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Treatment of uncomplicated hepatic cystic echinococcosis (hydatid disease) (Review)

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TABLE OF CONTENTS

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[Intervention Review]

Treatment of uncomplicated hepatic cystic echinococcosis (hydatid disease)

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ABSTRACT

Background

Cystic echinococcosis is a parasitic infection mainly impacting people living in low- and middle-income countries. Infection may lead to cyst development within organs, pain, non-specific symptoms or complications including abscesses and cyst rupture. Treatment can be difficult and varies by country. Treatments include oral medication, percutaneous techniques and surgery.

One Cochrane review previously assessed the benefits and harms of percutaneous treatment compared with other treatments. However, evidence for oral medication, percutaneous techniques and surgery in specific cyst stages has not been systematically investigated and the optimal choice remains uncertain.

Objectives

To assess the benefits and harms of medication, percutaneous and surgical interventions for treating uncomplicated hepatic cystic echinococcosis.

Search methods

We searched CENTRAL, MEDLINE, two other databases and two trial registries to 4 May 2023. We searched the reference lists of included studies, and contacted experts and researchers in the field for relevant studies.

Selection criteria

We included randomized controlled trials (RCTs) in people with a diagnosis of uncomplicated hepatic cystic echinococcosis of World Health Organization (WHO) cyst stage CE1, CE2, CE3a or CE3b comparing either oral medication (albendazole) to albendazole plus percutaneous interventions, or to surgery plus albendazole. Studies comparing praziquantel plus albendazole to albendazole alone prior to or following an invasive intervention (surgery or percutaneous treatment) were eligible for inclusion.

Data collection and analysis

We used standard Cochrane methods. Our primary outcomes were symptom improvement, recurrence, inactive cyst at 12 months and all-cause mortality at 30 days. Our secondary outcomes were development of secondary echinococcosis, complications of treatment and duration of hospital stay. We used GRADE to assess the certainty of evidence.

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Main results

We included three RCTs with 180 adults and children with hepatic cystic echinococcosis. Two studies enrolled people aged 5 to 72 years, and one study enrolled children aged 6 to 14 years. One study compared standard catheterization plus albendazole with puncture, aspiration, injection and re-aspiration (PAIR) plus albendazole, and two studies compared laparoscopic surgery plus albendazole with open surgery plus albendazole. The three RCTs were published between 2020 and 2022 and conducted in India, Pakistan and Turkey. There were no other comparisons.

Standard catheterization plus albendazole versus PAIR plus albendazole

The cyst stages were CE1 and CE3a.

The evidence is very uncertain about the effect of standard catheterization plus albendazole compared with PAIR plus albendazole on cyst recurrence (risk ratio (RR) 3.67, 95% confidence interval (CI) 0.16 to 84.66; 1 study, 38 participants; very low-certainty evidence).

The evidence is very uncertain about the effects of standard catheterization plus albendazole on 30-day all-cause mortality and development of secondary echinococcosis compared to open surgery plus albendazole. There were no cases of mortality at 30 days or secondary echinococcosis (1 study, 38 participants; very low-certainty evidence).

Major complications were reported by cyst and not by participant. Standard catheterization plus albendazole may increase major cyst complications compared with PAIR plus albendazole, but the evidence is very uncertain (RR 10.74, 95% CI 1.39 to 82.67; 1 study, 53 cysts; very low-certainty evidence).

Standard catheterization plus albendazole may make little to no difference on minor complications compared with PAIR plus albendazole, but the evidence is very uncertain (RR 1.03, 95% CI 0.60 to 1.77; 1 study, 38 participants; very low-certainty evidence).

Standard catheterization plus albendazole may increase the median duration of hospital stay compared with PAIR plus albendazole, but the evidence is very uncertain (4 (range 1 to 52) days versus 1 (range 1 to 15) days; 1 study, 38 participants; very low-certainty evidence).

Symptom improvement and inactive cysts at 12 months were not reported.

Laparoscopic surgery plus albendazole versus open surgery plus albendazole

The cyst stages were CE1, CE2, CE3a and CE3b.

The evidence is very uncertain about the effect of laparoscopic surgery plus albendazole on cyst recurrence in participants with CE2 and CE3b cysts compared to open surgery plus albendazole (RR 3.00, 95% CI 0.13 to 71.56; 1 study, 82 participants; very low-certainty evidence). The second study involving 60 participants with CE1, CE2 or CE3a cysts reported no recurrence in either group.

The evidence is very uncertain about the effect of laparoscopic surgery plus albendazole on 30-day all-cause mortality in participants with CE1, CE2, CE3a or CE3b cysts compared to open surgery plus albendazole. There was no mortality in either group (2 studies, 142 participants; very low-certainty evidence).

The evidence is very uncertain about the effect of laparoscopic surgery plus albendazole on major complications in participants with CE1, CE2, CE3a or CE3b cysts compared to open surgery plus albendazole (RR 0.50, 95% CI 0.13 to 1.92; 2 studies, 142 participants; very low-certainty evidence).

Laparoscopic surgery plus albendazole may lead to slightly fewer minor complications in participants with CE1, CE2, CE3a or CE3b cysts compared to open surgery plus albendazole (RR 0.13, 95% CI 0.02 to 0.98; 2 studies, 142 participants; low-certainty evidence).

Laparoscopic surgery plus albendazole may reduce the duration of hospital stay compared with open surgery plus albendazole (mean difference (MD) −1.90 days, 95% CI −2.99 to −0.82; 2 studies, 142 participants; low-certainty evidence).

Symptom improvement, inactive cyst at 12 months and development of secondary echinococcosis were not reported.

Authors' conclusions

Percutaneous and surgical interventions combined with albendazole can be used to treat uncomplicated hepatic cystic echinococcosis; however, there is a scarcity of randomised evidence directly comparing these interventions.

There is very low-certainty evidence to indicate that standard catheterization plus albendazole may lead to fewer cases of recurrence, more major complications and similar complication rates compared to PAIR plus albendazole in adults and children with CE1 and CE3a cysts.

There is very low-certainty evidence to indicate that laparoscopic surgery plus albendazole may result in fewer cases of recurrence or fewer major complications compared to open surgery plus albendazole in adults and children with CE1, CE2, CE3a and CE3b cysts. Laparoscopic surgery plus albendazole may lead to slightly fewer minor complications.

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Firm conclusions cannot be drawn due to the limited number of studies, small sample size and lack of events for some outcomes.

PLAIN LANGUAGE SUMMARY

Treatment of liver cystic echinococcosis (hydatid disease)

Key messages

– We do not know if standard catheterization plus albendazole is more effective or safer compared to puncture, aspiration, injection and re-aspiration (PAIR) plus albendazole for treating cystic echinococcosis at specific cyst stages (CE1 and CE3a).

– People undergoing laparoscopic (keyhole) surgery plus albendazole may have slightly fewer minor complications and shorter hospital stay than people who receive open surgery plus albendazole. We do not know if laparoscopic surgery plus albendazole may lead to fewer cases of recurrence or major complications. These results also apply to specific cyst stages (CE1, CE2, CE3a or CE3b).

– Healthcare workers caring for people with cystic echinococcosis should consider the safety of different treatment options and patient preferences.

What is cystic echinococcosis?

Cystic echinococcosis, also known as hydatid disease, is a parasitic infection that is caused by a tapeworm. People living in low- and middle-income countries in areas with livestock (sheep, cattle, pigs, goats) are mostly affected as the tapeworm lifecycle involves a stage of livestock infection and a stage affecting dogs.

When a human is infected, cysts may develop in any organ of the body; however, the liver is the most affected organ. The cysts may grow and progress through different stages, in which their composition changes from liquid to semi-solid to solid content. The cyst stages reflect how active the cyst is, for example, whether it has produced daughter cysts, or whether it is inactive and solid. The cysts may cause no symptoms or lead to symptoms depending on their location in the body. In the liver, cysts can lead to abdominal pain and other non-specific symptoms. Sometimes complications such as abscesses, cyst rupture with possible serious allergic reactions or secondary echinococcosis (i.e. spread into the abdominal cavity with formation of many new cysts) can occur.

This review focused on cystic echinococcosis in active stages occurring in the liver.

How is cystic echinococcosis treated?

Treatment can be difficult and varies across countries. Treatment options depend on the characteristics of the cyst (stage, number, size, location), the health resources available and the general health of the patient. Treatment options include oral antiparasitic medication (albendazole), surgical removal of the cyst and percutaneous techniques that involve passing a needle through the skin into the cyst within the liver to empty the cyst.

One percutaneous technique is known as PAIR (**p**uncture, **a**spiration (drawing out the cyst contents), **i**njection of a medicine to kill the parasite and **r**e-aspiration). After treatment, the patient can usually return home on the same day following the removal of all antiparasitic substances from the cyst. Another percutaneous technique is known as standard catheterization. This is similar to PAIR, except that a larger plastic tube (a catheter) is also inserted into the cyst to help thoroughly evacuate cyst content with antiparasitic substances. The catheter is then left in the cyst to drain out all the fluid over the next 24 hours or longer.

What did we want to find out?

We wanted to find out which treatment led to the most improvement in symptoms, the least recurrence of the disease and fewer side effects/complications.

What did we do?

We searched for studies that compared one treatment option for cystic echinococcosis (oral medication, surgery, percutaneous techniques) with a different treatment option for people with liver cystic echinococcosis at different active stages.

What did we find?

We included three studies. One study of 38 adults and children aged 5 to 72 years in Turkey compared different percutaneous treatments plus albendazole (standard catheterization plus PAIR), and two studies with 142 adults and children aged 6 to 60 years from India and Pakistan compared laparoscopic surgery plus albendazole to open surgery plus albendazole. We found no data on symptom improvement or on whether more cysts became inactive at 12 months after treatment.

The evidence is very uncertain about the effect of standard catheterization plus albendazole on cyst recurrence, deaths and secondary echinococcosis compared to PAIR plus albendazole. Standard catheterization plus albendazole may increase major complications and

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may make little to no difference on minor complications, but the evidence is very uncertain. Standard catheterization plus albendazole may increase duration of hospital stay, but the evidence is very uncertain.

The evidence is very uncertain about the effect of laparoscopic surgery plus albendazole on cyst recurrence, death and major complications compared to open surgery plus albendazole. Laparoscopic surgery plus albendazole may lead to slightly fewer minor complications and may reduce the duration of hospital stay compared to open surgery plus albendazole.

What are the limitations of the evidence?

We are not confident in the evidence because we included only three studies with a small number of participants. The studies did not report all the treatments that we were interested in, and they did not report results on the outcome measures that we were interested in, such as symptom improvement. All results applied to specific cyst stages.

How up to date is this evidence?

The evidence is up to date to 4 May 2023.

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SUMMARY OF FINDINGS

Summary of findings 1. Standard catheterization plus albendazole versus PAIR plus albendazole for hepatic cystic echinococcosis

Population: adults and children with hepatic cystic echinococcosis (WHO CE1 and CE3a stage, diameter ≥ 4 cm)

Intervention: standard catheterization plus albendazole

Comparator: PAIR plus albendazole

Setting: inpatient setting in Turkey

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with PAIR plus albendazole	Risk with standard catheterization plus albendazole				
Symptom improvement	—	—	—	—	—	Not reported
Recurrence Mean follow-up • Standard catheterization group: 71 months • PAIR group: 78.1 months	0 in 21[a]	1 in 17[b]	**RR 3.67** (0.16 to 84.66)	38 (1 RCT)	⨁◯◯◯ **Very low**[c]	The evidence is very uncertain about the effect of standard catheterization plus albendazole on recurrence compared to PAIR plus albendazole.
Inactive cyst stage at 12 months	—	—	—	—	—	Not reported
All-cause mortality at day 30 Mean follow-up • Standard catheterization group: 71 months • PAIR group: 78.1 months	0 cases of mortality	0 cases of mortality	Not estimable[d]	38 (1 RCT)	⨁◯◯◯ **Very low**[e]	0 cases of all-cause mortality reported at day 30. The evidence is very uncertain about the effect of standard catheterization plus albendazole on 30-day all-cause mortality.
Development of secondary echinococcosis Mean follow-up	0 cases of secondary echinococcosis	0 cases of secondary echinococcosis	Not estimable[d]	38 (1 RCT)	⨁◯◯◯ **Very low**[e]	0 participants developed secondary echinococcosis.

