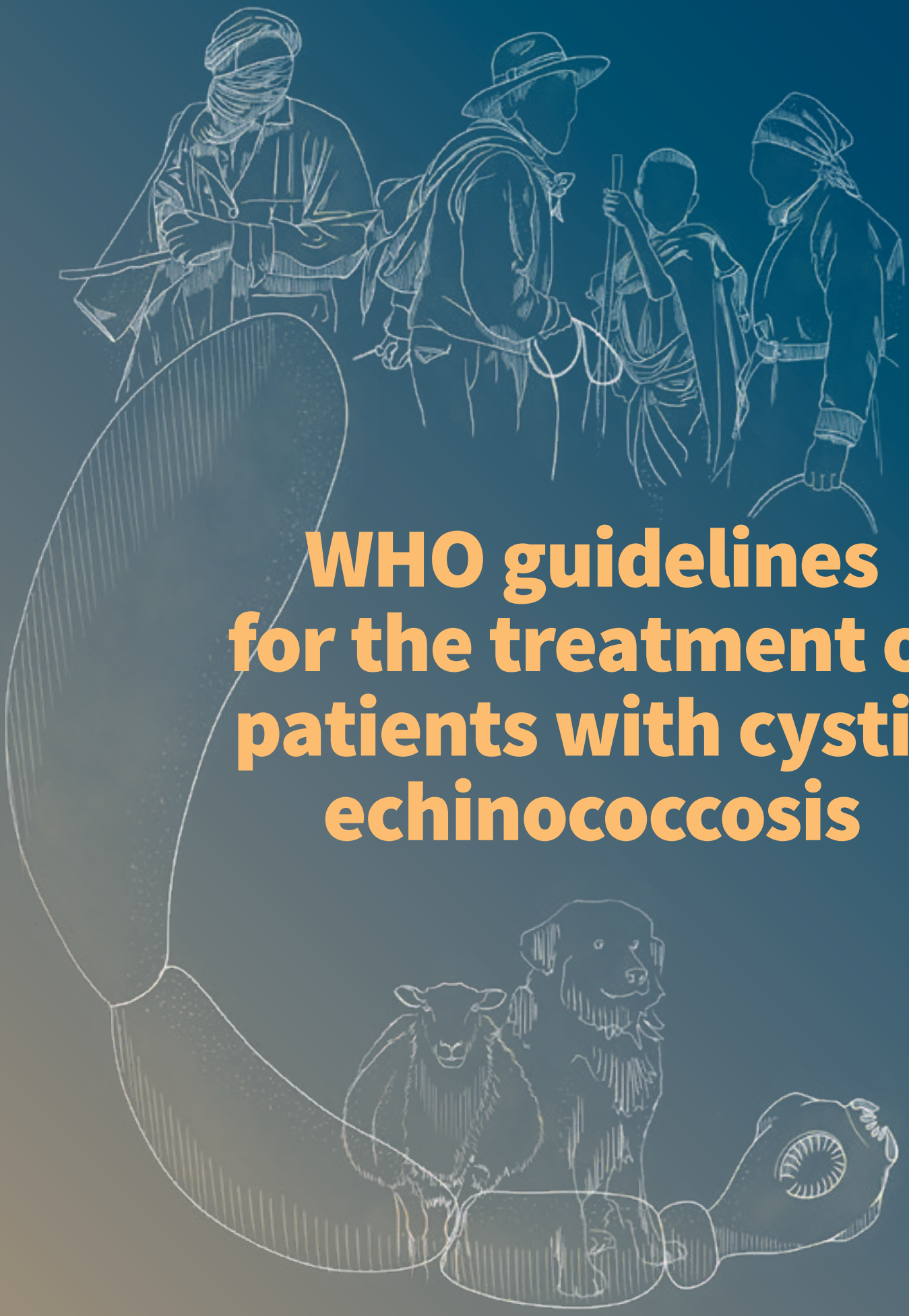

WHO guidelines for the treatment of patients with cystic echinococcosis

World Health Organization

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Contents

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Abbreviations and acronyms

ALB	albendazole
CE	cystic echinococcosis
CT	computed tomography
EtD	evidence to decision
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICU	intensive care unit
Mo-CAT	modified catheterization technique
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
NTD	neglected tropical disease
PAIR	Puncture, Aspiration, Injection, Re-aspiration
PICO	population, intervention, comparator, and outcome
PCR	polymerase chain reaction
RCT	randomized controlled trial
S-CAT	standard catheterization
WHO	World Health Organization
WHO-IWGE	WHO Informal Working Group on Echinococcosis

Glossary

The definitions given below apply to the terms used in this document. They may have different meanings in other contexts.

active cysts	Cysts which are biologically viable, as evidenced by the integrity of cyst wall layers and the presence of cyst fluid in their cavities.
complicated cyst	A cyst with complications which might include rupture (outside, or internally in structures of the infected organ); cysts causing clinically significant compression of internal structures of the infected organ or of neighbouring organs, superinfection of the cyst with bacteria or fungi; and anaphylactic reactions to echinococcal antigens due to loss of integrity of the cyst wall. For example, a complicated hepatic cyst might present an infection, rupture to abdominal cavity, fistula to biliary tree or migration to thorax (pleura or lung). A complicated echinococcal lung cyst is any cyst ruptured into the bronchi or into the pleural cavity, or a cyst that is infected.
cystic echinococcosis	Disease due to *E. granulosus sensu lato.*
fertile cysts	Active cysts that contain viable protoscoleces.
health tier categories	The treatment options for patients with CE will depend on the capacity of the health facility to deliver the particular treatment option safely. The Guideline Development Group defined the surgical, radiological and laboratory infrastructure as well as the technical expertise required for each option as part of the guidelines process, defining four health tier categories as described in Table 2. The recommendations were linked to these health tiers.
inactive cysts	Cysts that are biologically inactive (i.e. not producing hydatid fluid). Inactive cysts have a solid content and are unlikely to be fertile. Egg-shell calcification of the cyst wall, or complete calcification of an inactive (i.e. solid) cyst most likely indicates a non-viable cyst.
modified catheterization technique (Mo-CAT)	Procedure for treatment of CE cysts that consists of the percutaneous placement of a catheter with removal of the laminated and germinal layers and its content, including daughter cysts if present.
non-radical surgery (in relation to CE)	Partial cystectomy. Surgical intervention that removes all content of the cyst (laminated and germinal layer, cyst fluid, protoscoleces and daughter cysts if present) but only partially removes the host tissue adventitial layer of the CE cyst. This type of surgery also includes "subtotal cystectomy" that is nearly total cystectomy with incomplete removal of the adventitial layer of a CE cyst.
Puncture, Aspiration, Injection, Re-aspiration (PAIR)	Minimally invasive therapeutic percutaneous drainage of echinococcal cysts located in the liver and other abdominal locations that aims to destroy the germinal layer. It involves: (i) percutaneous puncture of cysts using ultrasonographic guidance, (ii) aspiration of cyst fluid, (iii) injection of a protoscolecidal agent for 10–20 min and (iv) re-aspiration of the fluid *(1)*.
radical surgery (in relation to CE)	Total cystectomy. Complete removal of a CE cyst, including the content (fluid, protoscoleces and daughter cysts if present) and all layers of the cyst (germinal and laminated parasite layers and host tissue adventitial layers).
reactivation	Appearance of daughter cyst(s) in the solid matrix of spontaneously inactivated CE4 cysts that shows an evolution towards a CE3b stage.
recurrence	Appearance of an active CE cyst (stages CE1–3) in the same location where a treated cyst was located, independent of the type of previous treatment.
standard catheterization (S-CAT)	Modification of the PAIR technique for the treatment of selected CE cysts; it includes the insertion of a catheter, whether or not it is temporarily left in the cyst (*2*).
uncomplicated cysts	Cysts without complications (see complicated cyst).
viable (metacestode, germinal layer, cyst, protoscoleces)	Parasitic structure of the metacestode which contains living cells able to proliferate in appropriate conditions.

Executive summary

Rationale and target audience

The purpose of this document is to provide technical guidance on the treatment of patients with cystic echinococcosis (CE). The aim is to ensure that such patients are not subjected to unnecessary invasive procedures; and that any procedure recommended is only provided in the context of infrastructure and expertise sufficient to ensure this is done safely.

These guidelines are intended for clinicians, health facility managers and health practitioners at different levels of health services and at all resource levels (low, middle- and high-income countries) that provide care for patients with CE. They will also be of relevance to health care policy-makers, health system administrators and implementors of neglected tropical disease (NTD) programmes.

The guidelines cover liver and lung CE cysts. For liver CE cysts, these guidelines are confined to choices for uncomplicated liver cysts. For complicated CE liver cysts, expert opinion is usually to use open surgery where services and medical expertise can carry this out safely. Pulmonary CE is usually managed surgically; these guidelines evaluate treatment of small (≤ 5 cm) lung cysts.

Methods

These guidelines were developed in accordance with WHO's procedures for guideline development.[1] This process included developing an algorithm to help identify the 11 priority questions set out using the population, intervention, comparator, and outcome (PICO) framework; retrieving evidence by the systematic review team; and assessing and synthesizing the evidence using the standard Cochrane "Risk of Bias" tool, the Review Manager (RevMan) software to assess the data, and the GRADE evidence profile system to assess the certainty of the evidence.

The Guideline Development Group (GDG) defined health service requirements for the various procedures, or "tiers", based on technical expertise, laboratory capacity, radiological equipment and surgical infrastructure to formulate tier-specific recommendations. Where it made sense to do so, the assessment of more than one PICO question was used to produce a recommendation.

Summary of recommendations

Overall, comparative reliable research on treatment options was absent, and decision was based on discussions by experts to develop a consensus. These guidelines include seven new conditional recommendations with the corresponding research evidence assessed as very low certainty. The cyst stages are described in section 1.2 and Fig. 3.

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1 A WHO guideline is any document, whatever its title, containing WHO recommendations about health interventions, whether they be clinical, public health or policy interventions. A standard guideline is produced in response to a request for guidance in relation to a change in practice, or controversy in a single clinical or policy area; it is not expected to cover the full scope of the condition or public health problem. A recommendation provides information about what policy-makers, health-care providers or patients should do; it implies a choice between different interventions that have an impact on public health and that have ramifications for the use of resources. All publications containing WHO recommendations are approved by the WHO Guideline Review Committee.

