosuppression and chronic bacterial infection often observed in AE patients. Invisible or unrecognized parasitic remnants may re-grow and disseminate to other organs even after years have passed.

Strength of recommendation: C Quality of Evidence: II

G. Medical requirements

Hospitalization in a surgical ward with easy access to blood supply facilities is mandatory. The surgical team should be experienced in major (liver) surgery and in treating AE. LT requires a highly specialized team and equipment. Supportive medical care includes post-transplantation follow-up, adjustment of immunosuppressive drugs, and diagnosis and management of complications of the immunosuppressive regimen combined with continuous chemotherapy with BMZ.

4.4.4. Endoscopic and percutaneous interventions (EPI)

A number of local complications may occur for which interventional procedures have to be considered (Bresson-Hadni et al., 2006).

A. Indications

EPIs are indicated for complications if surgery is felt to be too high a risk and total resection of the lesions cannot be safely performed. Main indications include liver abscess due to bacterial infection of necrotic lesions, jaundice due to bile duct obstruction with or without acute cholangitis, hepatic or portal vein thrombosis and bleeding of oesophageal varices secondary to portal hypertension.

B. Contraindications

EPIs may spread parasite material and should be avoided if post-interventional BMZ is not possible.

C. Principle and techniques

Percutaneous bile or abscess drainage has now advantageously replaced palliative surgery with jejuno-biliary anastomosis to treat life-threatening cholangitis or liver abscess (Bresson-Hadni et al., 2000, 2006). However, bile drainage necessitates a permanent external drain, generally for life, and regular changing to prevent obstruction.

Endoscopic dilation of bile duct strictures followed by insertion of multiple plastic stents is an interesting alternative to PI since it immediately allows internal bile drainage (Bresson-Hadni et al., 2006). Additional treatment with ursodeoxycholic acid (UDCA) is given in some centres; its usefulness in preventing stent obstruction should be studied prospectively.

D. Benefits

EPIs together with BMZ avoid palliative surgery and can improve life expectancy and quality of life of AE patients. In addition, radical resection which was not possible initially may become feasible following the shrinkage of a necrotic cavity after percutaneous drainage.

E. Risks

Risks of EPIs include haemorrhage (for all procedures) and internal bile leakage or prolonged bile leakage through an external drain for bile duct drainage.

F. Medical requirements

Short-term hospitalization is usually necessary. Specific equipment that allows US (and/or CT) guidance of PI and/or an appropriate endoscope is required. In addition, medical professionals with a large experience of such procedures are essential to their success.

Strength of recommendation: B Quality of Evidence: III

4.4.5. Monitoring of patients with AE

After initiation of any type of treatment, long-term follow-up by US at shorter intervals and CT and/or MRI at intervals of 2–3 years, should be planned. Progression is documented by enlargement of lesions over time.

Determination of ABZ sulfoxide blood levels, 4 h after the morning dose, is recommended 1, 4 and 12 weeks after starting treatment, and 2–4 weeks after each dose adjustment with an estimated therapeutic range of 0.65–3 μmol/L. ABZ dosage should be reduced if 2 sequential measurements are above 10 μmol/L. Monitoring of MBZ plasma level is possible; plasma levels should be over 250 nmol/L (WHO-IWGE, 1996).

Complete surgical removal of the lesions results in a rapid decrease of anti-Em2- and anti-Em18-antibodies which subsequently become undetectable (Scheuring et al., 2003). Interpretation of serological results in patients treated with BMZ without radical resection is more complex (Tappe et al., 2009). Presence of anti-II/3-10/Em18-antibodies is more likely to reflect the presence of a viable metacestode with disappearance of such antibodies indicating lesions dying-out (Ammann et al., 2004).

BMZ are only parasitostatic and many studies have demonstrated that they do not kill *E. multilocularis* metacestodes (WHO-IWGE, 1996). After several years of BMZ administration, however, the question of treatment interruption may be raised, in the absence of progression of the lesions assessed by conventional imaging, and indirect assessment of viability using PET/CT (Reuter et al., 2004; Stumpe et al., 2007). Although it does not provide direct evidence of *E. multilocularis* viability, and recurrence may occur, this technique, together with the follow-up of specific serum antibodies, may support decision-making and follow-up after BMZ withdrawal in highly selected patients.

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