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• Standard catheterization group: 71 months • PAIR group: 78.1 months						The evidence is very uncertain about the effect of standard catheterization plus albendazole on secondary echinococcosis.
Major complications of treatment Mean follow-up • Standard catheterization group: 71 months • PAIR group: 78.1 months	1 in 34 **cysts**[a]	6 in 19 **cysts**[a]	**RR 10.74**[f] (1.39 to 82.67)	53 **cysts** (1 RCT)	⨁◯◯◯ **Very low**[g]	Major complications were reported by cyst and thus we have no data on major complications by individual participant. Standard catheterization plus albendazole may increase major cyst complications, but the evidence is very uncertain.
Minor complications of treatment Mean follow-up • Standard catheterization group: 71 months • PAIR group: 78.1 months	57 per 100	59 per 100 (34 to 100)	**RR 1.03** (0.60 to 1.77)	38 (1 RCT)	⨁◯◯◯ **Very low**[h]	Standard catheterization plus albendazole may make little to no difference on minor complications, but the evidence is very uncertain.
Duration of hospital stay Mean follow-up • Standard catheterization group: 71 months • PAIR group: 78.1 months	The median duration of hospital stay in the PAIR combined with albendazole group was **1 days** (range 1 to 15 days)[a]	The median duration of hospital stay in the standard catheterization combined with albendazole group was **4 days** (range 1 to 52 days)[a]	Not estimable[i]	38 (1 RCT)	⨁◯◯◯ **Very low**[e]	Standard catheterization plus albendazole may increase the duration of hospital stay, but the evidence is very uncertain.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk on the comparison group and the **relative effect** of the intervention (and its 95% confidence interval).

CI: confidence interval; **PAIR:** puncture, aspiration, injection and re-aspiration; **RCT:** randomized controlled trial; **RR:** risk ratio; **WHO:** World Health Organization.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: 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 the possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

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Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Number as reported in the study (Akhan 2020).
[b]Number as reported in the study (Akhan 2020). It was not possible to calculate the corresponding risk using the RR due to zero events in the control group.
[c]Downgraded one level for risk of bias (unclear details concerning random sequence generation, blinding of outcome assessment and incomplete outcome data), and two levels for serious imprecision (low number of participants, low number of events and very wide CIs).
[d]The effect estimate could not be calculated due to zero events in the intervention and comparator groups.
[e]Downgraded two levels for serious imprecision (very low number of participants; zero events), and one level for risk of bias (unclear details on random sequence generation and incomplete outcome data). Unclear risk of bias regarding blinding of outcome assessment was not judged to have impacted this outcome.
[f]RR calculated using number of cysts as the event and the total number of cysts as the denominator in each group. The total number of participants in each group was not reported for this outcome.
[g]Downgraded one level for risk of bias (unclear details on random sequence generation, blinding of outcome assessment and incomplete outcome data), and two levels for serious imprecision (low number of cysts, low number of events, very wide CIs).
[h]Downgraded one level for risk of bias (unclear details concerning random sequence generation, blinding of outcome assessment and incomplete outcome data), and two levels for serious imprecision (low number of participants, low number of events, CIs included the possibility of benefit, no effect and harm).
[i]Mean difference could not be calculated due to no available data on mean and standard deviation.

Summary of findings 2. Laparoscopic surgery plus albendazole versus open surgery plus albendazole for hepatic cystic echinococcosis

Population: adults and children with hepatic cystic echinococcosis (WHO stage CE1, CE2, CE3a, CE3b)

Intervention: laparoscopic surgery plus albendazole

Comparator: open surgery plus albendazole

Setting: inpatient settings in India and Pakistan

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with open surgery plus albendazole	Risk with laparoscopic surgery plus albendazole				
Symptom improvement	—	—	—	—	—	Not reported
Recurrence Follow-up: 12 months	0 in 41[a]	1 in 41[a]	**RR 3.00** (0.13 to 71.56)	82 (1 RCT)	⊕⊖⊖⊖ **Very low**[b]	The evidence is very uncertain about the effect of laparoscopic surgery plus albendazole on recurrence compared to open surgery plus albendazole.

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						1 further study of 60 participants reported no events in both groups (follow-up 2 years).
Inactive cyst at 12 months	—	—	—	—	—	Not reported
All-cause mortality at day 30 Follow-up: 12 months (1 study) and 24 months (1 study)	0 cases of mortality	0 cases of mortality	Not estimable[c]	142 (2 RCTs)	⊕⊖⊖⊖ **Very low**[d]	0 cases of all-cause mortality reported at day 30. The evidence is very uncertain about the effect of laparoscopic surgery plus albendazole on all-cause mortality at day 30 compared to open surgery plus albendazole.
Development of secondary echinococcosis	—	—	—	—	—	Not reported
Major complications of treatment Follow-up: 12 months (1 study) and 24 months (1 study)	8 per 100	4 per 100 (1 to 16)	**RR 0.50** (0.13 to 1.92)	142 (2 RCTs)	⊕⊖⊖⊖ **Very low**[e]	The evidence is very uncertain about the effect of laparoscopic surgery plus albendazole on major complications compared to open surgery plus albendazole.
Minor complications of treatment Follow-up: 12 months (1 study) and 24 months (1 study)	10 per 100	1 per 100 (0 to 10)	**RR 0.13** (0.02 to 0.98)	142 (2 RCTs)	⊕⊕⊖⊖ **Low**[f]	Laparoscopic surgery plus albendazole may lead to slightly fewer minor complications compared to open surgery plus albendazole.
Duration of hospital stay Follow-up: 12 months (1 study) and 24 months (1 study)	The mean duration of hospital stay was **5.96 days**	The mean duration of hospital stay was **1.9 days shorter** (2.99 days shorter to 0.82 days shorter)	**MD −1.90** (−2.99 to −0.82)	142 (2 RCTs)	⊕⊕⊖⊖ **Low**[g]	Laparoscopic surgery plus albendazole may reduce duration of hospital stay when compared to open surgery plus albendazole.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk on the comparison group and the **relative effect** of the intervention (and its 95% confidence interval).

CI: confidence interval; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio; **WHO:** World Health Organization.

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GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: 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 the possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

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[a]Number as reported in the study.

[b]Downgraded one level for risk of bias (unclear details regarding random sequence generation in one study, unclear details of allocation concealment in one study and unclear details regarding blinding of outcome assessment in both studies), and two levels for serious imprecision (low number of participants, low number of events and very wide CIs).

[c]The effect estimate could not be calculated due to zero events in the intervention and comparator groups.

[d]Downgraded two levels for serious imprecision (low participant numbers, zero events) and one level for risk of bias (unclear details concerning random sequence generation on one study). Unclear risk of bias concerning allocation concealment in two studies and unclear risk of bias concerning blinding of outcome assessment in one study was not judged to impact certainty in this outcome.

[e]Downgraded one level for risk of bias (unclear details regarding allocation concealment in one study, unclear details concerning random sequence generation on one study and unclear details regarding blinding of outcome assessment in both studies), and two levels for serious imprecision (low number of participants, low number of events, CIs included possibility of harm, benefit and no difference between intervention and comparator groups).

[f]Downgraded one level for risk of bias (unclear details regarding allocation concealment in one study, unclear details concerning random sequence generation on one study and unclear details regarding blinding of outcome assessment in both studies), and one level for imprecision (low number of participants, low number of events). This outcome was not downgraded two levels for very serious imprecision as we judged this to have a lower likelihood of being a chance event and is in keeping with clinical expectation of the intervention and comparator treatment modalities.

[g]Downgraded one level for risk of bias (unclear details regarding allocation concealment in one study, unclear details concerning random sequence generation on one study and unclear details regarding blinding of outcome assessment in both studies), and one level for imprecision (low number of participants, low number of events).

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BACKGROUND

Description of the condition

Cystic echinococcosis, or hydatid disease, is a zoonosis caused by infection with the larval stage (echinococcal cyst) of the cestode *Echinococcus granulosus sensu lato* species complex (a tapeworm), found in dogs (definitive host harbouring the adult parasite stage) and in livestock including sheep, cattle, pigs and goats (intermediate hosts harbouring the larval stage). Humans are accidental intermediate hosts.

Prevalence, incidence and burden of the condition

Cystic echinococcosis is present worldwide, except for Antarctica. The most affected areas of the world include Western China, Central Asia, the Mediterranean, South America and East Africa (Deplazes 2017). The prevalence, incidence and burden of human cystic echinococcosis are difficult to estimate due to underdiagnosis of both asymptomatic and symptomatic cases, misreporting of cases, and general lack of robust evaluation of the human and financial costs of infection. It is estimated that over one million human cystic echinococcosis cases would be present at any one time globally, accounting for over 3.5 million disability-adjusted life years lost (Budke 2006; Craig 2007). In hyperendemic regions, incidence rates for cystic echinococcosis can reach more than 50 per 100,000 person-years, and prevalence levels as high as 5% to 10% (Deplazes 2017).

Natural history

Following human ingestion of the eggs of *Echinococcus granulosus sensu lato* species, the infection is asymptomatic and hence the exact moment of acquisition cannot be determined.

The incubation period of cystic echinococcosis can be prolonged for several years until cyst growth produces symptoms either due to mechanical effects or the development of complications. Liver (approximately 80%) and lung (approximately 15%) are the most common organs affected by the development of cystic echinococcosis cysts (Kern 2017). Other possible sites include other abdominal organs (spleen, kidney, peritoneal cavity), bones, and the central nervous system, but all organs and tissues can be affected. Cystic echinococcosis in the liver usually grows slowly and may not cause any symptoms for months to years (if ever). Symptoms may arise due to the cyst size or localization (including abdominal pain or other non-specific symptoms), or the development of complications (including secondary infection and possible abscess formation), or cysts may rupture, leading to peritonitis, an open connection to hollow structures such as the biliary tree (fistula), or allergic reactions including anaphylaxis. In the lung, cystic echinococcosis cysts are believed to grow and manifest clinically more rapidly (Santivanez 2010). Lung cysts may develop complications including rupture into the bronchi leading to vomica (expectoration of solid or semi-solid content from the respiratory tract of cystic echinococcosis material) or airway obstruction, or into the pleural cavity leading to a pleural effusion and dissemination.

Within an organ, cystic echinococcosis may evolve through several stages, that is, changes in cyst morphology as described in Table 1 (Brunetti 2010).

In terms of viability, CE1, CE2 and CE3b stages are viable; CE3a stages can be biologically viable or not (transitional cyst); CE4 stage is most likely not viable (especially if this inactive stage is reached spontaneously); and CE5 stage is not viable (Hosch 2008; Lissandrin 2018; Rinaldi 2014; Stojkovic 2016). The actual biological processes and factors inducing changes in cyst morphology (stages) are not completely known. When an echinococcal cyst in an active or transitional stage is diagnosed, treatment is often commenced, even in the case of small asymptomatic cysts, to avoid progression and any potential complications. Due to all these factors, there is poor knowledge of the actual natural history of cystic echinococcosis (with the possible exception of CE4 and CE5 inactive cysts, which are followed up by observation with imaging after diagnosis in these stages), and extremely few data exist on the actual rate of cyst evolution or rate of complications in the absence of treatment (Lissandrin 2018; Piccoli 2014; Rinaldi 2014; Stojkovic 2016). Data on cyst stage distribution in a population is available from cross-sectional ultrasound-based studies (Chebli 2017; Tamarozzi 2017; Tamarozzi 2018). Results from the very few studies that could evaluate infected patients by ultrasonography in the absence of treatment over time show that, generally speaking, cysts progress naturally from CE1 to inactive CE4 and CE5 stages, but cysts can persist in any stage without further development or can evolve from one stage to another through additional stages (Larrieu 2004; Rogan 2006; Solomon 2017).

Diagnosis

Most often cysts remain asymptomatic and are diagnosed incidentally. The diagnosis of cystic echinococcosis relies on the visualization on imaging of the echinococcal cyst. In organs explorable by ultrasonography (such as the abdomen where most cysts develop), this is the reference imaging technique for both diagnosis and staging. Other imaging techniques such as magnetic resonance imaging and computed tomography do not perform as well in detecting the pathognomonic features of echinococcal cysts, which allow aetiological diagnosis and staging (Stojkovic 2012), and may be used to better define features of the cyst in specific circumstances (e.g. presurgery, complications) or to exclude the diagnosis of cystic echinococcosis (e.g. in the presence of contrast enhancement of the internal cyst structures, which is a feature ruling out cystic echinococcosis with certainty). Performance of currently available seroassays for the detection of anti-*Echinococcus* antibodies do not allow, applied alone, a diagnosis of cystic echinococcosis (at both individual patient and population level). Serology can be used to complement imaging when this is inconclusive, and can support a diagnosis of cystic echinococcosis, if positive and in selected circumstances, while a negative serology cannot rule out a diagnosis of cystic echinococcosis (Tamarozzi 2021). Currently, no antigen detection test or similar test to detect infection in clinical samples of body fluids is available for diagnosis. Definitive diagnosis of cystic echinococcosis can also be achieved by observation of seroconversion or change in cyst morphology after medical treatment (diagnosis ex-juvantibus) (or both), or by microscopic or molecular analysis of cystic material obtained invasively (Siles-Lucas 2017). Several conventional and multiplex polymerase chain reaction (PCR) protocols for species/genotype identification are described, mainly applied for epidemiological purposes (Siles-Lucas 2017). More recently, the possibility to detect cell-free DNA of the parasite circulating in blood has been explored, with

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encouraging results, but there is no standardized protocol, and it is not validated in routine practice (Zhao 2021).