► Recommendations for the clinical management of uncomplicated hepatic CE cysts according to their classification.

Uncomplicated hepatic cysts: types CE1 or CE3a < 5 cm	**Recommendation 1:** In patients with uncomplicated hepatic cyst types CE1 or CE3a < 5 cm, treatment with albendazole (ALB) is suggested. This recommendation is applicable in any tier. Conditional recommendation with very low certainty evidence.
Uncomplicated hepatic cysts: types CE1 or CE3a 5–10 cm	**Recommendation 2:** In patients with uncomplicated hepatic cyst types CE1 or CE3a 5–10 cm, PAIR (Puncture, Aspiration, Injection, Re-aspiration) combined with ALB is suggested. PAIR should not be used if biliary communication is present. This recommendation requires tier 3 or tier 4 settings. Conditional recommendation with very low certainty evidence.
Uncomplicated hepatic cysts: types CE1 or CE3a > 10 cm	**Recommendation 3:** In patients with uncomplicated hepatic cyst types CE1 or CE3a > 10 cm, percutaneous treatment combined with ALB is suggested. PAIR is suggested rather than standard catheterization or surgery. PAIR should not be used if biliary communication is present. This recommendation requires tier 3 or tier 4 settings. Conditional recommendation with very low certainty evidence (where there was relevant research), or expert consensus (where there was no relevant research).
Uncomplicated hepatic cysts: types CE2 or CE3b ≤ 5 cm	**Recommendation 4:** In patients with uncomplicated hepatic cyst types CE2 or CE3b ≤ 5 cm, initial treatment with ALB alone is suggested. This recommendation is applicable in any tier. Conditional recommendation based on expert consensus.
Uncomplicated hepatic cysts: types CE2 or CE3b > 5 cm	**Recommendation 5:** In patients with uncomplicated hepatic cyst types CE2 or CE3b > 5 cm, surgery combined with ALB is suggested. This can be open surgery (in tiers 2–4) or laparoscopy (in tiers 3–4). Conditional recommendation with very low certainty evidence (where there was relevant research), or expert consensus (where there was no relevant research).
Use of praziquantel combined with ALB post-percutaneous/ surgical procedures for hepatic cyst types CE1, CE2, CE3a, CE3b	**Recommendation 6:** In CE patients undergoing percutaneous or surgical interventions, when spillage is suspected or has occurred, the combination praziquantel and ALB is suggested. Conditional recommendation based on expert consensus.

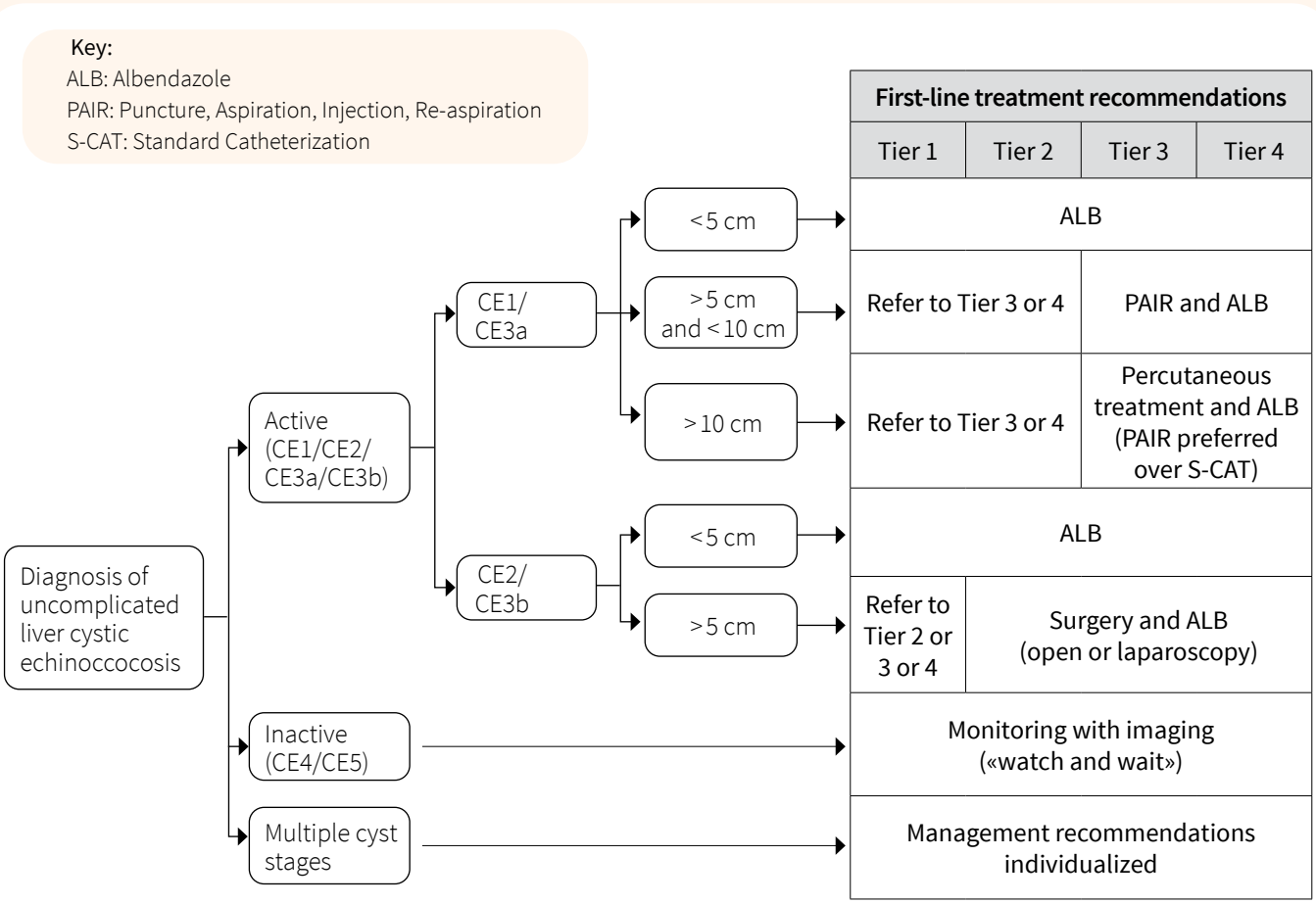
▶ Recommendations for the clinical management of uncomplicated lung CE cysts < 5 cm

Uncomplicated lung CE cysts ≤ 5 cm	**Recommendation 7:** In patients with uncomplicated active lung CE cysts < 5 cm, surgery is suggested. ALB should not be given before surgery. When spillage is suspected or has occurred, ALB after surgery is suggested. Lung surgery requires tier 4 settings. Conditional recommendation based on expert consensus.

Uncomplicated inactive cysts are not covered in these guidelines. Current practice is to "watch and wait", that is, to follow-up with imaging (ultrasonography or MRI). Surgery should be avoided as far as possible unless the inactive cyst is causing complications (e.g. cyst causing portal hypertension).

Patients with multiple hepatic cysts, with hepatic cysts in different stages, and with two or more organs involved (multi-organ involvement) will require individualized management.

Fig. 1 summarizes the recommendations for the first-line treatment of uncomplicated hepatic cysts, relating this to the tiers specified in the recommendations for each option.



Footnotes: Tiers (for full details see Table 2, p.7):
Tier 1: Medical doctor, basic laboratory capacity, ultrasound referral availability.
Tier 2: Tier 1 plus general surgeon, anaesthetic and operating theatre capacity, on-site ultrasonography.
Tier 3: Tier 2 plus laparoscopic surgeon, physician trained in PAIR, S-CAT, CT and fluoroscopy capacity.
Tier 4: Tier 3 plus thoracic surgery and interventional radiology capacity, MRI and MRCP capacity, advanced laboratory capacity.

Fig. 1. Algorithm for first-line treatment of uncomplicated liver CE cysts according to different health tiers based on health provider resources and capabilities

1. Introduction

1.1 Background

Human echinococcosis is part of a parasitic disease group that includes cystic echinococcosis (CE) caused by *Echinococcus granulosus sensu lato (s.l.)*, alveolar echinococcosis (AE) caused by *E. multilocularis*, and neotropical echinococcosis caused by *E. oligarthrus* and *E. vogeli.* The diseases of greatest relevance to human health are CE and AE. These guidelines refer to CE.

E. granulosus s.l. is genetically complex, involving numerous species or genotypes, not all of which cause infection in humans. Two species of *E. granulosus s.l.* are responsible for almost all recorded CE human infections *(3)*: *E. granulosus sensu stricto* (*s.s.*; G1, G3) and *E. canadensis* (G6, G7). These guidelines refer to all *E. granulosus* infections, as there is no convincing evidence for different treatment strategies based on the infecting species.

The life cycle of *E. granulosus s.l.* involves two animal hosts (Fig. 2): a carnivorous definitive host (typically canids, mainly dogs) and an intermediate host (typically livestock, mainly sheep, although other animals such as cattle, goats, camels, yaks, pigs and wild herbivores can also be infected). Humans become infected by accidentally ingesting parasite eggs from the faeces of an infected definitive host. The adult tapeworm (measuring up to 7 mm) resides in the definitive host's small intestine, producing microscopic eggs that are excreted in faeces. These eggs contaminate the environment (soil, grass, vegetables, water) and can be ingested by intermediate hosts, leading to larval (hydatid or metacestode or echinococcal cysts) development in body organs. Transmission to definitive hosts occurs when they ingest infected intermediate host tissues containing fertile cysts (those containing viable protoscoleces), resulting in the development of adult tapeworms *(4)*.

Human infection with *E. granulosus s.l.* leads to the development of one or more CE cysts located most often in the liver and lungs, and less frequently in the bones, kidneys, spleen, muscles, heart, central nervous system and virtually any other body location. These cysts may or may not be fertile (contain protoscoleces). Larger cysts may develop secondary (daughter) cysts internal to the primary cyst. The impact of the infection varies with the number, location and size of the cysts and, when symptomatic, manifests commonly with pain and compromised organ function, worsening as the cysts enlarge. The asymptomatic incubation period can last many months, years or even be lifelong, until the CE cysts grow to an extent that triggers symptoms or signs. Untreated cysts might pose a risk of rupture, which can result in severe complications such as anaphylactic shock, disseminated infection or mortality.