Treatment

The treatment of uncomplicated hepatic active/transitional cystic echinococcosis depends on the cyst characteristics, including the cyst stage, size and location within the liver, and overall patient health conditions (Brunetti 2010).

Treatment options include:

- antiparasitic treatment with benzimidazoles;
- invasive intervention such as:
  - percutaneous techniques including:
    - **p**uncture, **a**spiration, **i**njection with protoscolecidal agents and **r**e-aspiration (PAIR);
    - standard catheterization (the cyst is punctured by a needle, the fluid content aspirated, saline injection undertaken and a catheter inserted to allow cyst cavity irrigation with absolute alcohol followed by fluid drainage until minimal fluid remains); or
    - modified catheterization techniques (MoCat) (similar to standard catheterization except that a guidewire may also be passed into the cyst through the catheter to mechanically break down cyst contents, or cyst contents may be broken down by multiple sessions of intensive irrigation with isotonic saline);
  - surgery (open or laparoscopic), which involves removal of the cyst, both in conjunction with pre- and postoperative administration of benzimidazoles.

Cysts with any complications usually require surgical intervention, often with specialized procedures including endoscopic retrograde cholangiography, a therapeutic method often used to relieve biliary obstruction after a cyst rupture. There is uncertainty regarding the safety and efficacy of these different treatment options for clinically equivalent cysts. The conservative clinical management approach of only observing a cyst with no active intervention, also termed 'watch and wait,' is applied for uncomplicated hepatic cysts in CE4 and CE5 stages (solid, inactive cysts).

Mortality and fatality rates are difficult to estimate and vary greatly depending on cyst location and characteristics; complications; and expertise, treatment modalities available, and health facilities where the patient is managed. Expertise can vary between and within different settings, depending on the experience of the health professional in the treatment modality utilized. On average, the reported figures for mortality range between 0.5% and 5%. Rates of recurrence after surgery and reactivation after medical treatment depend on a combination of factors (e.g. treatment method/schedule of antiparasitic drug applied, stage of the cyst); in the literature, reported figures range from 2% to 40% for recurrence after surgery and 9% to 60% for reactivation after medical treatment (McManus 2003).

Follow-up

It is recommended that follow-up is for at least five years with imaging (ultrasonography for accessible locations) after treatment of cystic echinococcosis or after the first observation of an inactive cyst. Serology is not recommended for the follow-up of cystic echinococcosis since the presence (or absence) of detectable antibodies does not correlate with the presence (or absence) of echinococcal cysts or their viability (Siles-Lucas 2017).

Description of the intervention

Two clinical management options are available for treatment of viable (active/transitional) uncomplicated hepatic cystic echinococcosis: medical treatment with antiparasitic oral medication or invasive treatment (percutaneous methods or surgery).

The watch and wait approach (monitoring over time using ultrasound surveillance) is recommended for uncomplicated CE4 and CE5 hepatic cysts (Brunetti 2010), and will not be considered in this review (Lissandrin 2018; Stojkovic 2016).

1. Medical treatment: benzimidazoles with or without praziquantel

Benzimidazoles (albendazole, mebendazole) and praziquantel are oral antiparasitic drugs used in people with hepatic cystic echinococcosis. Benzimidazoles may be used as monotherapy or as an adjunct to invasive intervention (peri-interventional prophylaxis starting from days/weeks before and ending one month after intervention) as prophylaxis for secondary echinococcosis (i.e. to avoid the formation of new parasitic cysts which may derive from spillage of cyst fluid containing protoscoleces during invasive procedures on the cyst) (Brunetti 2010).

Albendazole is the most common benzimidazole drug used for pharmacological treatment of hepatic cystic echinococcosis in both adults and children (Moroni 2016; Tamarozzi 2020), and is currently recommended as the sole treatment for small CE1 and CE3a cysts (Brunetti 2010; Stojkovic 2009). Treatment may be administered for several months, requires laboratory and imaging follow-up, and is not always available or affordable in endemic areas, with consequent variability and problems in its practical use. It is used at 10 mg/kg/day to 15 mg/kg/day in two divided doses (or 400 mg twice a day in adults) with continuous intake over the scheduled treatment period. The most common adverse effects of albendazole include gastrointestinal symptoms such as nausea and an increase in liver enzymes; bone marrow depression and alopecia are less frequent. Adverse effects are generally mild and resolve upon treatment interruption.

Mebendazole has lower efficacy than albendazole (Horton 2003). It can be used at 40 mg/kg/day to 50 mg/kg/day divided into three doses. Adverse effects of mebendazole are similar to those of albendazole with a slightly better gastrointestinal tolerance.

Praziquantel has been suggested to be added to benzimidazoles at a dose of 40 mg/kg/day to 50 mg/kg/day only for peri-invasive intervention prophylaxis of secondary echinococcosis due to its ability to increase plasma concentration of albendazole sulphoxide and its efficacy on protoscoleces (Bygott 2009). It is not recommended as a monotherapy since it is not effective in isolation at treating established cystic echinococcosis cysts (Bygott 2009). The adjunct of praziquantel plus albendazole in peri-prophylaxis is currently carried out in some centres, but not applied systematically as a standard of care.

2. Invasive interventions: percutaneous methods or surgery

The options for invasive treatment of hepatic cystic echinococcosis are percutaneous methods or surgery (open or

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laparoscopic). Invasive treatment modalities require prophylaxis with albendazole, at the same doses used for treatment in the case of monotherapy. Used as prophylaxis, albendazole is generally administered from one week up to one month before and continuing at least one month after the procedure. The aim of albendazole prophylaxis is to prevent secondary echinococcosis in the event of spillage of protoscoleces during an invasive procedure.

2.1. Percutaneous methods

Percutaneous treatment is a minimally invasive method for hepatic cystic echinococcosis. Depending on the type of procedure applied, possible chemical inactivation (using different protoscolecidal substances) or evacuation of the parasitic material is made through a percutaneous route. The step of injection of protoscolecidal agent for chemical inactivation can only be implemented if communication of the cyst with the biliary tree (fistula) is excluded. All procedures require the presence of resuscitation capacity.

There are several percutaneous methods in use for the treatment of hepatic as follows.

2.1.1. Puncture, aspiration, injection of scolicidal substance, and re-aspiration (PAIR)

PAIR involves puncture of the cyst via an 18- to 22-gauge needle passed through the skin and liver tissue, aspiration of fluid content of the cyst, exclusion of cyst-biliary fistula, injection of a protoscolecidal agent (most commonly hypertonic saline solution or ethanol) and re-aspiration of all fluid. It is performed under ultrasound with or without fluoroscopic guidance. It can be an outpatient procedure. However, patients may be admitted to hospital overnight for observation and recovery. This technique has been associated with faster recovery, lower complication rates, lower costs and less pain experienced by patients compared with surgery (Menezes da Silva 2015). This intervention has been recommended for CE1 and CE3a hepatic cysts (Brunetti 2010).

2.1.2. Standard catheterization

Catheterization technique is usually undertaken for large CE1 and CE3a cysts (cysts greater than 10 cm) (Balli 2019; Men 2006). Standard catheterization is performed under ultrasound and fluoroscopic guidance and patients are typically admitted to hospital for several days depending on drainage times. The cyst is punctured by an 18- to 22-gauge needle, the fluid content aspirated and after injection of contrast media and exclusion of a biliary tree communication, saline injection is done. With a Seldinger technique, a 6- to 8-French catheter is placed. The cyst cavity is then irrigated with absolute alcohol and the catheter is left in situ for drainage. When drainage becomes less than 10 mL in 24 hours, a cystogram can be performed to assess for the presence of biliary fistula; if there is no evidence of fistula, 95% alcohol is administered to sclerose the cyst wall, and the catheter is then withdrawn. If a biliary fistula is present, the catheter remains in situ until all drainage stops (Balli 2019).

PAIR procedures that become technically difficult after commencement may be converted to a standard catheterization procedure.

2.1.3. Modified catheterization technique

Modified catheterization is currently used in some centres for CE2 and CE3b hepatic cysts (Akhan 2017). It is a potential alternative to surgery for these cyst stages as the large bore catheter allows removal of solid cystic components. The technique requires admission to hospital, sedation (an anaesthesiologist), as well as ultrasound and fluoroscopy equipment (i.e. settings with high healthcare resources are required).

This technique involves a 12- to 14-French catheter placed inside the cyst. A metal guidewire may also be passed into the cyst through the catheter to mechanically break down cyst contents, or cyst contents may be broken down by intensive irrigation with isotonic saline solution. If complete evacuation of the cavity is not achieved on the first day, additional irrigation sessions are performed on the following days. The catheter is then fixed to allow drainage. When the drainage fluid is clear, cavitography may be performed to assess complete evacuation of the cavity and for the presence of biliary fistula. When the daily drainage volume is less than 10 mL, sclerosis of the cavity with 95% ethanol can be performed before removal of the catheter.

2.2. Surgery

Surgery may be recommended for uncomplicated hepatic cysts of stage CE2/CE3b; large CE1/CE3a cysts; cysts superficially located in the liver with a high risk of rupture; or when percutaneous treatment is not available, difficult or contraindicated (Brunetti 2010). Surgery is the recommended method for complicated cystic echinococcosis cysts in all stages.

Surgical techniques can be classified according to the AORC (Approach, Opening, Resection and Completeness) framework that describes surgical interventions in cystic echinococcosis (Vuitton 2020).

Approach: the surgical approach can be open (laparotomy) or laparoscopic. The laparoscopic approach is less invasive than laparotomy, and has several potential benefits including smaller incisions, reduced blood loss, less pain, lower incidence of wound infections, shorter hospital stay and faster recovery. However, this requires surgical experience in open surgery for cystic echinococcosis and high complexity laparoscopy skills (Wan 2022).

Opening: the resection of a cystic echinococcosis cyst can be performed by opening or not opening the cyst.

Resection: the resection can be performed by removing only the cyst (cystectomy) or the cyst plus a part of the surrounding liver (hepatectomy).

Completeness: refers to the amount of cyst resected. This can be total, subtotal or partial. In subtotal or partial resection, the germinal and laminated layer of the cyst is always resected completely and part of the adventitial layer is left (preserved for surgical safety). The ideal surgical procedure is total cystectomy, which consists of the excision of the entire cyst.

How the intervention might work

1. Medical treatment: albendazole monotherapy

Benzimidazoles interfere with parasite glucose metabolism and the beta-tubulin structure, and are considered parasitostatic (Brehm 2014). Studies carried out on the closely related parasite *Echinococcus multilocularis* have shown that these drugs bind differently to tubulin isoforms preferentially expressed by different parasite cell types, with stem cells (the proliferative cells of the

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metacestode) expressing a tubulin isoform binding weakly to the drug (Brehm 2014).

Albendazole, the most effective and recommended drug, has limited gastrointestinal absorption and is metabolized in the liver to its active metabolite, albendazole sulphoxide, which reaches its peak plasma concentration at 4.75 hours (Ceballos 2018), and then is eliminated primarily via bile. Albendazole is variably absorbed with significant differences in metabolite levels between individuals.

The estimated terminal half-life of albendazole sulphoxide is 8.5 hours. The drug penetrates the cyst, and it is active on protoscoleces and germinal layer somatic cells, while stem cells are less prone to its action (Brehm 2000). In the event of stable parasite inactivation, the cyst content becomes solid and remains solid over time. The cyst size then generally decreases, but complete cyst disappearance can only be observed rarely, and is not expected.

Albendazole is given at a dose of 10 mg/kg/day to 15 mg/kg/day (800 mg daily as standard dose for adults), divided into two doses, in a continuous treatment course (i.e. without the monthly treatment interruptions that were recommended in the 1980s but were not as effective in impacting cyst viability and did not have a safer profile in terms of adverse effects) (Tamarozzi 2020). There are limited data on the optimal duration of treatment for different stages of hepatic cystic echinococcosis.

2. Invasive interventions: percutaneous methods or surgery

Percutaneous methods treat hepatic cystic echinococcosis cysts through chemical inactivation of the germinal layer of the cyst, which contains stem cells from which the cyst further develops with or without drainage of parasitic cyst material.

Surgery aims to remove, as much as is possible, all cyst material from the liver.

In both cases, complete chemical inactivation or complete removal of the germinal layer aims at avoiding the recurrence of the cyst (i.e. re-appearance of an active cyst in the same location where a treated cyst was located).

Prophylactic albendazole (alone or in combination with praziquantel) from days/weeks before to one month after percutaneous intervention or surgery aims to inactivate any protoscoleces that may have been inadvertently spilt outside a cyst during an intervention (Brunetti 2010; Bygott 2009). This aims to prevent the development of secondary echinococcosis arising from the development of new parasitic cysts from any spilt protoscoleces.

Why it is important to do this review

The treatment of uncomplicated cystic echinococcosis varies around the world, between and within countries. The treatment of uncomplicated cystic echinococcosis is currently not standardized; current World Health Organization (WHO) treatment recommendations published in 2010 by the Informal Working Group on Echinococcosis (IWGE), in the form of an Expert Consensus, relied on expert clinician technical expertise and data from retrospective cohort studies and case series for this condition, due to the lack of a higher quality evidence base on treatment options (Brunetti 2010). Individual patient clinical characteristics, available healthcare practitioner expertise and healthcare infrastructure, in addition to individual patient values and preferences for treatment options may all influence the chosen management strategy. Ideally, clinical management should be adapted to the individual patient's clinical context (such as a cystic echinococcosis cyst stage specific approach) as well as the healthcare resources and expertise available.

There is no known methodologically robust systematic review that assesses the effectiveness of different treatment modalities for uncomplicated hepatic cystic echinococcosis by cyst stage or size (or both) to support clinical practice. A Cochrane review aiming to compare the benefits and harms of PAIR with or without benzimidazole coverage for people with uncomplicated hepatic echinococcal cysts in comparison with sham/no intervention, surgery, or medical treatment was undertaken in 2011 (Nasseri-Moghaddam 2011); however, it identified no randomized controlled trials (RCT) comparing PAIR versus no or sham intervention.

This review aimed to address areas of equipoise in the treatment of uncomplicated hepatic cystic echinococcosis. Findings from this review may contribute to a more comprehensive evidence base and identify knowledge gaps in the current understanding of the safety and effectiveness of different interventions for hepatic cystic echinococcosis of different cyst stages or sizes (or both). Review findings may inform clinical decision-making and health guideline processes, lead to improved patient outcomes and aid development of future clinical trials.

OBJECTIVES

To assess the benefits and harms of medication, percutaneous and surgical interventions for treating uncomplicated hepatic cystic echinococcosis.

METHODS

Criteria for considering studies for this review

Types of studies

Our review protocol is registered on PROSPERO (CRD42023421407).

We included RCTs, quasi-RCTs or cluster-RCTs conducted in people with uncomplicated hepatic cystic echinococcosis. We excluded cross-over RCT designs.

The following studies were also ineligible.

- Studies that concerned alveolar echinococcosis (infection with *Echinococcus multilocularis*).
- Studies that did not include participants with hepatic cystic echinococcosis.
- Studies in which an invasive intervention was not given with albendazole.
- Studies conducted in animals.
- Studies that involved participants with complicated hepatic cystic echinococcosis.
- Studies that concerned inactive (CE4-CE5) hepatic echinococcal cysts.
- Studies that did not provide details on the cyst stage according to the WHO Classification System (Brunetti 2010) or, in case of use of the Gharbi classification (Gharbi 1981), did not allow the

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unequivocal assignation of a cyst stage to the corresponding stage within the WHO Classification System.

Studies published in English, Italian or Spanish were eligible for inclusion due to author team language proficiency.

Types of participants

We included all participants, regardless of age, with uncomplicated hepatic cystic echinococcosis (*E granulosus*) in stage CE1/CE2/CE3a/CE3b according to the WHO-IWGE Classification system as defined in the Description of the condition section (Brunetti 2010). We also included studies in which participants had both hepatic and extrahepatic cystic echinococcosis and where participants were diagnosed with imaging (ultrasound, computed tomography or magnetic resonance imaging).

We included studies conducted in any country or setting, including inpatient and outpatient settings.

Uncomplicated hepatic cystic echinococcosis is defined as the participant having the following characteristics:

- asymptomatic or non-specific symptoms such as upper abdominal pain; and
- hepatic cystic echinococcosis confirmed either by imaging appearance with pathognomonic signs of cystic echinococcosis (on diagnosis or appearing after treatment) or examination of the cyst material obtained invasively and identifying the cyst as echinococcal, or a hepatic cyst image appearance without pathognomonic signs of cystic echinococcosis but with associated positive serology; and
- hepatic cystic echinococcosis cyst wall before treatment is intact with no clinical or biochemical suspicion of cyst rupture, communication with the biliary tree, thorax or abdominal cavity or suggestion of secondary bacterial infection.

Types of interventions

Experimental interventions

1. Albendazole monotherapy

Albendazole at any dose and duration, administered continuously.

Intermittent courses (e.g. cycles of 21 days intake interspersed by 15 days of interruption) of albendazole were not eligible.

2. PAIR plus albendazole

Studies in which albendazole was not given in conjunction with PAIR were not eligible.

Studies in which praziquantel was given in conjunction with albendazole were eligible.

3. Standard catheterization plus albendazole

Studies using multisession catheterization, in which the 6- to 8-French catheter is left in place until the remaining fluid drainage is less than 10 mL in 24 hours were eligible.

Studies in which albendazole was not given in conjunction with percutaneous intervention were not eligible.

Studies in which praziquantel was given in conjunction with albendazole were eligible.

4. Modified catheterization technique plus albendazole

Modified catheterization utilizing a 12- to 24-French catheter plus albendazole.

Studies in which albendazole was not given in conjunction with this percutaneous intervention were not eligible.

Studies in which praziquantel was given in conjunction with albendazole were eligible.

5. Surgery (open surgery, i.e. laparotomy, or laparoscopic) plus albendazole

Surgical treatment, whether using an open (laparotomy) or laparoscopic approach, and where the surgeon used a subtotal, partial or total cystectomy technique were eligible.

Studies that focused on comparing different surgical techniques, such as capitonnage, drainage and marsupialization of cysts were not eligible.

Studies in which albendazole was not given in conjunction with percutaneous intervention were not considered.

Study in which praziquantel was given in conjunction with albendazole were eligible.

Comparator interventions

Any one of the following, as defined above, that was not used as the experimental intervention in a study.

- Albendazole monotherapy
- PAIR plus albendazole (praziquantel as an additional drug eligible)
- Standard catheterization plus albendazole (praziquantel as an additional drug eligible)
- Modified catheterization technique plus albendazole (praziquantel as an additional drug eligible)
- Surgery (laparotomy or laparoscopic) plus albendazole (praziquantel as an additional drug eligible)

Types of outcome measures

This review addressed outcomes selected as important by members of the WHO IWGE.

Primary outcomes

- **Symptom improvement**
  - Defined as any patient, clinician or trial investigator report of symptom improvement, measured as the number of participants experiencing the outcome, at any time point reported in the study.
- **Recurrence**
  - Defined as development of one or more new cysts (as determined by ultrasound, magnetic resonance imaging or computed tomography) or presence of an active echinococcal cyst in the same place where a treated cyst was located (as determined by ultrasound or magnetic resonance imaging appearance) within five years after the end of treatment, or the longest follow-up period reported by the study authors.
- **Inactive cyst stage**

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- Defined as a solid appearance on ultrasound, or magnetic resonance imaging consistent with CE4 or CE5 stage, as per the WHO Classification system (Brunetti 2010), at more than 12 months or at the longest follow-up period.

- **All-cause mortality**
  - Defined as any death within 30 days of intervention prior to discharge measured as an absolute number.

Secondary outcomes

- **Development of secondary echinococcosis**
  - Defined as newly formed cysts from the dissemination of parasite material in the peritoneum, within five years after the end of treatment, or the longest follow-up period reported by the study authors.
  - Measured by the number of participants experiencing the outcome, as determined by clinical or trial investigator report or ultrasound, computed tomography or magnetic resonance imaging consistent with disseminated cystic echinococcosis.
- **Complications of treatment**
  - Measured by the number of participants experiencing the outcome, as determined by study investigators.
  - Complications due to treatment categorized as major or minor.
    - Major complications defined as those requiring a prolonged hospital stay, readmission or that are a threat to life.
    - Minor complications all events not considered major.
- **Duration of hospital stay**, measured in days.

Search methods for identification of studies

We attempted to identify all potential studies regardless of publication status (published, unpublished, in press and in progress).

Electronic searches

The Cochrane Infectious Diseases Group Information Specialist searched the following databases using the search terms and strategy described in Appendix 1.

- Cochrane Central Register of Controlled Trials (CENTRAL) (2023, Issue 5)
- MEDLINE (PubMed, from 1966 to 4 May 2023)
- Science Citation Index – Expanded (from 1900), Conference Proceedings Citation Index – Science (CPCI-S, from 1990), from the Web of Science (Clarivate Analytics) (searched 4 May 2023)
- WHO Global Index Medicus (www.globalindexmedicus.net/, accessed 4 May 2023).

She also searched ClinicalTrials.gov (clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (who.int/clinical-trials-registry-platform), for trials in progress.

We used the Cochrane Highly Sensitive Search Strategies for identifying randomized trials in MEDLINE (Lefebvre 2023).

There were no language limits on the search.

Searching other resources

We checked the references of relevant studies to identify additional trials.

Data collection and analysis

Selection of studies

Two review authors (RK and FT) independently screened the title, abstract and keywords of each record identified in the electronic database searches. We retrieved the full-text articles for all potentially relevant studies and all studies where the relevance was unclear from screening. The two review authors (RK and FT) independently applied the inclusion criteria to each of these studies in order to determine their eligibility for inclusion. We resolved any disagreements through discussion, or by consulting the third review author (LU) where appropriate.

We attempted to contact the study authors if clarification regarding any aspects of a study was required. We presented excluded studies and reasons for their exclusion in the Characteristics of excluded studies table.

Data extraction and management

Two review authors (RK and FT) independently extracted data from studies identified in the search and screening process as eligible for inclusion in the review. We entered data onto a prewritten data extraction form including information about the study year of publication; study population; country; cyst stage; cyst size; intervention used (for albendazole and praziquantel information on the drug used, dose, and duration of treatment); if surgery was used whether a laparotomic or laparoscopic approach was undertaken; if a percutaneous intervention was used, details on the method used whether PAIR, standard catheterization, modified catheterization or any variation; outcomes and length of follow-up. In studies in which participants had both hepatic and extra-hepatic cystic echinococcosis, we only extracted data concerning the treatment of the hepatic cyst(s).

For dichotomous outcomes (change in symptoms, recurrence, inactive cyst, all-cause mortality at 30 days, development of secondary echinococcosis and complications), we extracted data concerning the total number of participants enrolled, the number of participants analysed and the total number of participants who experienced the event.

For the continuous outcome (duration of hospital stay), we extracted data concerning the total number of participants enrolled, the number of participants analysed, arithmetic means and standard deviations (SD). If the SD was not reported, we used the confidence interval (CI) to calculate it.

We contacted trial authors for additional data in the event of missing information or where it was not in the format required to undertake the planned analyses.

Two review authors compared the extracted data to identify errors with any conflicts resolved through discussion, or by consulting the third review author (LU) where appropriate. We entered data into Review Manager (RevMan 2024).

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Assessment of risk of bias in included studies

Two review authors (RK and FT) independently assessed the risk of bias for each included study using the Cochrane RoB 1 tool (Higgins 2011). This tool assessed whether adequate steps were taken to reduce the risk of bias across the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other bias. We categorized judgements as 'yes' (low risk of bias), 'no' (high risk of bias), 'unclear' or marked as not applicable.

We compared entries, and resolved any disagreements by discussion, or by consulting the third review author (LU) where appropriate.

Measures of treatment effect

We presented dichotomous data using risk ratios (RR), and continuous data using mean differences (MD). All results are presented with the corresponding 95% CI.

Unit of analysis issues

The unit of analysis for this review was the individual participant; we recorded events by the number of participants experiencing the event, not by the number of cysts involved.

If there were multi-arm trials, to enable individual intervention pairwise comparisons, we selected either relevant arms for inclusion in our analyses, or if more than two arms were relevant to the review, we combined intervention arms to allow a single comparison if appropriate (e.g. study arms with different doses of albendazole). If it was not reasonable to combine intervention groups, we planned to split the 'shared' comparator group to avoid double-counting of participants.