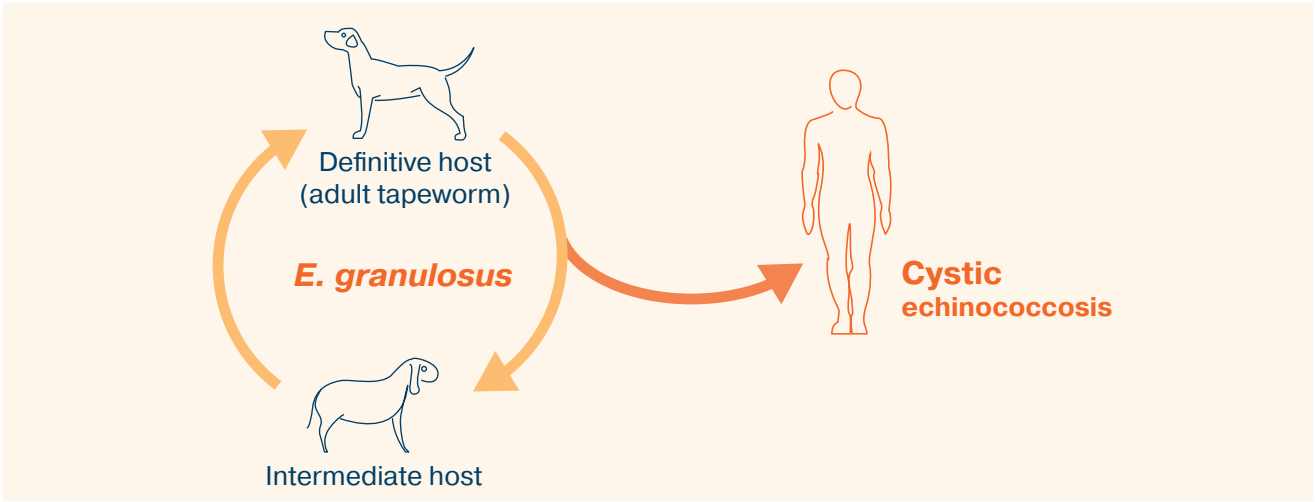


Fig. 2. Life cycle of *Echinococcus granulosus sensu lato*

1.1.1 Epidemiology

CE represents a substantial disease burden, especially in pastoral and rural communities in both low-income and upper-middle-income countries. It is a significant public health problem in large pastoral areas in South America, North Africa, Eastern and mediterranean Europe, the Middle East, Central Asia, the Russian Federation and China *(5)*. Consistently, highest prevalence is found among populations involved with sheep raising where people have close contact with their shepherd dogs.

1.1.2 Diagnosis

The diagnosis of CE is based on imaging techniques, primarily ultrasound or magnetic resonance imaging (MRI), while computed tomography (CT) is less reliable *(6)*, complemented by serology when imaging is not conclusive. Contrast-enhancement imaging allows excluding CE diagnosis in a case where the cyst takes contrast. No antigen detection tests are commercially available. Antibody detecting serological tests complement imaging findings, yet their limitations warrant careful consideration. In cases of sero-negativity, confirming a presumptive diagnosis might involve demonstrating the presence of protoscoleces and/or hooks by microscopic examination of the cyst fluid, histology, polymerase chain reaction (PCR) of cyst material *(7)* or observation of changes in the cyst ultrasound appearances on treatment, such as detachment of parasite layers in an unilocular cyst (suspected CE1) after percutaneous puncture or administration of ALB. Currently, there are no WHO guidelines for the diagnostic of CE, and this has been identified as a key research priority (section 6).

1.1.3 Prevention

The main tools for prevention of transmission are the regular deworming of dogs with praziquantel, and vaccination of sheep with the EG95 vaccine *(8)*. Infected livestock organs should be disposed of safely and should not be fed to dogs or other canids.

Strategies for the prevention of infection in humans include proper sanitation and hygiene practices, emphasizing thorough handwashing after contact with dogs, with their faeces or with soil contaminated with the parasite's eggs. In at-risk areas, it is important to wash vegetables that are eaten raw and to use safe water.

1.1.4 Treatment

Not all CE patients require treatment, and not all require invasive treatment. Inappropriate treatment may lead to iatrogenic complications. However, CE may result in severe complications which are disabling and even life-threatening if left untreated. With suboptimal or late treatment, patients often face reduced quality of life. CE is invariably expensive and complicated to treat, sometimes requiring extensive surgery and/or prolonged drug therapy. There are several options for the clinical management of CE: (i) antiparasitic drug treatment; (ii) percutaneous treatment of CE cysts with the PAIR (Puncture, Aspiration, Injection, Re-aspiration) technique, standard catheterization (S-CAT) or the modified catheterization technique (Mo-CAT); (iii) surgery; and (iv) the "watch and wait" approach.

The clinical management approach is primarily guided by an assessment of the signs and symptoms of the patient at presentation and involves patient factors such as age and comorbidities, and access to health infrastructures. The treatment of choice for uncomplicated CE is primarily based on the imaging characteristics of the cyst, following a stage-specific approach (when applicable), and on the health care infrastructure and human resources available *(9)*.

1.2 Staging of cystic echinococcosis cysts

The appropriateness of the various options for treatment of patients with hepatic CE depends on the stage of development of the parasitic cyst.
Cyst stages were first classified by ultrasound imaging by Gharbi et al *(10)* in relation to liver cysts, and later modified by the WHO Informal Working Group on Echinococcosis (WHO-IWGE) as described in Brunetti et al *(9)*. The classification *per se* applies to any cyst because it describes the morphology (except for osseous CE, as it

has an infiltrative morphology, so the classification does not apply here). However, the stage-specific treatment approach relates to hepatic CE and does not necessarily apply in all locations.
The WHO-IWGE Imaging sub-panel, provided updated definitions for these guidelines. They comprise the following stages (Fig. 3):

Active cysts, likely to contain viable protoscoleces:	
CE1. Active, unilocular, liquid content	Well-defined univesicular cyst, with round or oval shape, anechoic content, posterior acoustic enhancement, with or without low intensity floating echoes upon decubitus change (moving "hydatid sand") and with visible pathognomonic "double wall sign" consisting in the inner hyperechoic laminated layer and outer hypoechoic adventitial layer.
CE2. Active, multivesicular, liquid content	Well-defined multivesicular cyst, with round or oval shape, posterior acoustic enhancement, one or more daughter cysts filling in part or completely the fluid-filled cyst; the pathognomonic "honeycomb" appearance is provided by the thin, regular, continuous and avascular clearly distinguishable adjacent walls of juxtaposed daughter cysts (giving a septated appearance), without solid content.
CE3a. Transitional unilocular, liquid content with detached parasitic layers	Well-defined univesicular cyst with round or oval shape, posterior acoustic enhancement, and with partial or complete detachment of the laminated layer, visible as a hyperechoic thin and regular layer floating in the anechoic cyst content, giving a pathognomonic appearance, referred to as the "water lily sign". The whole layer must be identified as a continuous hyperechogenic structure, in different views. Low-intensity floating echoes upon decubitus change (moving "hydatid sand") may be present.
CE3b. Active multivesicular cyst, with partially solid content with daughter cysts	Well-defined multivesicular cyst with round or oval shape, posterior acoustic enhancement, and heterogeneous structure, encompassing avascular solid components and hypoechoic folded structures deriving from degenerating layers and one or more round daughter cysts with anechoic content, giving the pathognomonic "Swiss cheese" appearance.
Inactive stages:	
CE4. Solid content	Well-defined round or oval mass with or without posterior acoustic enhancement and with heterogeneous avascular solid content formed by the degenerated cyst layers, and hypoechoic folded structures deriving from degenerating layers in the mass and giving the pathognomonic "ball of wool" or "canalicular" or "cerebroid" appearance. Unlikely to contain viable protoscoleces.
CE5. Solid content with eggshell calcified wall	Well-defined round or oval mass with posterior acoustic shadow deriving from a complete or nearly complete egg-shell calcified wall, and heterogeneous avascular solid content (when acoustic shadow allows visualization) formed by the degenerated cyst layers and hypoechoic folded structures deriving from degenerating layers in the mass and giving the pathognomonic "ball of wool" or" canalicular" appearance. Non-viable.

NB: All CE cyst stages can show some wall calcification, so this feature, *per se*, does not indicate viability or non-viability of the cyst.

The WHO-IWGE Expert Consensus document *(9)* also included a "cystic lesions (CL)" cyst. CL is not a CE stage but indicates a cyst that could be a suspected young echinococcal cyst. CL is described as an unilocular cyst with anechoic content, without double wall sign, nor evident signs of non-parasitic aetiology (e.g. clear features of a biliary cyst). If serological and/or epidemiological criteria apply, this is a suspected CE case. The etiological diagnosis of CL cysts (CE or biliary cyst) necessitates further diagnostic steps *(11-13)*.