We did not anticipate identifying cluster-randomized studies in this field that would meet the inclusion criteria for this review. However, if we had found any that met the inclusion criteria, we planned to undertake analyses at individual level while accounting for the clustering in the data.

Dealing with missing data

We attempted to address all sources of missing data.

We contacted study authors to obtain missing study characteristics, missing outcomes and missing individual data. When the eligibility of any study was unclear, and we were unable to obtain the required characteristics from study authors, we listed the study in the Characteristics of studies awaiting classification table.

The RoB 1 tool assessed the relevance of missing outcome data (see Assessment of risk of bias in included studies).

If we were unable to obtain missing summary data, we had planned to calculate the required data from other reported statistics using formulas specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). This was not required.

For missing individual data, if study authors did not respond or were unable to provide data, we included only complete participant data, and performed the planned sensitivity analyses to investigate the impact of missing data. This was not required.

Assessment of heterogeneity

We assessed the extent of clinical and methodological heterogeneity by examining study characteristics (e.g. participant characteristics, severity of clinical disease).

We assessed statistical heterogeneity following the presentation of results of meta-analyses in forest plots. We visually inspected the plots (including the presence of overlapping CIs), and used the Chi^2 test with a P value of less than 0.1 to indicate statistical heterogeneity. We quantified any heterogeneity using the I^2 statistic, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. We interpreted this statistic using the following guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022).

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity[a]
- 50% to 90%: may represent substantial heterogeneity[a]
- 75% to 100%: considerable heterogeneity[a]

[a]The importance of the observed value of the I^2 statistic depends on magnitude and direction of effects and strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a CI for the I^2 statistic: uncertainty in the value of the I^2 statistic is substantial when the number of studies is small).

Assessment of reporting biases

We planned to investigate the presence of publication bias using a funnel plot if there were 10 or more studies available for analysis of each primary outcome.

Studies missing from this review may be the result of reporting bias. We tried to identify all studies that met our predefined eligibility criteria, including completed non-published trials in trial registers. We planned to list ongoing trials for which results (either published or unpublished) are not available in the Characteristics of ongoing studies table.

Data synthesis

We assessed the evidence around the efficacy and safety of interventions for the treatment of uncomplicated hepatic cystic echinococcosis with presentation of data of comparisons addressing the following questions.

- For uncomplicated hepatic cystic echinococcosis in WHO stage CE1 or CE3a, is PAIR plus albendazole more effective than albendazole alone?
- For uncomplicated hepatic cystic echinococcosis in WHO stage CE1 or CE3a, is surgery plus albendazole more effective than PAIR plus albendazole?
- For uncomplicated hepatic cystic echinococcosis in WHO stage CE1 or CE3a, is standard catheterization plus albendazole more effective than PAIR plus albendazole?
- For uncomplicated hepatic cystic echinococcosis in WHO stage CE1 or CE3a, is standard catheterization plus albendazole more effective than surgery plus albendazole?
- For uncomplicated hepatic cystic echinococcosis in WHO stage CE2 or CE3b, is surgery plus albendazole more effective than albendazole alone?

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- For uncomplicated hepatic cystic echinococcosis in WHO stage CE2 or CE3b, is laparoscopic surgery plus albendazole more effective than open surgery plus albendazole?
- For uncomplicated hepatic cystic echinococcosis in WHO stage CE2 or CE3b, is modified catheterization plus albendazole more effective than surgery plus albendazole?
- For uncomplicated hepatic cystic echinococcosis in WHO stage CE1, CE2, CE3a or CE3b, is praziquantel plus albendazole more effective than albendazole alone before or after (or both) an invasive intervention?

When clinical and methodological characteristics of individual trials were sufficiently homogeneous, we planned to pool the data in meta-analyses. When there were no concerns of clinical or statistical heterogeneity, we used the fixed-effect model in meta-analyses. Where there was clinical or statistical heterogeneity, and we still considered it appropriate to pool the data, we used the random-effects model.

Subgroup analysis and investigation of heterogeneity

Data permitting, we had planned to conduct subgroup analyses for the following groups.

- Age (paediatric population defined as aged 0 to less than 18 years and adults aged 18 years or greater).
- Cyst size within the following parameters: 5 cm or less (small cyst), 5 cm to 10 cm (medium cyst), 10 cm or greater (large cyst).

Sensitivity analysis

Praziquantel, when added to albendazole, may provide an additive or synergistic effect and thus may skew the meta-analyses effect estimate. We had planned to perform sensitivity analyses with praziquantel included compared to excluded in all applicable analyses to assess the impact on the effect estimate.

To assess the robustness of the data, we had planned to perform sensitivity analyses of summary assessments of the risk of bias including studies that were at low risk of bias for the following key domains: random sequence generation, allocation concealment, blinding of outcome assessors and incomplete outcome data.

Summary of findings and assessment of the certainty of the evidence

The main results of the review are presented in summary of findings tables, including a rating of the certainty of evidence based on the GRADE approach.

Two review authors (RK, FT) assessed the certainty of evidence, considering risk of bias, inconsistency, imprecision, indirectness and publication bias, following current GRADE guidance as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022), and guidance for rating the certainty of evidence in the absence of a single effect estimate (Murad 2017).

We rated each outcome as described by Balshem 2011 as follows.

- High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: 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 the possibility that it is substantially different.
- Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We created summary of findings tables for the comparisons.

- Standard catheterization plus albendazole versus PAIR plus albendazole
- Laparoscopic surgery plus albendazole versus open surgery plus albendazole

The summary of findings tables include all primary and secondary outcomes as predefined in the Types of outcome measures section.

RESULTS

Description of studies

Results of the search

The literature search up to 4 May 2023 resulted in 419 records. After deduplication, 415 records remained. During title and abstract screening, we excluded 395 clearly irrelevant records. We proceeded to retrieve the full-text reports for 20 records. Of these, we excluded 13 studies (14 full-text articles) for reasons summarized in the Characteristics of excluded studies table. Three studies are awaiting classification (see Characteristics of studies awaiting classification table), and we identified no ongoing studies.

We included three studies (Characteristics of included studies table). Our study selection process is illustrated in Figure 1.

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Figure 1.

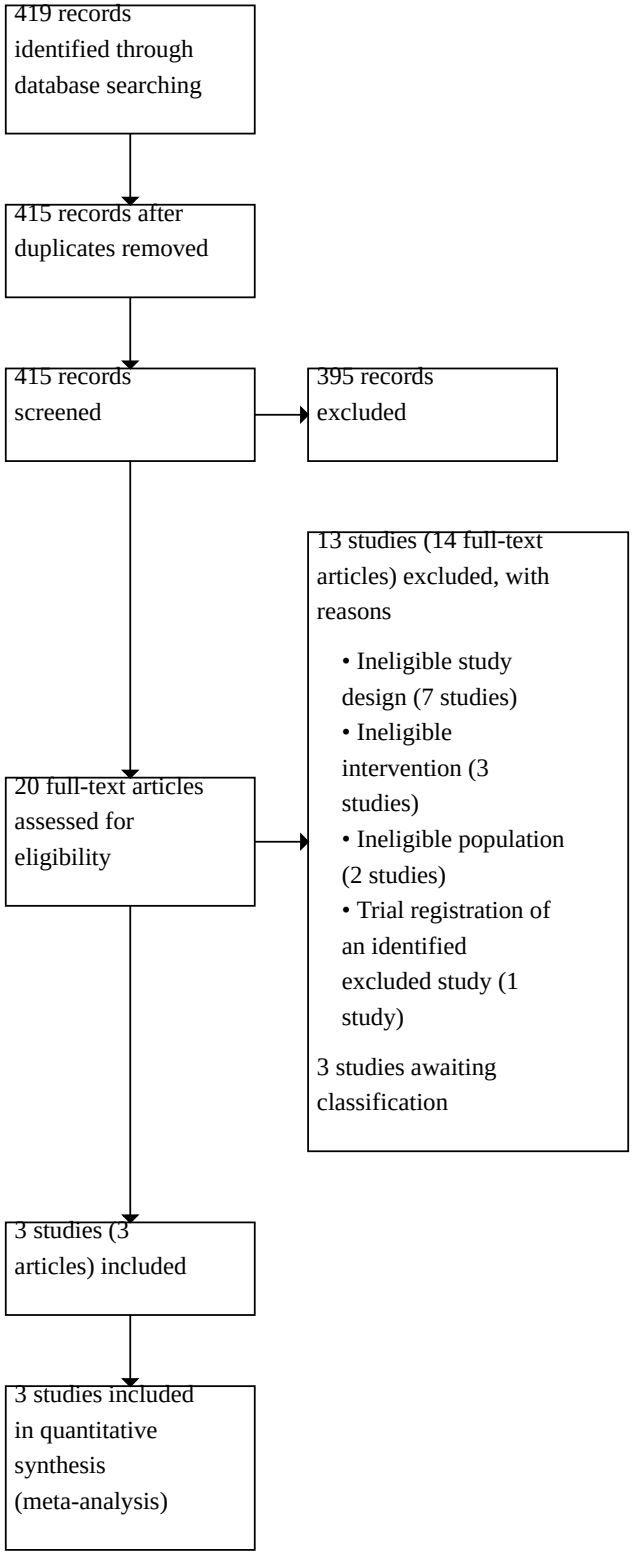

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Figure 1. (Continued)

Included studies

Three RCTs including 180 participants were eligible for inclusion (Ahmad 2020; Akhan 2020; Masood 2022).

All trials were small and lacked statistical power to detect differences between the treatment regimens. The smallest trial had 30 participants and the largest had 82 participants.

Settings

The trials were conducted an inpatient setting in India (Masood 2022), Pakistan (Ahmad 2020), and Turkey (Akhan 2020).

Participants

In total, there were 95 female participants and 85 male participants.

Akhan 2020 included both adults and children (catheterization group: median age 11 years, range 5 to 57 years; PAIR group: median age 13 years, range 5 to 72 years). Ahmad 2020 included adults and children aged 15 to 60 years (laparoscopic group: mean age 40.63 (SD 8.87) years; open surgery group: mean age 39.88 (SD 10.52) years). Masood 2022 included children only (laparoscopic group: mean age 10.82 years; open surgery group: mean age 10.9 years; range 6 to 14 years in both groups).

All studies used ultrasonography to diagnose and classify cysts. Two studies included cyst stages using the WHO cyst classification system: CE2 and CE3b (Ahmad 2020) and CE1 and CE3a (Akhan 2020). One study included cyst stages using the Gharbi classification system (Masood 2022). The Gharbi stages were reclassified into the WHO stage classification using the reported cyst characteristics within the study (see Table 2).

Interventions

One study compared standard catheterization plus albendazole versus PAIR plus albendazole in adults and children with CE1 and CE3a cysts (Akhan 2020). Two senior interventional radiologists who had at least 10 years of experience performed all procedures.

Two studies compared laparoscopic surgery plus albendazole versus open surgery plus albendazole in adults and children with CE1, CE2, CE3a and CE3b cysts (Ahmad 2020; Masood 2022). Neither study reported the number and experience of the surgeons undertaking the operations.

We did not find any trials assessing the following.

- Albendazole alone versus PAIR plus albendazole
- Surgery plus albendazole versus PAIR plus albendazole
- Albendazole alone versus surgery plus albendazole
- Modified catheterization technique plus albendazole versus surgery plus albendazole
- Albendazole plus praziquantel versus albendazole alone before or after (or both) an invasive intervention

Outcomes

Three studies reported recurrence, all-cause mortality, minor complications and duration of hospital stay.

Two studies reported major complications by participant (Ahmad 2020; Masood 2022), and one study by cyst (Akhan 2020).

One study reported development of secondary echinococcosis (Akhan 2020).

No studies reported symptom improvement or inactive cyst at 12 months.

Excluded studies

Of the 13 excluded studies, we excluded seven studies due to an ineligible study design (not an RCT or cluster-RCT), three studies due to an ineligible intervention, two studies for an ineligible participant population and one study as it was the trial registration of an identified excluded study.

Studies awaiting classification

One study is awaiting classification due to uncertainty regarding the number of events for the outcome of recurrence; the study reported data for this outcome inconsistently (Mijbas 2020). We received no reply from the corresponding author of this study and were unable to verify the data.

Two studies did not report information on the use of albendazole or cyst stage (CTRI/2013/07/003844; NCT01643018).

For further details, see Characteristics of excluded studies table.

Ongoing studies

We identified no ongoing studies.

Risk of bias in included studies

We summarized the risk of bias judgements in Figure 2 and Figure 3.

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Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

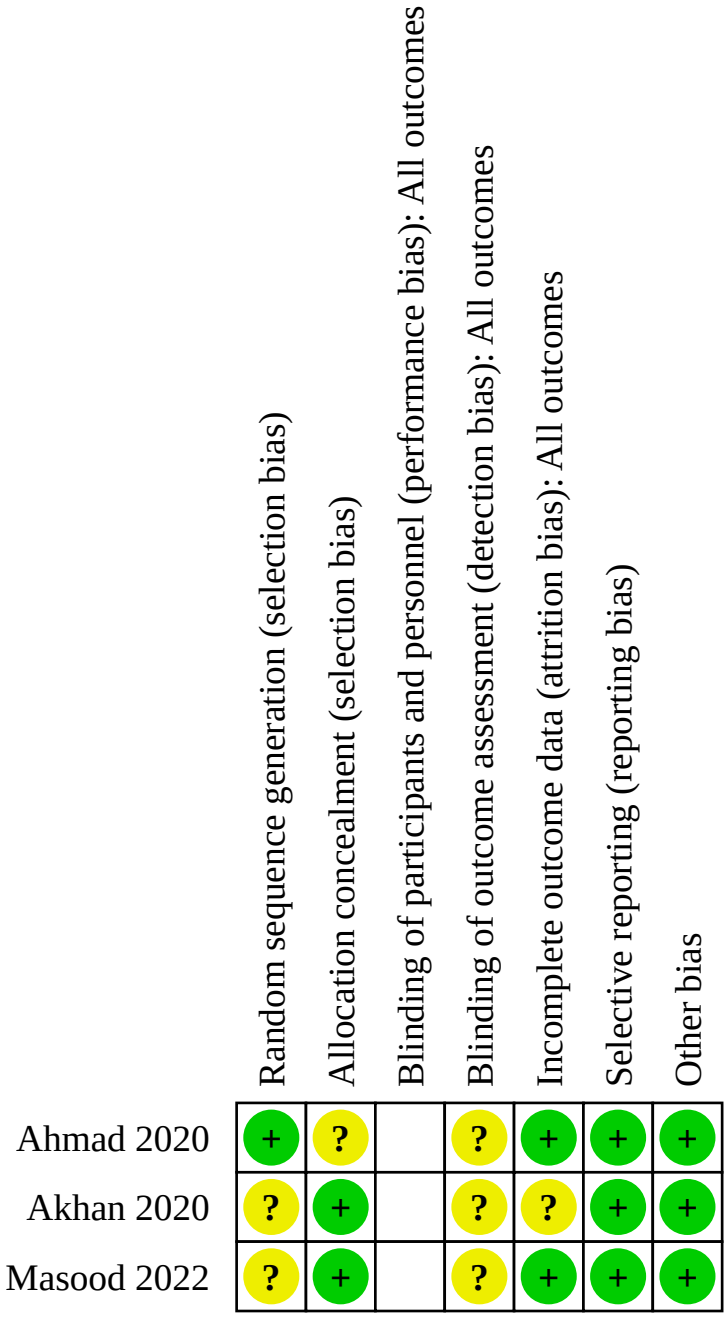

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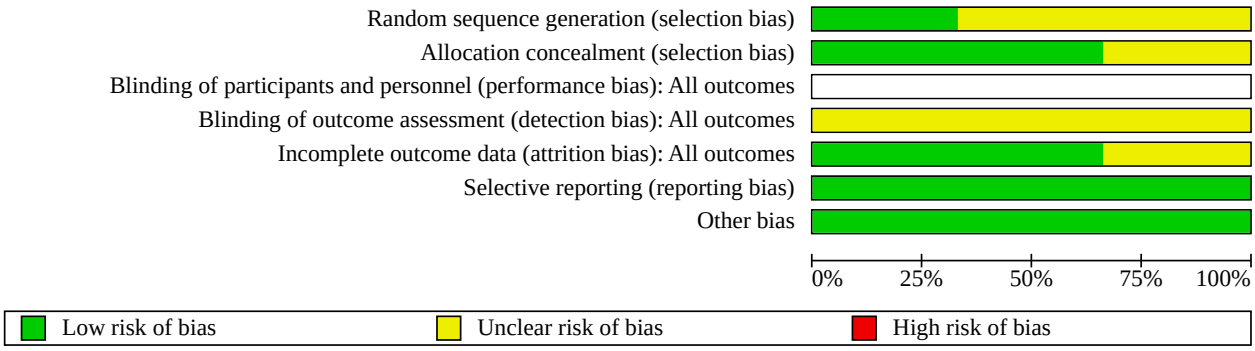
Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation was at low risk of bias for one study (Ahmad 2020). Akhan 2020 and Masood 2022 were at unclear risk of bias as there was insufficient information to determine the method of random sequence generation.

We judged allocation concealment at low risk of bias for two studies as they described use of a sealed envelope technique (Akhan 2020; Masood 2022). One study reported no details on allocation concealment and the risk of bias for allocation concealment was unclear (Ahmad 2020).

Blinding

Blinding of participants and personnel (performance bias) was not considered possible and this risk of bias domain was not applicable. Intervention and comparator groups were oral medication (albendazole), a percutaneous procedure or surgery; all participants and personnel would have been aware of which intervention they received.

Three studies did not report details concerning blinding of outcome assessment (detection bias); we judged all studies at unclear risk of bias.

Incomplete outcome data

We judged two studies at low risk of attrition bias (Ahmad 2020; Masood 2022). One study did not report data on numbers lost to follow-up and was at unclear risk (Akhan 2020).

Selective reporting

All studies were at low risk of selective reporting bias; each study reported data for prespecified outcomes.

Other potential sources of bias

There were no other potential sources of bias.

Effects of interventions

See: **Summary of findings 1** Standard catheterization plus albendazole versus PAIR plus albendazole for hepatic cystic echinococcosis; **Summary of findings 2** Laparoscopic surgery plus albendazole versus open surgery plus albendazole for hepatic cystic echinococcosis

Standard catheterization plus albendazole versus PAIR plus albendazole

See Summary of findings 1.

One study assessed this comparison (Akhan 2020). The mean length of follow-up was 71 months (range 6 to 164 months) in the standard catheterization plus albendazole group and 78.1 months (range 12 to 188 months) in the PAIR plus albendazole group. The cyst stages included in the trial were CE1 and CE3a.

Primary outcomes

Symptom improvement

The study did not report this outcome (Akhan 2020).

Recurrence

The evidence is very uncertain about the effect of standard catheterization plus albendazole on cyst recurrence. Recurrence was reported in 1/17 (5.9%) participants in the standard catheterization plus albendazole group compared with 0/21 participants in the PAIR plus albendazole group (RR 3.67, 95% CI 0.16 to 84.66; 1 study, 38 participants; very low-certainty evidence; Analysis 1.1).

Recurrence in the one participant in the standard catheterization plus albendazole group was detected five months following the intervention.

Inactive cyst stage

The study did not report this outcome (Akhan 2020).

All-cause mortality

The evidence is very uncertain about the effect of standard catheterization plus albendazole on all-cause mortality compared to PAIR plus albendazole. There were no cases of all-cause mortality at 30 days in either group (38 participants; very low-certainty evidence).

Secondary outcomes

Development of secondary echinococcosis

The evidence is very uncertain about the effect of standard catheterization plus albendazole on the development of secondary echinococcosis compared to PAIR plus albendazole. There were no

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cases of secondary echinococcosis in either group (38 participants; very low-certainty evidence).

Complications of treatment

The study reported major complications by cyst and not by participant (Akhan 2020). Standard catheterization plus albendazole may increase major complications compared to PAIR plus albendazole, but the evidence is very uncertain. There were 6/19 (31.6%) cysts in the standard catheterization plus albendazole group associated with a major complication (abscess in 2 cysts, cysto-biliary fistula in 1 cyst, both abscess and cysto-biliary fistula in 3 cysts). There were 1/34 (2.9%) cysts in the PAIR plus albendazole group associated with a major complication (abscess in 1 cyst). Calculations using the number of cysts as the event and the total number of cysts as the denominator in each group gave an RR of 10.74 (95% CI 1.39 to 82.67; 1 study, 53 cysts; very low-certainty evidence).

Standard catheterization plus albendazole may make little to no difference on minor complications, but the evidence is very uncertain. There were minor complications in 10/17 (58.8%) participants in the standard catheterization plus albendazole group compared with 12/21 (57.1%) participants in the PAIR plus albendazole group (RR 1.03, 95% CI 0.60 to 1.77; 1 study, 38 participants; very low-certainty evidence; Analysis 1.2).

Duration of hospital stay

Standard catheterization plus albendazole may increase the duration of hospital stay compared to PAIR plus albendazole, but the evidence is very uncertain. The median length of hospital stay was four days (range 1 to 52 days) in the standard catheterization plus albendazole group compared with one day (range 1 to 15 days) in the PAIR plus albendazole group (1 study, 38 participants; very low-certainty evidence).

Laparoscopic surgery plus albendazole versus open surgery plus albendazole

See Summary of findings 2.

Two studies reported this comparison (Ahmad 2020; Masood 2022). The cyst stages included in the trial were CE1, CE2, CE3a and CE3b.

Primary outcomes

Symptom improvement

Neither study reported this outcome.

Recurrence

Two studies reported recurrence. The evidence is very uncertain about the effect of laparoscopic surgery plus albendazole on cyst recurrence compared to albendazole plus open surgery.

Masood 2022 reported no cases of recurrence in either group (60 participants) at two-year follow-up. In Ahmad 2020, there was recurrence in 1/41 (2.4%) participants in the laparoscopic surgery plus albendazole group and zero recurrences amongst the 41 participants (0%) in the open surgery plus albendazole group (RR 3.00, 95% CI 0.13 to 71.56; 1 study, 82 participants; very low-certainty evidence; Analysis 2.1). The duration of follow-up in this study was 12 months.

Inactive cyst stage

Neither study reported this outcome.

All-cause mortality

The evidence is very uncertain about the effect of laparoscopic surgery plus albendazole on all-cause mortality in participants with CE1, CE2, CE3a or CE3b cysts compared to open surgery plus albendazole. Both studies reported zero cases of all-cause mortality at 30 days in both groups (2 studies, 142 participants; very low-certainty evidence; Ahmad 2020; Masood 2022).

Secondary outcomes

Development of secondary echinococcosis

Neither study reported this outcome.

Complications of treatment

The evidence is very uncertain about the effect of laparoscopic surgery plus albendazole on major complications compared to open surgery plus albendazole (RR 0.50, 95% CI 0.13 to 1.92; 2 studies, 142 participants; very low-certainty evidence; Analysis 2.2). The main complication was the development of a biliary fistula. Participants were followed up for one to two years.

Laparoscopic surgery plus albendazole may lead to slightly fewer minor complications compared to open surgery plus albendazole (RR 0.13, 95% CI 0.02 to 0.98; 2 studies, 142 participants; low-certainty evidence; Analysis 2.2). Wound infections were the most common minor complication reported. Participants were followed up for one to two years.

Duration of hospital stay

Laparoscopic surgery plus albendazole may reduce the duration of hospital stay compared with open surgery plus albendazole (MD −1.90 days, 95% CI −2.99 to −0.82; 2 studies, 142 participants; low-certainty evidence; Analysis 2.3).

DISCUSSION

This Cochrane review aimed to assess the safety and efficacy of surgical, percutaneous and drug interventions for treating uncomplicated hepatic cystic echinococcosis in areas of equipoise for WHO-IWGE cyst stages CE1, CE2, CE3a and CE3b cysts.

Summary of main results

This review included one study of 38 adults and children with CE1 and CE3a cysts in Turkey comparing standard catheterization plus albendazole to PAIR plus albendazole, and two studies of 142 adults and children with CE1, CE2, CE3a and CE3b cysts in India and Pakistan comparing laparoscopic surgery plus albendazole to open surgery plus albendazole. Studies were conducted between 2020 and 2022. The number of studies per outcome was low and studies lacked statistical power to detect differences between the treatment regimens.

The main findings of the review are summarized in Summary of findings 1 and Summary of findings 2.

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Standard catheterization plus albendazole versus PAIR plus albendazole

We are very uncertain about the effect of standard catheterization plus albendazole on recurrence, all-cause mortality and development of secondary echinococcosis compared to PAIR plus albendazole for adults and children with CE1 and CE3a cysts. We have no data on major complications by individual participants, only by cysts. Standard catheterization plus albendazole may increase major cyst complications compared with PAIR plus albendazole, but the evidence is very uncertain. Standard catheterization plus albendazole may increase the duration of hospital stay compared with PAIR plus albendazole, but the evidence is very uncertain.