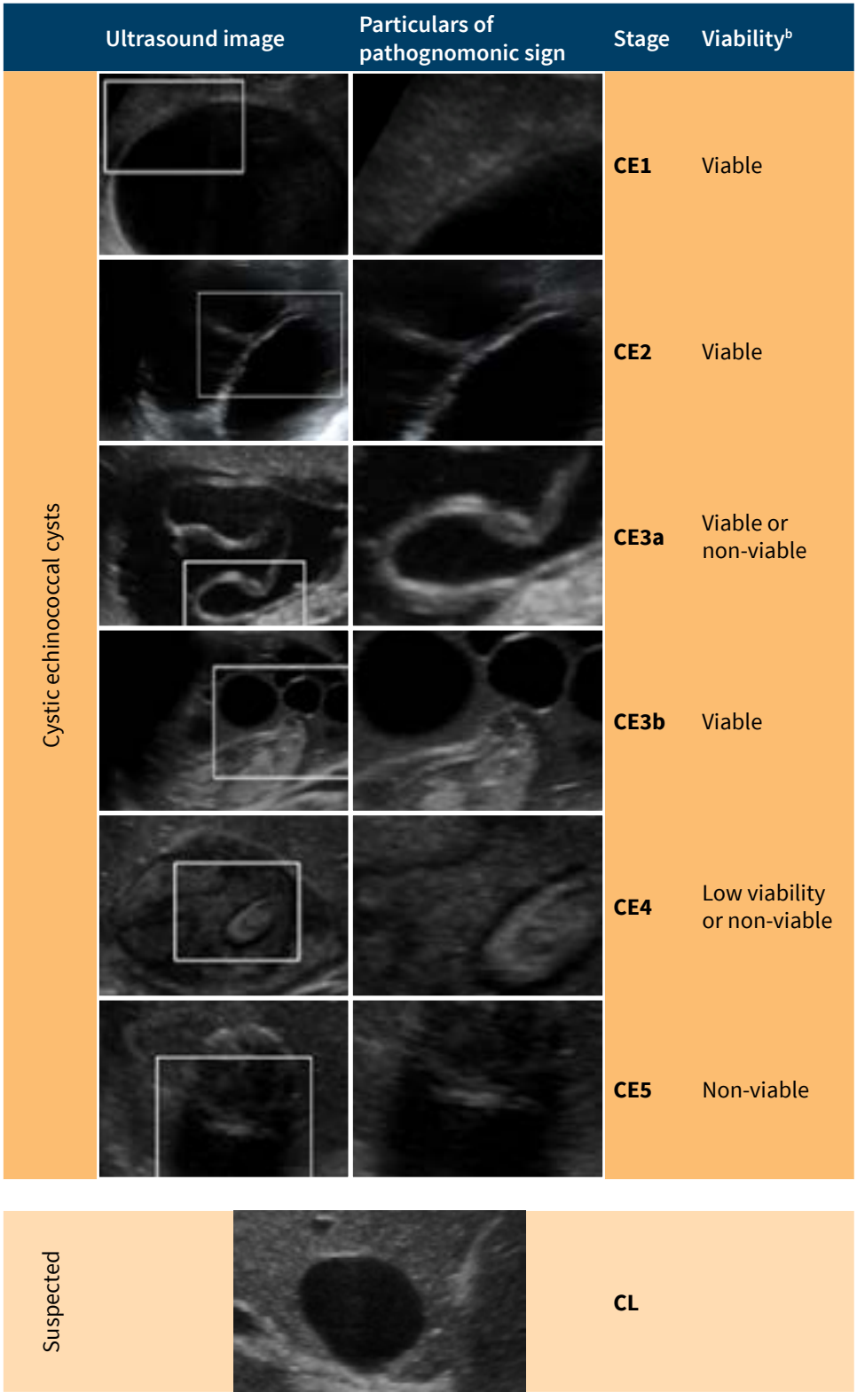


Fig. 3. Classification of CE cysts and description of CL[a] (suspected case of CE)

[a] CL: Cystic lesions with no visible pathognomonic features of *E. granulosus s.l.* aetiology. If serological and/or epidemiological criteria apply, this is a SUSPECTED CE case. Further diagnostic steps are required.
[b] Viability refers to the metacestode containing living cells able to proliferate in appropriate conditions. Does not imply fertility (i.e. presence of protoscoleces in the cyst, which may cause secondary CE upon dissemination).

1.3 Objectives and scope of these guidelines

The purpose of these guidelines is to provide guidance on the choice of treatment so that patients (adults and children) with CE cysts can be offered and receive appropriate and equitable treatment. The aim is to ensure that patients receive the most appropriate and affordable management in the context of infrastructure and expertise sufficient to ensure its safety, and without unnecessary invasive procedures or treatment, to avoid iatrogenic complications by using invasive interventions.

For complicated CE liver cysts, surgery is usually the treatment of choice, based on best medical practice as conveyed by the WHO-IWGE *(9)*. These guidelines are focused on the different choices for uncomplicated liver cysts. Pulmonary CE is usually managed by surgical intervention, but these guidelines evaluate the option of using ALB alone to treat small pulmonary cysts.

For uncomplicated inactive cysts, there are no recommendations in these guidelines since current best medical practice is follow-up with imaging (ultrasonography, CT or MRI), also known as the "watch and wait" approach *(9, 14)*. Surgery should be avoided as far as possible unless the inactive cyst is causing complications (e.g. cyst causing portal hypertension).

1.4 Target audience

These guidelines were developed for clinicians, health facility managers and health practitioners practising at all levels of health services (primary, secondary and tertiary health care) and at all resource levels (low, middle- and high-income countries) that provide care for patients with CE. They were also developed to inform health care policy-makers, health system administrators, insurance companies and NTD programme implementors.

2. Guideline development process and methods

2.1 WHO guideline development process

These guidelines were developed in accordance with the *WHO handbook for guideline development (15)* and with international standards for generating evidence-based guidelines. The process included:

- identifying priority questions using the population, intervention, comparator and outcome (PICO) framework;
- retrieving evidence by the systematic review team;
- assessing and synthesizing the evidence; and
- developing the recommendations.

2.2 Contributors to the guideline development process

The contributors to the guidelines include the WHO Guideline Steering Group, the Systematic Review Team, the Guideline Development Group (GDG), the External Review Group and the WHO Guideline Review Committee.

The GDG consisted of 17 members, 11 male and 6 female, representing the different regions of the world endemic for CE. It did not include patients or their representatives.

2.3 Declarations of interests

All members of the GDG, non-WHO staff participating in meetings or guideline development and external peer reviewers were required to submit a WHO Declarations of Interest form and confidentiality statements to the WHO secretariat. After reviewing the declarations, the WHO secretariat Steering Group concluded that there were no conflicts of interest sufficient to preclude any member from participating in the guideline development process.

The names and affiliations of the contributors to the guidelines and confirmation of the absence of significant conflicts of interest are listed in the Annex to this document.

2.4 Research question development

Through consultation and discussion within the GDG and the Systematic Review Team, 11 PICO questions were developed concerning areas of equipoise in the treatment of people with uncomplicated hepatic or pulmonary CE. These PICO questions are summarized in Table 1, and the detailed PICO questions are included in Web Annex A. Question development employed expert knowledge and literature reviews of relevant evidence, mapped to a clinical pathway algorithm to identify areas of variation in practice. This methodology algorithm is included in Web Annex A.

Table 1. PICO questions used to develop these guidelines (the elements of each PICO question are included in Web Annex A)

	Research (PICO) questions
P1	For treating uncomplicated hepatic cyst types CE1 or CE3a < 5 cm, is PAIR combined with ALB as effective and safe as ALB alone?
P2	For treating uncomplicated hepatic cyst types CE1 or CE3a 5–10 cm, is PAIR combined with ALB as effective and safe as ALB alone?
P3	For treating uncomplicated hepatic cyst types CE1 or CE3a 5–10 cm, is surgery combined with ALB as effective and safe as PAIR combined with ALB?
P4	For treating uncomplicated hepatic cyst types CE1 or CE3a > 10 cm, is standard catheterization combined with ALB as effective and safe as PAIR combined with ALB?
P5	For treating uncomplicated hepatic cyst types CE1 or CE3a > 10 cm, is standard catheterization combined with ALB as effective and safe compared to surgery combined with ALB?
P6	For treating uncomplicated hepatic cyst types CE2 or CE3b ≤ 5 cm, is surgery combined with ALB as effective and safe as ALB alone?
P7	For treating uncomplicated hepatic cyst types CE2 or CE3b 5–10 cm, is surgery combined with ALB as effective and safe as ALB alone?
P8	For treating uncomplicated hepatic cyst types CE2 or CE3b of any size, is laparoscopic surgery combined with ALB as effective and safe as open surgery combined with ALB?
P9	For treating uncomplicated hepatic cyst types CE2 or CE3b of any size, is modified catheterization technique (Mo-CAT) combined with ALB as effective and safe as surgery combined with ALB?
P10	Is praziquantel combined with ALB as effective and safe as ALB alone for treating active cysts (cyst types CE1, CE2 or CE3a, CE3b) when given pre- and post- percutaneous or surgical interventions?
P11	For treating uncomplicated lung CE cysts of ≤ 5 cm, is ALB as effective and safe as surgery combined with ALB?

The GDG were cognisant that safe delivery of optimal treatment would depend on the available health care professional expertise and health care facility resources (laboratory capacity, radiological equipment and surgical infrastructure).

The GDG first examined the WHO health systems classification, including the Universal Health Coverage Service Planning Delivery & Implementation (SPDI) platform. While the SPDI platform provided an overarching framework, the treatment options for CE have very specific requirements in terms of health care professional

expertise and health care resources. The GDG then developed health system tiers. This required several meetings and broader correspondence to come to a consensus. Each treatment option was mapped to a tier considered to have sufficient expertise and resources to deliver that treatment option safely. The tiers were categorized into four, ranging from the least sophisticated (tier 1) to the most sophisticated and well-resourced category (tier 4). The tiers are based on the health provider resources and do not account for the patient's financial resources, health insurance or accessibility. The tiers were then mapped to each research question. The tiers are described in Table 2.

Table 2. Health care system tiers for managing different treatment options for CE, according to available expertise and resources

Tier	Health care worker technical expertise required	Surgical infrastructure required	Radiological capacity required	Laboratory required	Intervention(s) possible
Tier 1	Medical doctor	Not available	Referral access to ultrasonography	Access to facilities for complete blood cell count, liver function tests.	Albendazole
Tier 2	General surgeon Anaesthesiologist Nursing care	Operating theatre Inpatient facility with monitoring	Ultrasound on site	Laboratory tests as needed for anaesthesia	Tier 1 and Surgery (non-radical only)
Tier 3 (includes expertise and facilities available in tier 2)	Surgeon with laparoscopic skills and surgeon, radiologist or physician with a relevant speciality trained in PAIR and S-CAT	General surgery and laparoscopic surgery facilities Inpatient facility with monitoring and access to ICU	CT scan Fluoroscopy	Laboratory tests as needed for anaesthesia	Tier 2 and Surgery (radical and non-radical) Laparoscopic Surgery PAIR Standard catheterization
Tier 4 (includes expertise and facilities available in tier 3)	General and laparoscopic surgeons Interventional Radiologists Thoracic Surgeon	Interventional Radiology Facilities and Procedure Room	MRI and MRCP	Routine clinical pathology, biochemistry and microbiology	Tier 3 and Modified Catheterization Technique Thoracic (lung) surgery

CT: computed tomography, PAIR: Puncture-Aspiration-Injection-Re-aspiration, ICU: Intensive care unit, MRCP: Magnetic resonance cholangiopancreatography, MRI: Magnetic resonance imaging, S-CAT: Standard catheterization.

2.5 Evidence synthesis and assessment

Details of the literature search, including search strategies, study selection process and results, are given in Web Annex A; it also identifies the studies excluded, with reasons for their exclusion.

The outcomes assessed were inactivity of cysts at > 12 months, change in symptoms, cyst recurrence, secondary dissemination, other complications due to disease progression, complications due to the intervention, duration of hospital admission and death within 28 days.

Data extraction was conducted by the Systematic Review Team, including characteristics of the study population, intervention, comparator, and outcomes. The same team conducted the risk of bias analysis using the standard Cochrane Collaboration's "Risk of Bias" tool *(16)*. The summary of the risk of bias assessments

of included studies is included in Web Annex B. Data were analysed using pair-wise comparisons by research question using Review Manager (RevMan) software from Cochrane *(17)*.

The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) evidence profiles system for assessing the certainty of evidence was applied as recommended in the *Cochrane handbook for systematic reviews of interventions (18)*. GRADE has four levels of evidence, also known as certainty in evidence: very low, low, moderate and high (Table 3).

When no research evidence was identified, expert consensus was used to formulate recommendations within the evidence-to-decision framework (as explained below).

Table 3. Certainty of evidence used in GRADE and its interpretation

Certainty of evidence	What it means
High	We are very confident that the true effect lies close to the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Source: WHO handbook for guideline development *(15)*.

2.6 From evidence to recommendations

Evidence-to-decision frameworks were used to produce the recommendations and were produced for each PICO question. They included the following criteria: benefits and harms (desirable and undesirable effects); certainty of the evidence about the effects, values and preferences; balance of effects; resources required; certainty of evidence of required resources; cost effectiveness; health equity; acceptability; and feasibility. For patients values and preferences, a qualitative literature review and interviews with care providers of people with CE was undertaken to provide insights on patient treatment preferences (summary available in Web Annex A). Evidence-to-decision evaluations and the summary of judgements for each PICO question are available in Web Annex B. For some recommendations, more than one PICO question was used.

Strength and interpretation of recommendations

There are two types of recommendations: strong recommendations in which the GDG is confident that the desirable effects (benefits) of adherence to the recommendation outweigh the undesirable consequences (harms); and conditional or weak recommendations in which the GDG is less certain about the balance between the benefits and harms or disadvantages of implementing a recommendation. The interpretation of the different types of recommendations by different kinds of stakeholder is shown in Table 4 *(15)*.

Table 4. Interpretation of strong and conditional recommendations for an intervention

Audience	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action; only a small proportion would not. Formal decision aides are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Most individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Adherence to the recommendation could be used as a quality criterion or performance indicator.	Different choices will be appropriate for individual patients, who will require assistance in arriving at a management decision consistent with his or her values and preferences. Decision aides may be useful in helping individuals make decisions consistent with their values and preferences.
Policy makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

Source: WHO handbook for guideline development *(15)*.

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3. Evidence and recommendations

3.1 Recommendations for the clinical management of uncomplicated hepatic CE cysts according to their classification

3.1.1 Uncomplicated hepatic cyst types CE1 or CE3a < 5 cm

Recommendation 1	**In patients with uncomplicated hepatic cyst types CE1 or CE3a < 5 cm, treatment with ALB is suggested. This recommendation is applicable in any tier.** ***Conditional recommendation with very low certainty evidence.***
Background	ALB is an accepted treatment in early active cyst stages. PAIR is available in some centres (tiers 3 and 4), but it is not without risk.
Summary of the evidence	This recommendation is based on PICO question 1 which compared PAIR combined with ALB to the use of ALB alone for small uncomplicated CE cysts. The evidence was limited to a single small randomized trial of 20 participants published in 1993 with limited follow up in which data concerning cysts < 5 cm could not be disaggregated from data concerning larger cysts *(19)*. The GDG recognized the risks and possible complications of using PAIR and concluded that this limited the feasibility and acceptability of this intervention.
Certainty of the evidence	The overall certainty of evidence was very low.
Additional factors considered	• ***Benefits and harms*** The GDG reviewed the desirable and undesirable effects and came into a consensus that the balance of effects favours ALB alone. • ***Health equity*** ALB is widely available as listed on the WHO Model List of Essential Medicines and is a low-cost medication in most settings. PAIR availability is limited and expensive due to the technical and skilled expertise required. Recommending PAIR will likely create inequity between those who can afford it versus those who cannot, and in places where it is available freely versus where it is not. • ***Acceptability*** ALB is considered to be acceptable to most people as an oral medication with a known safety profile. The acceptability of using PAIR combined with ALB among different stakeholders is likely to vary. • ***Resource implications*** Health facilities in most settings have access to ALB. It is a low-resource intensive treatment. • ***Feasibility*** In most primary care settings and in some resource limited settings, PAIR is not feasible. The feasibility of implementing this intervention widely varies depending on the country and even the health care setting.
Implementation considerations	1. ALB should be given orally, at a dosage of 10–15 mg/kg/day in two divided doses (up to 400 mg twice a day), with a fat rich meal to increase its bioavailability *(9)*. It should be administered continuously, without the monthly treatment interruptions recommended in the 1980s. The treatment duration depends on the individual situation, stage and size of the CE cyst. Current recommendations suggest continuous treatment for 3–6 months *(14)*. It is

Implementation considerations (continued)	important to use high-quality ALB (branded or generic) that contains the required amount of bioavailable drug. 2. ALB is contraindicated in cysts at risk of rupture and in the first trimester of pregnancy *(9)*. Later in pregnancy, potential benefits may warrant use of ALB despite potential risks. Contraceptive measures are necessary for women of reproductive age while on long-term ALB. Benzimidazoles must be used with caution in patients with chronic hepatic disease and avoided in those with bone-marrow depression. Monitoring of side-effects is based on liver enzymes for hepatotoxicity and blood cell count. 3. Follow-up imaging at 3–6 months and thereafter once a year for a minimum of 5 consecutive years after inactivation may help evaluate the success of treatment and monitor for any recurrence of the cysts. 4. A lack of response is defined as an absence of cyst changes after 3 months of treatment (detachment of the parasitic layers from the outer cyst wall, size reduction, or stage modification). Complete response should be evaluated not earlier than 12 months after treatment end.
Remarks	Based on expert opinion, if there is a lack of response to an initial course of ALB, a repeat course of ALB could be considered.

3.1.2 Uncomplicated hepatic cyst types CE1 or CE3a 5–10 cm

Recommendation 2	**In patients with uncomplicated hepatic cyst types CE1 or CE3a 5–10 cm, PAIR combined with ALB is suggested. PAIR should not be used if biliary communication is present. This recommendation requires tier 3 or tier 4 settings.** ***Conditional recommendation with very low certainty evidence***.
Background	Treatment options for individuals with medium-sized active cysts in stage CE1 or CE3a include PAIR combined with ALB or surgery combined with ALB. These interventions require different levels of health professional expertise as well as differing radiological and surgical facilities.
Summary of the evidence	This recommendation is based on PICO questions 2 and 3. In comparison to albendazole alone, the evidence for the use of PAIR with ALB was limited to one randomized trial of 20 participants from 1993 with limited follow-up and no disaggregated data on outcomes specifically for cysts > 5 cm and < 10 cm *(19)*. In comparison to surgery, we identified two small randomized controlled trials (RCTs) conducted in India 20 years apart, including a total of 92 participants, in which surgery (combined with ALB in one study) was compared to PAIR or another percutaneous method (the double percutaneous aspiration injection technique, DPAI) with ALB *(20, 21)*. Participants undergoing surgery in both studies underwent open drainage and simple cystectomy. The older study did not report whether the surgical group received ALB, and classified cysts as either univesicular or multivesicular. Outcome data for both studies were unable to be separated by cyst stage or size. The mean follow-up time in the older study was 17 months *(20)*, and 26 months with high losses to follow-up in the more recent study *(21)*. All these factors limit the applicability of evidence. The GDG also recognized the risks and possible complications for surgery when the cyst size was > 5 cm and < 10 cm. The GDG also considered the data summarized from three observational single arm studies regarding therapeutic application of PAIR in medium sized cysts *(22-24)*. These authors reported cyst volume reduction, solidification and low relapse rate (< 3.5%) after PAIR.

Certainty of the evidence	The certainty of evidence available for the use of PAIR and ALB was low to very low.
Additional factors considered	• ***Benefits and harms*** The GDG agreed that the evidence is limited and, based on expert opinion, it is believed that there is increased treatment success, reduced recurrence rates and symptom improvement with PAIR and ALB over surgery and ALB. PAIR would provide a shorter duration of the overall treatment, faster recovery and would be preferred by both clinicians and patients considering that when done by expert physicians with technical support, the success rate is very high, and the chance of major complications is low. However, it is important to consider individual patient characteristics (location and size of cyst) and available resources and skill sets when determining the most appropriate treatment approach. The undesirable effects of percutaneous treatments and surgical interventions can vary in terms of their magnitude and likelihood. Adverse events like anaphylaxis or other complications of PAIR are rare when the technique is undertaken by experts with the required facilities. The GDG acknowledged the possible long-term complications of PAIR while surgery could be curative. • **Health equity** PAIR availability is limited compared to surgery; however, PAIR is less expensive. This may create inequity between those who can afford PAIR versus those who cannot, and in places where it is available versus those where it is not. • **Acceptability** The GDG considered that PAIR is acceptable to both patients and clinicians. • **Resource implications** Either PAIR or surgery could increase out-of-pocket costs related to the procedure, travel and time in hospital. • **Feasibility** The feasibility of implementing PAIR or surgery widely varies depending on the country, the health care setting, the availability of skilled manpower and resources, and on infrastructure.
Implementation considerations	1. PAIR is only recommended where there is no biliary communication. If bile-stained cyst fluid is aspirated (the assessment is made through visual inspection of aspirate for bile contamination and checking for bilirubin in the aspirated cyst fluid) or contrast is observed in the biliary tract after having been injected into the cyst during a planned PAIR procedure, it is strongly recommended that injection of a protoscolecidal agent after aspiration is not performed. An alternative treatment is percutaneous drainage (S-CAT) without injection of protoscolecidal agent and prolonging administration of ALB to 6 months. Surgery or medical management can also be considered. 2. Standard practice is to give ALB for 1–7 days prior to PAIR and then continue for 1–3 months post-PAIR *(25)*, at a dose of 10–15 mg/kg/day (up to 400 mg twice a day) in two divided doses with a fat-rich meal to increase its bioavailability; duration can be extended if considered appropriate. It is important to use high-quality ALB (branded or generic) that contains the required amount of bioavailable drug. A two-week post-procedure course of praziquantel in addition to ALB may be considered if there is spillage of cyst contents (see recommendation 6).