No studies reported symptom improvement or inactive cyst at 12 months.

Laparoscopic surgery plus albendazole versus open surgery plus albendazole

We are very uncertain about the effect of laparoscopic surgery plus albendazole on recurrence, all-cause mortality and major complications compared to open surgery plus albendazole in adults and children with CE1, CE2, CE3a, CE3b cysts.

No studies reported symptom improvement or inactive cyst at 12 months.

Other comparisons

We did not find any trials assessing the following.

- Albendazole alone versus PAIR plus albendazole
- Surgery plus albendazole versus PAIR plus albendazole
- Albendazole alone versus surgery plus albendazole
- Modified catheterization technique plus albendazole versus surgery plus albendazole
- Albendazole plus praziquantel versus albendazole alone before or after (or both) an invasive intervention

Overall completeness and applicability of evidence

There is a paucity of RCTs available to inform the review objective. There are too few trials within each comparison, and the trials themselves are underpowered. We found no eligible studies including albendazole alone in comparison to other treatments and no studies including praziquantel plus albendazole before or after (or both) surgery or a percutaneous intervention. No studies reported the outcomes of symptom improvement and inactive cysts at 12 months.

Studies included adults and children and were conducted in healthcare facilities in which cystic echinococcosis is endemic. The included participants are likely to represent the wider population with cystic echinococcosis in endemic settings. Healthcare settings can vary widely with regard to healthcare resources and clinical expertise; treatments such as surgery or percutaneous interventions for cystic echinococcosis should not be embarked upon in settings where resources and expertise are lacking, and patient safety is at risk.

Adequate follow-up periods are important for outcomes including recurrence, inactive cyst and development of secondary echinococcosis. Mean time to recurrence from non-randomized studies is most commonly within two years, ranging from one month to eight years (Franchi 1999; Gollackner 2000; Kapan 2006; Prousalidis 2008; Stojkovic 2009). Amongst our included studies, one had a follow-up period of five years, but did not report details of participant dropout during the follow-up period (Akhan 2020). One study had a follow-up period of one year (Ahmad 2020), and one study had a follow-up period of two years (Masood 2022).

The lack of RCTs was expected, as these trials are very difficult to undertake in single treatment centres. Multicentre trials could help aspects such as participant recruitment. However, there are other factors to consider, including the long follow-up times to inform outcomes and in the circumstance of different treatment centres often using different standard procedures for different cyst stages.

Certainty of the evidence

The certainty of evidence for reported outcomes ranged from very low to low (Summary of findings 1; Summary of findings 2).

Certainty of evidence for all outcomes was downgraded due to risk of bias (no study gave details concerning blinding of outcome assessment and unclear details regarding participant loss to follow-up in one study) and risk of imprecision (low participant numbers and low numbers of events in all studies). We downgraded the outcome of recurrence due to a short follow-up period of 12 months in the comparison of laparoscopic surgery plus albendazole compared to open surgery plus albendazole.

Studies reporting the outcome of mortality and the development of secondary echinococcosis included zero events in control and intervention groups. This meant an effect estimate could not be calculated.

We did not consider downgrading for publication bias due to the comprehensive nature of the search strategy in combination with two review authors being experts in this topic on the WHO Guideline Development Group for cystic echinococcosis and no knowledge of any further RCTs that had been missed.

We identified no studies reporting on the outcomes of symptom improvement or inactive cyst stage at 12 months.

Potential biases in the review process

The search methods were thorough and included contact with topic experts, healthcare workers and researchers in this field. We could not have included studies reported in a language other than English, Italian or Spanish due to limitations in author team language proficiency outside these languages.

One trial reported outcome data inconsistently; we contacted the authors of this trial for data clarification, but were unsuccessful (Mijbas 2020).

No review authors have any affiliation with any stakeholder group who favours or disapproves of any treatment method used in the included studies.

Agreements and disagreements with other studies or reviews

One Cochrane review in 2011 of two RCTs included the comparisons of PAIR plus albendazole to albendazole alone and PAIR plus

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surgery compared to PAIR plus albendazole (Nasseri-Moghaddam 2011). Our literature search identified these studies but excluded them due to lack of reporting of cyst stage (Khuroo 1993; Khuroo 1997). No studies included in our review addressed the treatment comparisons of the 2011 Cochrane review.

This review did not find any conflicting evidence compared to an expert consensus (Brunetti 2010).

There is no other known systematic review comparing the treatment options for uncomplicated hepatic cystic echinococcosis.

AUTHORS' CONCLUSIONS

Implications for practice

Percutaneous interventions plus albendazole or surgery (open or laparoscopic) plus albendazole may effectively and safely treat adults and children with uncomplicated hepatic cystic echinococcosis, but the evidence is very uncertain.

There are limited implications for practice due to the lack of available evidence. We found no eligible studies including albendazole alone in comparison to other treatments. We are unable to draw any firm general conclusions on the comparative effectiveness of included treatment options due to the limited number of trials, small number of participants and lack of events for some outcomes.

Treatment choice needs to consider the number of cysts, stage of the cysts, health resources available, general health of the patient and their treatment preference.

Implications for research

This review has important research implications. It highlights the limited evidence base from randomized controlled trials to guide management of cystic echinococcosis, lack of standardized outcomes and long-term follow-up of outcomes, and the absence of multicentre studies.

As such, well-designed randomized controlled trials comparing albendazole, percutaneous treatments combined with albendazole and surgery combined with albendazole for cyst stages CE1, CE2, CE3a and CE3b are necessary to inform treatment options.

Due to the heterogeneity of clinical disease, long period of observation needed between intervention and assessment of outcomes, and differing expertise and resources available in endemic areas, such prospective studies can only be carried out through well-funded multicentre studies, allowing the required follow-up time. These conditions have been, so far, virtually impossible to realize, and the lack of listing echinococcosis amongst the priority list of research funders is contributing to the difficulty in addressing these fundamental questions.

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this review.

- Sign-off Editor (final editorial decision): Hellen Gelband, Cochrane Infectious Diseases
- Managing Editor (provided editorial guidance to authors, edited the article): Joey Kwong, Cochrane Central Editorial Service
- Editorial Assistant (selected peer reviewers, conducted editorial policy checks, collated peer-reviewer comments and supported the editorial team): Jacob Hester, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Anne Lawson, Cochrane Central Production Service
- Peer reviewers (provided comments and recommended an editorial decision): Laura E Nabarro, Department of Clinical Parasitology, The Hospital for Tropical Diseases, London (clinical/content review); Jennifer Hilgart and Clare Miles, Cochrane Evidence Production and Methods Directorate (methods review); Jo Platt, Cochrane Evidence Production and Methods Directorate (search review). One additional peer reviewer provided clinical/content peer review but chose not to be publicly acknowledged.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahmad 2020

Study characteristics	
Methods	Trial design: prospective randomized controlled study
	Diagnostic method: history, examination, ultrasound and computed tomography scan

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Ahmad 2020 *(Continued)*

	Time period: December 2015 to December 2019 Follow-up: 12 months
Participants	82 participants 41 in laparoscopic surgery plus albendazole group 41 in open surgery plus albendazole group Gender: 47 male, 35 female Age: 15–60 years Laparoscopic surgery plus albendazole group: mean 40.68 (SD 8.87) years; open surgery plus albendazole group: mean 39.88 (SD 10.52) years; range 15–50 years reported across both groups Setting: Pakistan Cyst stage: CE2 and CE3b Cyst size: ≥ 5 cm Inclusion criteria: liver cystic echinococcosis diagnosed based on history, examination, ultrasound and computed tomography scan Exclusion criteria: cystic echinococcosis in organs outside the liver; recurrent disease; cysto-biliary communication; ruptured cysts
Interventions	All participants received albendazole 10 mg/kg 1 week prior to surgery and continued for 3 months following surgery. • Laparoscopic surgery plus albendazole Involved pneumoperitoneum and insertion of 30-degree laparoscope through the 10-mm umbilical port. Another 10-mm trocar was placed at the epigastrium with 2 other 5 mm trocars placed at standard sites in midclavicular line and anterior axillary line. Hypertonic saline-soaked gauze was placed around the cyst. 20% saline was injected into cyst and left for 10 minutes, contents were aspirated. A wide cystostomy was performed with a hook. The cyst cavity was explored and viewed with the camera to extract any remaining daughter cysts. The bulged pericyst wall was excised using ligasure. The excised pericyst wall and germinal membrane were placed in a plastic bag and removed through epigastric port and omentoplasty of the residual cavity was performed. • Open surgery plus albendazole Open surgery involved opening the abdominal cavity via a right subcostal incision, hypertonic saline-soaked packs placed around the cyst. 20% saline was injected into the cyst and left for 10 minutes and then contents were aspirated with large bore suction tip. Starting from the puncture site, cystotomy was performed and the bulged pericyst wall was excised using electrocautery. All the germinal membrane and daughter vesicles were extracted and omentoplasty of residual cavity was performed.
Outcomes	• Recurrence • Duration of hospital stay • Complications • Death
Notes	No funding source reported.

Risk of bias

Bias	Authors' judgement	Support for judgement

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Ahmad 2020 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "They were randomly allocated into two groups A and B using lottery method." We considered the lottery method to be an adequate method of simple randomization.
Allocation concealment (selection bias)	Unclear risk	No details given.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients were followed for one year."
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported.
Other bias	Low risk	No other concerns identified.

Akhan 2020

Study characteristics	
Methods	Trial design: prospective randomized controlled study Diagnostic method: ultrasound Time period: (quote) "within a five year period" Participants were allocated to 2 treatment groups: PAIR plus albendazole and standard catheterization plus albendazole Mean follow-up: standard catheterization group: 71 months (range 6–164 months); PAIR group: 78.1 months (range 12–188 months)
Participants	38 participants; 56 cysts; 27 females, 11 males Setting: Turkey Age: 5–72 years Intervention group: median 11 years, range 5–57 years; control group: median 13 years, range 5–72 years Cyst stage: WHO CE1 and CE3a cysts Cyst size: diameter ≥ 4 cm Data unable to be separated by cyst size Inclusion criteria: WHO CE1 and CE3a liver hydatid cysts with diameter ≥ 4 cm irrespective of the presence of absence of symptoms Exclusion criteria: WHO CE2 or CE3b or CE4 or CE5 cysts; presence of extrahepatic cysts; CE1 and CE3a cysts with diameter < 4 cm

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Akhan 2020 *(Continued)*

Interventions	• Standard catheterization plus albendazole Albendazole 10–15 mg/kg daily starting 1 week prior to catheterization and continuously for 4 weeks after the procedure. Catheterization performed under general anaesthetic with ultrasound and fluoroscopic guidance. • PAIR plus albendazole Albendazole 10–15 mg/kg daily starting 1 week prior to PAIR plus continuously for 4 weeks after the procedure. PAIR performed under general anaesthesia with ultrasound and fluoroscopic guidance.
Outcomes	• Recurrence • Duration of hospital stay • Complications
Notes	Authors reported that the study was not supported by any funding.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomisation was done with sealed envelope technique." There was insufficient information to determine the method of random sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "randomisation was done with sealed envelope technique." We judged this to be related to allocation concealment rather than random sequence generation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants lost to follow-up not reported.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported.
Other bias	Low risk	No other concerns identified.