Implementation considerations (continued)

3. For larger hepatic CE cysts, especially for CE1 cyst types which are more prone to ALB-related perforation, ALB should be given for a shorter period before procedure (sometimes only once) to reduce the risk of perforation.
4. After PAIR, patients must be closely monitored for potential complications including anaphylaxis, infection or bleeding. Monitoring of adverse events to ALB treatment should also be implemented (see 5 below).
5. ALB is contraindicated in cysts at risk of rupture and in the first trimester of pregnancy *(9)*. Later in pregnancy, potential benefits may warrant use of ALB despite potential risks. Contraceptive measures are necessary for women of reproductive age while on long-term ALB. Benzimidazoles must be used with caution in patients with chronic hepatic disease and avoided in those with bone-marrow depression. Monitoring of side-effects is based on liver enzymes for hepatotoxicity and blood cell-count.
6. In cases where surgical intervention is chosen for individuals with uncomplicated CE1 or CE3a cysts 5–10 cm in size, the surgical procedure can be performed either through an open or laparoscopic approach, depending on the location of the cyst, the expertise of the surgical team and the availability of resources. For any patient in which surgery is an option, individual patient factors such as general health, co-morbidities and age should be considered before the final decision is made.
7. Follow-up imaging at 3–6 months and thereafter once a year for a minimum of 5 consecutive years after inactivation may help evaluate the success of treatment and monitor for any recurrence of the cysts.
8. A lack of response is defined as an absence of cyst changes after 3 months of treatment (detachment of the parasitic layers from the outer cyst wall, size reduction, or stage modification). Complete response should be evaluated not earlier than 12 months after treatment end.

3.1.3 Uncomplicated hepatic cyst types CE1 or CE3a > 10 cm

Recommendation 3	**In patients with uncomplicated hepatic cyst types CE1 or CE3a > 10 cm, percutaneous treatment combined with ALB is suggested. PAIR is suggested rather than standard catheterization or surgery. PAIR should not be used if biliary communication is present. This recommendation requires tier 3 or tier 4 settings.** ***Conditional recommendation with very low certainty of evidence (where there was relevant research), or expert consensus (where there was no relevant research).***
Background	Treatment options for individuals with large, active CE1 or CE3a cysts include percutaneous aspiration techniques (either S-CAT or PAIR) with ALB, or surgery with ALB. These interventions require different levels of health professional expertise as well as differing radiological and surgical facilities.
Summary of the evidence	This recommendation is based on PICO questions 4 and 5. The evidence to compare PAIR and ALB versus S-CAT and ALB was limited to one randomized trial conducted in Türkiye with 38 participants *(26)*. Data disaggregated by cyst size were not reported; the median cyst size was 4 cm, suggesting most of the evidence synthesis was applicable only to smaller cysts. However, the GDG judged that the evidence would likely also be applicable to larger cysts. Data were reported on recurrence, complications and duration of hospital admission. There were no prospective comparative trial studies comparing S-CAT and ALB versus surgery and ALB. The GDG agreed that in health care centres where both S-CAT and surgery were available and safe, S-CAT and ALB would be associated with the benefits of lower costs, shorter duration of hospital admission, fewer complications and a higher patient safety profile (including when a biliary communication is suspected).
Certainty of the evidence	Evidence was uncertain for recurrence and minor complications (very low certainty evidence) when S-CAT and ALB was compared to PAIR and ALB. There seemed to be a trend towards longer hospital stay and increased minor complications when using S-CAT and ALB, but the evidence was uncertain. The GDG agreed that the certainty of evidence available in favour of PAIR and ALB is very low.
Additional factors considered	• ***Benefits and harms*** The GDG favoured a percutaneous approach, either PAIR or S-CAT, over ALB and surgery. Centres proficient in both percutaneous techniques generally opt for PAIR. The choice between PAIR and S-CAT varies depending on location and type of cyst, and on the capabilities and experience of the clinician. Recurrence and complications are higher with S-CAT and the duration of hospitalization tends to be longer as compared with PAIR. The difference between the two methods is very small, and the GDG emphasized the need to consider additional factors such as clinician and patient preferences. The GDG emphasized the risks associated with protoscolecidal agents with PAIR in cases of biliary communication. • ***Health equity*** Health equity would vary depending on values and preferences. • ***Acceptability*** The GDG believed that patients would likely opt for a procedure with lower complication rates and PAIR or S-CAT would be easier to accept over major abdominal surgery.

Additional factors considered (continued)	• ***Resource implications*** The decision between S-CAT and PAIR is influenced by the experience of the clinician. Surgery also demands specific expertise in hepatobiliary surgery. The GDG agreed that PAIR is cost–effective, and several GDG members opined that the costs were higher when S-CAT was used in the centres which used both. Experts anticipate longer hospital stays and more complications with surgery, implying potential higher direct and indirect costs. • ***Feasibility*** It will vary depending on the settings. PAIR is practised more widely than S-CAT
Implementation considerations	1. Many health care settings may not have the appropriate expertise and resources available to safely deliver PAIR, S-CAT or surgery. In these settings, the safest treatment option utilizing available expertise and resources with consideration of patient treatment preferences is recommended. 2. PAIR is only recommended where there is no biliary communication, and cysts > 10 cm have high risk of such fistulas, so special care should be taken. If bile-stained cyst fluid is aspirated (the assessment is made through visual inspection of aspirate for bile contamination and checking for bilirubin in the aspirated cyst fluid) or contrast is observed in the biliary tract after having been injected into the cyst during a planned PAIR procedure, it is strongly recommended that injection of a protoscolecidal agent after aspiration is not performed. An alternative treatment is percutaneous drainage (S-CAT) without injection of protoscolecidal agent and prolonging the administration of ALB to 6 months. Surgery or medical management can also be considered. 3. Standard practice is to give ALB for 1–7 days prior to the percutaneous treatment and then continue for 1–3 months post percutaneous treatment *(25)*, at a dose of 10–15 mg/kg/day (up to 400 mg twice a day) in two divided doses with a fat-rich meal to increase its bioavailability; duration can be extended if considered appropriate. It is important to use high-quality ALB (branded or generic) that contains the required amount of bioavailable drug. A 2-week post-procedure course of praziquantel in addition to ALB may be considered if there is spillage of cyst contents (see recommendation 6). 4. For larger hepatic CE cysts, especially for CE1 cyst types which are more prone to ALB- related perforation, ALB should be given for a shorter period before procedure (sometimes only once) to reduce the risk of perforation. 5. After percutaneous treatments, patients must be closely monitored for potential complications including anaphylaxis, infection or bleeding. Monitoring of adverse events to ALB should also be implemented (see 6 below). 6. ALB is contraindicated in cysts at risk of rupture and in the first trimester of pregnancy *(9)*. Later in pregnancy, potential benefits may warrant use of ALB despite potential risks. Contraceptive measures are necessary for women of reproductive age while on long-term ALB. Benzimidazoles must be used with caution in patients with chronic hepatic disease and avoided in those with bone-marrow depression. Monitoring of side-effects is based on liver enzymes for hepatotoxicity and blood cell count. 7. In cases where surgical intervention is chosen for individuals with uncomplicated CE1 or CE3a cysts > 10 cm in size, the surgical procedure can be performed either through an open or laparoscopic approach, depending on the location of the cyst, the expertise of the surgical team and the availability of resources. For any patient in which surgery is an option, individual patient factors such as general health, co-morbidities and age should be considered before the final decision is made.

Implementation considerations (continued)	8. Follow-up imaging at 3–6 months and thereafter once a year for a minimum of 5 consecutive years after inactivation may help evaluate the success of treatment and monitor for any recurrence of the cysts. 9. A lack of response is defined as an absence of cyst changes after 3 months of treatment (detachment of the parasitic layers from the outer cyst wall, size reduction, or stage modification). Complete response should be evaluated not earlier than 12 months after treatment end.

3.1.4 Uncomplicated hepatic cyst types CE2 or CE3b ≤ 5 cm

Recommendation 4	**In patients with uncomplicated hepatic cyst types CE2 or CE3b ≤ 5 cm, initial treatment with ALB alone is suggested. This recommendation is applicable in any tier.** ***Conditional recommendation based on expert consensus.***
Background	Treatment options for individuals with small to medium active cysts at stage CE2 or CE3b include ALB alone and surgery with ALB. These interventions require different levels of health professional expertise as well as differing radiological and surgical facilities.
Summary of the evidence	This recommendation is based on PICO question 6. No RCT or non-randomized prospective comparative trials were identified. The GDG formulated the recommendation based on expert consensus, risk–benefit assessment, global applicability, and consideration of clinician expertise/skill, infrastructure capacity and patient treatment preferences. The GDG agreed that surgery combined with ALB would be associated with large costs and possibly greater complications (inaccessible cysts in deep parenchyma) compared to ALB alone. Therefore, a trial of ALB alone should be offered initially as it might prevent an unnecessary surgical procedure. The GDG also acknowledged that relapse and treatment failure are higher with ALB alone than with surgery and ALB. Hence, though ALB may be tried initially, response should be closely monitored and escalated to surgery combined with ALB in the event of treatment failure.
Certainty of the evidence	The recommendation was formulated by the GDG using expert consensus within the evidence-to-decision framework.
Additional factors considered	• ***Benefits and harms*** The GDG expressed the view that surgery may be associated with iatrogenic morbidity and mortality and ALB alone may be effective in a proportion of these small cysts. • ***Health equity*** ALB is a low cost and generally widely available medication. Surgery is an expensive intervention and is likely to create inequity between those who can afford it and those who cannot; places where it is available freely and places where it is not. • ***Acceptability*** ALB is considered to be generally acceptable to most patients as an oral medication with a known safety profile.

Additional factors considered (continued)	• ***Resource implications*** ALB treatment is less invasive and requires less resources for implementation than surgery. In situations where surgery is required, resource requirements include the costs associated with the surgery itself, hospitalization, transportation and indirect expenses. • ***Feasibility*** Treatment with ALB is generally highly feasible to implement.
Implementation considerations	1. ALB should be given orally, at a dosage of 10–15 mg/kg/day in two divided doses (up to 400 mg twice a day), with a fat-rich meal to increase its bioavailability *(9)*. It should be administered continuously, without the monthly treatment interruptions recommended in the 1980s. The treatment duration depends on the individual situation, stage and size of the CE cyst. Current recommendations suggest continuous treatment for 3–6 months *(14)*. It is important to use high-quality ALB (branded or generic) that contains the required amount of bioavailable drug. 2. ALB is contraindicated in cysts at risk of rupture and in the first trimester of pregnancy *(9)*. Later in pregnancy, potential benefits may warrant use of ALB despite potential risks. Contraceptive measures are necessary for women of reproductive age while on long-term ALB. Benzimidazoles must be used with caution in patients with chronic hepatic disease and avoided in those with bone-marrow depression. Monitoring of side-effects is based on liver enzymes for hepatotoxicity and blood cell count. 3. Follow-up imaging at 3–6 months and thereafter once a year for a minimum of 5 consecutive years after inactivation may help evaluate the success of treatment and monitor for any recurrence of the cysts. 4. A lack of response is defined as an absence of cyst changes after 3 months of treatment (detachment of the parasitic layers from the outer cyst wall, size reduction or stage modification). Complete response should be evaluated not earlier than 12 months after end of treatment.
Remarks	Since ALB alone is known to have a higher risk of relapse, in the event of non-response at 3 months, based on expert opinion, surgery (non-radical or radical approaches) should be offered along with continued ALB. For any patient in which surgery is an option, individual patient factors such as general health, co-morbidities and age should be considered before the final decision is made.

3.1.5 Uncomplicated hepatic cyst types CE2 or CE3b > 5 cm

Recommendation 5	**In patients with uncomplicated hepatic cyst types CE2 or CE3b > 5 cm, surgery combined with ALB is suggested. This can be open surgery (in tiers 2–4) or laparoscopy (in tiers 3–4).** ***Conditional recommendation with very low certainty of evidence (where there was relevant research), or expert consensus (where there was no relevant research).***
Background	Treatment options for individuals with active hepatic cysts at stage CE2 or CE3b include ALB alone, surgery with ALB (laparoscopic or open) and modified catheterization technique (Mo-CAT) with ALB. These interventions require different levels of health professional expertise as well as differing radiological and surgical facilities.

Summary of the evidence	This recommendation is based on PICO questions 7, 8 and 9. No prospective comparative trials comparing ALB alone and surgery combined with ALB were identified. The evidence comparing laparoscopic surgery and ALB, and open surgery and ALB, was limited to two trials: one RCT conducted in Pakistan including 82 participants; and one prospective comparative trial conducted in the Islamic Republic of Iran including 73 participants *(27, 28)*. The trial in Pakistan included cysts 5 cm or greater in diameter; follow-up time was 12 months. The trial in the Islamic Republic of Iran did not report which cyst stages were included, and not all participants received ALB in conjunction with surgery; data were unable to be separated by participant receipt of ALB. No RCT or non-randomized prospective comparative trials comparing Mo-CAT to surgery were identified. The GDG acknowledged the limited expertise of Mo-CAT globally and the lack of information regarding possible undesirable effects. Resource considerations, such as costs and feasibility, underscore the challenges associated with implementing Mo-CAT even in tier 4 settings.
Certainty of the evidence	The certainty of the evidence for PICO question 8 is very low. The GRADE method could not be applied to PICO questions 7 and 9 due to a lack of evidence. The recommendation was formulated by the GDG using expert consensus within the evidence to decision framework.
Additional factors considered	• ***Benefits and harms*** In health care centres where surgery and ALB are available and safe, even if associated with larger costs, this option would have the benefits of lower relapses and fewer complications compared to ALB alone. Surgical complications are rare in the hands of experienced surgeons, but rare complications include risk of intraoperative cyst rupture leading to anaphylaxis or dissemination, especially in cases with multiple daughter cysts. There is not enough research evidence on the desirable and undesirable effects of the Mo-CAT procedures. • ***Values and preferences*** There are no studies that evaluate patients' values and preferences, but the qualitative research undertaken by the evidence team reveals that there is usually concern about the scar of surgery in young patients and children. • ***Health equity*** Surgery combined with ALB may be unaffordable for some patients and is likely to create inequity between those who can afford it versus those cannot; places where it is free of charge versus where it is not. • ***Acceptability*** Surgery combined with ALB is generally acceptable to patients and clinicians. • ***Resource implications*** Costs could be higher for open surgery than with laparoscopic surgery. Surgery is a familiar procedure in many settings; laparoscopy is only available in tiers 3 and 4, while Mo-CAT can only be implemented in tier 4, in a handful of centres with skilled personnel around the world. • ***Feasibility*** Feasibility will depend on clinician preference and health facilities available. Mo-CAT is a procedure with limited accrued experience in most settings, with evidence emerging only in a few centres in Asia.

Implementation considerations

1. For any patient in which an invasive procedure, especially surgery, is an option, individual patient factors such as general health, comorbidities and age should be considered before the final decision is made.
2. The choice between open or laparoscopic surgery will depend on the setting infrastructure, availability of laparoscopy, site of the cyst and cyst characteristics, expertise and experience of the local clinical team, surgeon's preference and patient choice. Laparoscopy is favoured for peripheral, superficial cysts, especially in paediatric cases, and open surgery should be chosen when a cyst is deep or in other complicated scenarios.
3. Surgical challenges include inaccessibility when dealing with small cysts deep within the liver parenchyma, particularly in segments 7 and 8, and in individuals with underlying comorbidities.
4. If opting for Mo-CAT, it is crucial to reduce the risk of recurrence by ensuring thorough removal of all cyst content and the germinal layer. T2-weighted MRI in addition to ultrasound and cavitography can be used to monitor the efficacy of treatment between sessions.
5. Standard practice is to give ALB for 1–7 days prior to the surgical procedure and then continue for 1–3 months post procedure, at a dose of 10–15 mg/kg/day (up to 400 mg twice a day) in two divided doses with a fat-rich meal to increase its bioavailability; duration can be extended if considered appropriate. It is important to use high-quality ALB (branded or generic) that contains the required amount of bioavailable drug. A two-week post-procedure course of praziquantel in addition to ALB may be considered if there is spillage of cyst contents (see recommendation 6).
6. For the larger hepatic CE cysts, ALB should be given for a shorter period before procedure (sometimes only once) to reduce the risk of perforation.
7. After surgery, patients must be closely monitored for potential complications including anaphylaxis, infection or bleeding. Monitoring of adverse events to ALB should also be implemented (see 7 below).
8. ALB is contraindicated in cysts at risk of rupture and in the first trimester of pregnancy *(9)*. Later in pregnancy, potential benefits may warrant use of ALB despite potential risks. Contraceptive measures are necessary for women of reproductive age while on long-term ALB. Benzimidazoles must be used with caution in patients with chronic hepatic disease and avoided in those with bone-marrow depression. Monitoring of side-effects is based on liver enzymes for hepatotoxicity and blood cell count.
9. Follow-up imaging at 3–6 months and thereafter once a year for a minimum of 5 consecutive years after inactivation may help evaluate the success of treatment and monitor for any recurrence of the cysts.
10. A lack of response is defined as an absence of cyst changes after 3 months of treatment (detachment of the parasitic layers from the outer cyst wall, size reduction or stage modification). Complete response should be evaluated not earlier than 12 months after treatment end.

3.1.6 Use of praziquantel combined with ALB post percutaneous/surgical procedures for hepatic cyst types CE1, CE2, CE3a, CE3b

Recommendation 6	**In CE patients undergoing percutaneous or surgical interventions, when spillage is suspected or has occurred, the combination of praziquantel and ALB is suggested.** ***Conditional recommendation based on expert consensus.***
Background	ALB is most often used in the treatment of CE, alone or in addition to invasive interventions. Recently, attention has been given to the addition of praziquantel pre- and post-intervention, combined with ALB.
Summary of the evidence	This recommendation is based on PICO question 10. No trials were identified. The GDG formulated the recommendation based on pharmacological data, expert consensus, risk benefit assessment and clinician experience. Praziquantel has been reported to have a protoscolecidal effect but is not parasiticidal for the cysts *(14)*. Pharmacological data indicate that the combination of praziquantel and ALB enhances efficacy by increasing ALB sulfoxide levels, the pharmacologically active metabolite, resulting in markedly increased protoscolecidal activity, enhancing the efficacy of treatment and reducing the risk of recurrence or complications associated with spillage. Biological plausibility has been reported by Cobo et al. *(29)*.
Certainty of the evidence	There is no evidence available to support the use of praziquantel combined with ALB when performing invasive interventions. The recommendation was formulated by the GDG using expert consensus within the evidence-to-decision framework.
Additional factors considered	• ***Benefits and harms*** The GDG acknowledges potential benefits, such as enhanced therapeutic activity, broader applicability and risk mitigation, associated with the praziquantel and ALB combination. The concerns raised include limited experience, cost issues and uncertainties regarding specific outcomes. There is a lack of data regarding undesirable effects. • ***Health equity, acceptability, resource implications, and feasibility*** The high cost of praziquantel in some countries could potentially create access barriers, highlighting a concern for health equity, acceptability and feasibility. Efforts should be made to make praziquantel more affordable and accessible, especially in low- and middle-income regions where CE is endemic.
Implementation considerations	1. In case of suspected or ascertained cyst fluid spillage, ALB should be given at a dose of 10–15 mg/kg/day in two divided doses (up to 400 mg twice a day) for a minimum of 3 months, usually, 6–12 months after the intervention, as considered appropriate by the clinician. 2. Praziquantel should be given at a dose of 40–50 mg/kg/day divided into two daily doses for 2 weeks after the intervention. Because praziquantel does not have an effect on the cyst (as compared to ALB), 2 weeks are suggested. However, the period can be increased to a maximum of 4 weeks if considered appropriate by the clinician. 3. ALB and praziquantel can be given simultaneously during a fat-rich meal to increase their bioavailability. 4. Some clinicians use praziquantel in combination with ALB for 2 weeks prior to procedure *(29)*. More evidence is needed to make this practice a recommendation.

3.2 Recommendations for the clinical management of uncomplicated lung CE cysts

3.2.1 Uncomplicated lung CE cysts ≤ 5 cm

Recommendation 7	**In patients with uncomplicated active lung CE cysts ≤ 5 cm, surgery is suggested. ALB should not be given before surgery. When spillage is suspected or has occurred, ALB after surgery is suggested. Lung surgery requires tier 4 settings.** ***Conditional recommendation based on expert consensus.***
Background	Pulmonary CE is mainly managed through surgical intervention. Pulmonary surgery requires a high level of health professional expertise as well as radiological and surgical facilities. It is uncertain whether ALB alone for 6 months can effectively treat small pulmonary CE (≤ 5 cm).
Summary of the evidence	This recommendation is based on PICO question 11. No trials were identified. The GDG formulated the recommendation based on expert consensus, risk benefit assessment, and consideration of clinician and patient treatment preferences. The recommendation for surgery combined with ALB rather than ALB alone for 6 months in uncomplicated CE lung cysts ≤ 5 cm is based on potential risk of complications, such as the risk of rupture. This recommendation is also supported by concerns that relying solely on ALB for 6 months may result in higher relapse and treatment failure rates.
Certainty of the evidence	The recommendation was formulated by the GDG using expert consensus within the evidence-to-decision framework.
Additional factors considered	• ***Benefits and harms*** Uncomplicated lung CE cysts (≤ 5 cm) represent a very specific and limited type. If only ALB is given, there is a chance that the cyst might rupture, whether exacerbated by the drug treatment or not. Surgery is useful in preventing potential complications, such as the risk of rupture. However, the GDG considered the possibilities of morbidity and mortality associated with surgery. No published data reporting follow-up of post-surgery patients could be identified. If there are multiple cysts, surgery may be challenging, depending on the skills and experience of the surgeon and the location of the cysts. • ***Health equity*** Surgery is an expensive intervention compared to ALB alone but is considered to be essential in lung cysts. • ***Acceptability*** Acceptability may frequently be dictated by clinician preferences. Often, patients might be initially reluctant to choose specialized thoracic surgery, if there is perceived to be an option to manage the disease with an oral medicine, but the risk of recurrence and the opportunity of achieving complete remission by surgery makes surgery the best option. • ***Resource implications*** The thoracic surgery that is required to excise these CE cysts requires high levels skills from specialized staff. • ***Feasibility*** The intervention is feasible in health facilities where infrastructure and technical expertise is available.

Implementation considerations

1. Pulmonary CE is primarily managed through surgical intervention. Medical treatment with ALB should only be contemplated if surgery is medically contraindicated or not feasible due to specific patient circumstances. During medical treatment, regular monitoring for secondary infection, or expectoration of laminated layer, is mandated. T2-weighted MRI can be applied to monitor the inactivation of the cyst over time.
2. For any patient in which an invasive procedure, especially surgery, is an option, individual patient factors such as general health, comorbidities and age should be considered before the final decision is made.
3. Standard practice is not to give ALB prior to the surgical procedure due to the perceived risk of rupture in the case of lung cysts. If there are concerns of intraoperative spillage, then give ALB for 1–3 months post procedure, at a dose of 10–15 mg/kg/day (up to 400 mg twice a day) in two divided doses with a fat-rich meal to increase its bioavailability; duration can be extended if considered appropriate. It is important to use high-quality ALB (branded or generic), that contains the required amount of bioavailable drug. A 2-week post-procedure course of praziquantel in addition to ALB may be considered if there is spillage of cyst contents (see recommendation 6).
4. After surgery, patients must be closely monitored for potential complications including anaphylaxis, infection, prolonged air leak or bleeding. Monitoring of adverse events to ALB should also be implemented (see 5 below).
5. ALB is contraindicated in the first trimester of pregnancy *(9)*. Later in pregnancy, potential benefits may warrant use of ALB despite potential risks. Contraceptive measures are necessary for women of reproductive age while on long-term ALB. Benzimidazoles must be used with caution in patients with chronic hepatic disease and avoided in those with bone-marrow depression. Monitoring of side-effects is based on liver enzymes for hepatotoxicity and blood cell count.
6. Follow-up imaging at 3–6 months and thereafter once a year for a minimum of 5 years after inactivation may help evaluate the success of treatment and monitor for any recurrence of the cysts.
7. A lack of response is defined as an absence of cyst changes after 3 months of treatment (detachment of the parasitic layers from the surrounding lung tissue, size reduction or morphological change). Complete response should be evaluated not earlier than 12 months after treatment end.

4. Publication, dissemination, monitoring and evaluation

4.1 Publication and dissemination

WHO will disseminate the guidelines through its regional and country offices, and different collaborators, to generate wide dissemination of these guidelines, including:

- Publication on the WHO website.
- Communication through WHO's regional and country offices to health ministries, provincial health authorities, central urban and district hospitals and health centres in endemic countries including supporting materials.
- Dissemination through regional and subregional events as well as through professional networks and associations.
- Communication through WHO Collaborating Centres on Echinococcosis and other NTDs.
- Dissemination to global subscribers, chief health executives, WHO depository libraries, WHO representatives, and WHO headquarters and regional office libraries.
- Publication of synthesized results in peer reviewed journals and sharing the URL of the published guidelines with key journals (international and those with readership from endemic countries).
- Promotion of the guidelines during workshops and scientific congresses.
- Embedding the guidelines within other relevant disciplines, such as clinical services and systems, safe surgery and diagnostic imaging.

4.2 Training and derivative products

To implement some recommendations, training may be required to develop and/or increase the required competences such as diagnostics, percutaneous treatment and mitigating or managing potential complications related to those procedures in specific settings. An OpenWHO course on the resources for control and management of CE is being prepared as a remote learning tool targeted at public and professional audience as well as on-site training of clinicians and health care providers. These guidelines will be an important component of that course.

4.3 Essential Medicines List

ALB and praziquantel are both included in the 22nd (2021) *WHO Model List of Essential Medicines (30)* as intestinal anthelminthics as well as cysticidal medicines. ALB is currently available as a donation to health ministries through WHO (*31*).

4.4 Adaptation

These guidelines have been developed considering different resource settings, but further adaptation, taking into account local circumstances and resource considerations, can be undertaken at regional and national levels. They will be translated into Chinese, French, Russian and Spanish. Additional translations into other official WHO languages may be considered depending on demand.

4.5 Monitoring and evaluating the impact of these guidelines

An evaluation will be made by the members of the WHO Guideline Steering Group and NTD programme managers. This evaluation will focus on the following aspects:

- access of the target audience to the guidelines;
- in-country acceptance and application of the recommendations; and
- observed obstacles in their implementation.

5. Updating

As per WHO standards, these guidelines will be reviewed periodically for currency and to ensure alignment with current and emerging evidence. Subject to operational priorities, WHO will review new evidence published in 7–10 years, unless significant new evidence mandating earlier revision becomes available before that date.

For future revisions, efforts will be made to include patients or their representatives.

6. Research priorities

	Research priorities
1	Prospective comparative trials to update recommendations.
2	Health services research on provision of access to services in endemic areas.
3	Survey on patient preferences for the treatment and management of CE.
4	For all PICO questions the duration of the ALB regimen needs to be assessed in RCT. In addition, for those where a procedure is recommended, the potential role of combination with praziquantel also needs to be addressed with a proper RCT.
5	Include additional questions to these guidelines such as the management of treatment failures after PAIR.
6	Develop WHO CE diagnostic guidelines.
7	Improved diagnostic tools for specific use cases.

Rec	Research questions per recommendation
1	A large RCT comparing PAIR with ALB vs ALB alone in hepatic CE cyst types CE1 and CE3a < 5 cm.
2	A large RCT comparing ALB alone versus PAIR and ALB versus surgery and ALB in hepatic cyst types CE1 or CE3a 5–10 cm.
3	A large RCT comparing S-CAT and ALB, PAIR and ALB or surgery and ALB in large hepatic cyst types CE1 or CE3a (> 10 cm).
4	A large RCT prospective trial comparing surgery combined with ALB vs ALB alone as initial treatment in hepatic cyst types CE2 or CE3b ≤ 5 cm in diameter.
5	A large RCT comparing ALB, laparoscopic surgery combined with ALB, non-laparoscopic surgery combined with ALB and Mo-CAT combined with ALB in hepatic cyst types CE2 or CE3b (> 5 cm).
6	a) A large comparative trial studying outcome of cyst inactivity, recurrence, spillage and complications in people with hepatic cyst types CE1, CE2, CE3a, CE3b (> 5 cm), undergoing a procedure, where the combination of praziquantel with ALB is compared with ALB alone is needed to obtain more evidence. b) Comparison of the addition of praziquantel to ALB pre-procedure; post-procedure; and pre- and post-procedure for the same cyst types is also needed.
7	A large RCT comparing a therapeutic trial of ALB for 6 months vs surgery with adjunctive ALB in people with lung CE cysts ≤ 5 cm.

A recent Cochrane Review on the treatment of CE draws similar conclusions to the evidence synthesis informing these guidelines and supports the identified research priorities (*32*).

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