Masood 2022

Study characteristics

Methods	Trial design: prospective randomized controlled trial Time period: participants recruited between January 2013 and January 2018. Setting: Srinagar, India

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Masood 2022 *(Continued)*

	Follow-up: minimum 2 years
Participants	Number of participants: 60 Age: 6–14 years Laparoscopic surgery plus albendazole: mean 10.82 years; open surgery plus albendazole: 10.9 years; range 6–14 years in both groups Gender: male 33, female 27 Diagnosis: hepatic cystic echinococcosis diagnosed by ultrasound abdomen, contrast-enhanced computed tomography abdomen pelvis and immunoglobulin G antibody Cyst characteristics: Gharbi stage: I, II, III Mean cyst size: 8.8 (standard deviation 2.39) cm Inclusion criteria: Gharbi stage I, II, III hepatic cysts; ≤ 3 hepatic cysts; superficial laparoscopically accessible cysts Exclusion criteria: stage IV and V cysts; > 3 cysts; inaccessible cysts
Interventions	All participants received albendazole 15 mg/kg daily for ≥ 4 weeks preoperatively and continued postoperatively for ≥ 3 cycles with each cycle extending up to 3 weeks with 1-week gap inbetween. • Laparoscopic surgery plus albendazole All laparoscopic procedures were performed in the supine position. Antibiotics were administrated 30 minutes before the incision. With the participant under general anaesthesia, pneumoperitoneum was created by open technique. An intra-abdominal pressure of 12 mmHg was achieved. A 30-degree scope was introduced through a 5-mm umbilical port and a 10-mm suction cannula through a subxiphoid port. 2 other 5-mm trocars were placed at the standard sites as per the location of cyst in the liver after performing diagnostic laparoscopy through 5-mm umbilical port. After initial laparoscopic evaluation, the suitability of the cyst for laparoscopic management was confirmed. Essentially, the following steps were adopted; pericystic packing with cetrimide-soaked or betadine-soaked gauze to take care of spillage, decompression of the cyst by aspiration using a wide bore needle introduced at an antigravity position through 1 of the 5-mm ports with placement of 2 × 5-mm suction cannulas next to the aspirating needle to control the spillage, naked eye examination of the fluid for the presence of bile or pus suggestive of cysto-biliary communications, injection of 3% hypertonic saline or cetrimide for 10 minutes to ensure complete killing of the organism, followed by aspiration. Cystotomy was made in the pericyst in non-dependent area with scissors or with the hook electrode, followed by removing the germinative membrane in a plastic bag or by using locally improvised specimen bags to prevent contamination followed by extraction through the epigastric port. Cyst cavity was telescoped for any remaining membranes or cysto-biliary communications. The management of the residual cavity was achieved by placement of omentum into the residual cavity if the location or the configuration of the cyst warranted or by simple tube drainage, unroofing partial pericystectomy. During the procedure, spillage of cyst contents was anticipated and its severity rated by an independent observer. • Open surgery plus albendazole Open technique used a right subcostal approach in most patients. The operative field was carefully protected from hydatid fluid spillage using packs soaked in cetrimide or betadine. The cyst was decompressed by inserting a large-bore angiocath needle and hydatid fluid was aspirated with a syringe after which cetrimide solution was injected into the cavity and left there for 10 minutes. The pericyst was opened and the cyst contents were evacuated including, the laminated membrane and hydatid fluid. The cavity was cleaned with gauze soaked in a cetrimide solution. At the end of the procedure, the cavity was examined for any bile duct leakage which, if found, was closed with vicryl suture. The residual cavity was finally managed by mainly either of the 2 techniques (external tube drainage or omentopexy).
Outcomes	Primary outcomes

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Masood 2022 *(Continued)*

- Operative time
- Recurrence at 2 years

Secondary outcomes

- Hospital stay
- Duration of analgesia
- Postsurgery pain on Visual Analogue Scale
- Time to ambulate
- Time to tolerate orals
- Bowel movements
- Time to remove drains

Notes	No sources of financial sponsorship reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The authors reported that (quote) "simple randomization with a sealed envelope 1:1 technique" was undertaken. We judged that this did not provide sufficient information to determine the method of simplified random sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Simple randomization with a sealed envelope 1:1 technique" We judged this to mean that participant allocations were placed in sealed envelopes and thus concealed.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participant was lost to follow-up.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported.
Other bias	Low risk	No other concerns identified.

PAIR: puncture, aspiration, injection and re-aspiration; SD: standard deviation; WHO: World Health Organization.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbas 2006	Ineligible study design (not an RCT)
Akhan 2002	Ineligible study design (abstract only); corresponding author contacted and full paper unavailable.
Akhan 2014	Ineligible intervention.
El Elshafey 2018	Ineligible study design (abstract only; unable to retrieve full text).

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Study	Reason for exclusion
Hamdy 2019	Ineligible study design (not an RCT).
Jabbari Nooghabi 2015	Ineligible study design (not an RCT).
Khuroo 1993	Ineligible population: no cyst stage reported.
Khuroo 1997	Ineligible population: no cyst stage reported.
Minaev 2017	Ineligible study design (not an RCT).
Shams-Ul-Bari 2011	Ineligible intervention.
Shera 2017	Ineligible intervention.
Tuxun 2014	Ineligible study design (not an RCT).
Yüksel 2008	Ineligible intervention.

RCT: randomized controlled trial.

Characteristics of studies awaiting classification *[ordered by study ID]*

CTRI/2013/07/003844

Methods	Study design: randomized, parallel group interventional trial Setting: India Recruitment status: open to recruitment Target sample size: 122 participants Method of generating random sequence: computer-generated randomization Method of concealment: sequentially numbered, sealed, opaque envelopes Registered: 26 July 2013
Participants	Inclusion criteria: all accessible hydatid liver disease diagnosed on computed tomography scan as a cyst with internal membrane; willing to give informed consent. Exclusion criteria: pregnancy; sepsis; calcified cysts; previous intervention (surgical or percutaneous); medial comorbidities making the patient unfit for anaesthesia.
Interventions	• Laparoscopic surgery • PAIR
Outcomes	• Cyst outcome, measured at the immediate postprocedure period (within 24 hours) and at 1 year thereafter • Complications • Conversion to open surgery • Re-intervention rate • Hospital stay • Cost
Notes	Reasons awaiting classification

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CTRI/2013/07/003844 *(Continued)*

- No information on cyst stage
- No information on whether participants receive albendazole in each group

Contact: Dhiraj John Sonbare; Christian Medical College, Vellore, India

Mijbas 2020

Methods	Trial design: prospective randomized study Time period: October 2016 to October 2018 Setting: Iraq Follow-up: 12 months
Participants	Number of participants: 60 (28 laparoscopic surgery, 32 open surgery) Age: 11–68 years Gender: 37 female, 23 male Diagnostic method: ultrasonography, computed tomography of the abdomen and chest X-ray Cyst stage: Gharbi stage I, III Inclusion criteria: hepatic cystic echinococcosis, absence of any exclusion criteria Exclusion criteria: having > 2 liver hydatid cysts; cyst located in liver segment 1 and 7; cyst set > 1-cm depth from the surface of the liver; cysts with thick calcified walls; recurrent hydatid cyst disease; previous multiple upper abdominal surgeries; severe cardiopulmonary disease; serious coagulation abnormalities; cyst < 3 cm in diameter.
Interventions	• Laparoscopic surgery group All operations were done under general anaesthesia and in the supine position. Surgery of the right lobe cyst, 3 ports placed, 1 infra-umbilical 5–10-mm port through which a 0-degree or 30-degree telescope inserted in, carbon dioxide pneumoperitoneum was established, and intra-abdominal pressure maintained at 8–16 mmHg. Another 10-mm port was made at the epigastric region as close to the cyst and used as a working port, and 1 additional 5-mm port inserted according to the location of the cyst. For the left lobe cyst, 1 × 10 mm and 1 × 5 mm port was placed in the midclavicular line at the level above the umbilicus, in addition to infra-umbilical ports. From the 10-mm working port, gauzes soaked with 10% povidone-iodine, a scolicidal agent, were inserted in the cavity of the abdomen and were placed around the cyst. The cyst pierced with long laparoscopic needles connected to suction vacuum through the epigastric port. Another suction was used through the right 5-mm port to avoid cystic spillage content accidentally. The fluid of the cystic was aspirated, and then 10% povidone-iodine was injected inside of the cyst cavity via the same needle, and then aspirated again. This procedure repeated 3 times, and then the needle was withdrawn while still connected to vacuum suction to prevent back spillage from the needle. A puncture needle in the cyst enlarged sufficient enough to allow the tip of suction enters inside the cyst then the suction tip introduced inside the cavity of the cyst, aspirated of the contents by the help of a suction cannula. The cystic wall after deflation held with a grasper and deroofing of the cyst performed using a hook electrical diathermy. The daughter cysts and the laminated membrane carefully extracted as in Figure 3 of the publication and using the endo-bag. Then a 30-degree telescope was introduced in the cavity for visualization and to find any biliary communication or remnant cysts. The cavity of the cyst was washed with povidone-iodine many times. The partial cystectomy performed using a monopolar electrocautery hook or scissor. 2 drains introduced, 1 inside the cavity of the cyst and 1 in the subhepatic space. Endobag with daughter cysts removed through the 10-mm port. • Open surgery group

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Mijbas 2020 *(Continued)*

	All operations performed under general anaesthesia and in the supine position. The right subcostal Kocher incision. The pericystic area and field of operation covered with gauze immersed with scolicidal material (10% povidone-iodine) to avoid the scolices spillage into the cavity of the peritoneum. The cyst was drilled, and fluid withdraw. The fluid that aspirated in uncomplicated cysts was clear and colourless and called rock water. Before injecting the scolicidal agent, as much fluid as possible was withdrawn to avoid the scolicidal material dilution. Then scolicidal agent was injected into a cyst cavity and left for approximately 10 minutes. However, if the aspiration of cyst fluid containing bile hinted a connection between the cyst and the bile duct, a scolicidal agent was not injected to avoid sclerosing cholangitis. Then, the scolicidal material was re-aspirated, and the cyst was deroofed. The contents of the cyst, such as daughter cysts and the germinative membrane, were removed. The cavity should have been opened accurately for any apparent connection with the biliary tree and the existence of exogenous cysts implanted in the cyst cavity wall. The following step was treating the residual cavity, which was performed by using different procedures such as external drainage and omentoplasty and capitonage. Postoperatively, in both laparoscopic surgery and open surgery, oral clear fluid intake was permitted on the next day of surgery. The drain inside the cyst was removed 72 hours after the operation if no significant drainage of bile and subhepatic drains removed after 4th day postsurgery. All participants were treated preoperatively with 3 courses of 21-day duration albendazole 10–15 mg/kg twice a day. Postoperatively all participants were given albendazole 10–15 mg/kg bodyweight for 6 weeks.
Outcomes	• Death • Recurrence • Complications • Duration of hospital stay • Operative time
Notes	Data on the number of events for the outcome of recurrence was inconsistently reported in the study. We were unable to verify the data.

NCT01643018

Methods	Methods: multicentre, balanced randomization, double-blind, active-controlled, parallel-group, non-inferiority study Setting: Turkey Commencement date: November 2006 Date of completion: May 2012 Last update posted: July 2012 Sample size: 350
Participants	Inclusion criteria: aged ≥ 18 years; diagnosed with cystic echinococcosis of the liver; < 3 cysts; cyst size > 3 cm Exclusion criteria: previous liver surgery; recurrent disease; hydatid cyst with multiorgan involvement; liver hydatid cyst complicated with infection; contraindication for general anaesthesia; contraindication for laparoscopic surgery; aged < 18 years; allergy to albendazole
Interventions	• Laparoscopic surgery Laparoscopy group had 3 trocars. First was 10 mm and inserted within the umbilicus for telescope, the second was 10 mm and inserted just below the xiphoid process and third was 5 mm and inserted at the right upper quadrant of the abdomen.

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NCT01643018 *(Continued)*	• Open surgery Traditional open surgery using a right subcostal incision.
Outcomes	• Recurrence at 24 months • Mortality at 24 months • Intraoperative complications • Pain score • Duration of hospital stay • Duration of operation • Quality of life
Notes	No information on use of albendazole or cyst stage. Principal investigator: Mehmet Kaplan, MD; Medical Park Gaziantep Hospital, Gaziantep, Turkey

PAIR: puncture, aspiration, injection and re-aspiration.

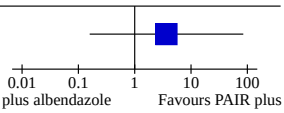
DATA AND ANALYSES

Comparison 1. Standard catheterization plus albendazole versus PAIR plus albendazole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Recurrence	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2 Minor complications of treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1: Standard catheterization plus albendazole versus PAIR plus albendazole, Outcome 1: Recurrence

Study or Subgroup	Standard catheterization plus albendazole Events	Total	PAIR plus albendazole Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Akhan 2020 (1)	1	17	0	21	3.67 [0.16 , 84.66]	



Footnotes

(1) The detection of daughter vesicles or double-layered wall sign on imaging during follow-up were considered events of recurrence.

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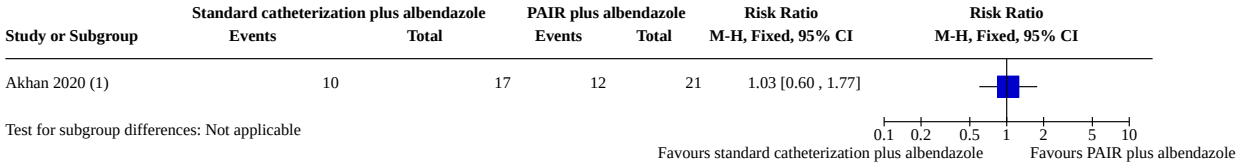
Analysis 1.2. Comparison 1: Standard catheterization plus albendazole versus PAIR plus albendazole, Outcome 2: Minor complications of treatment



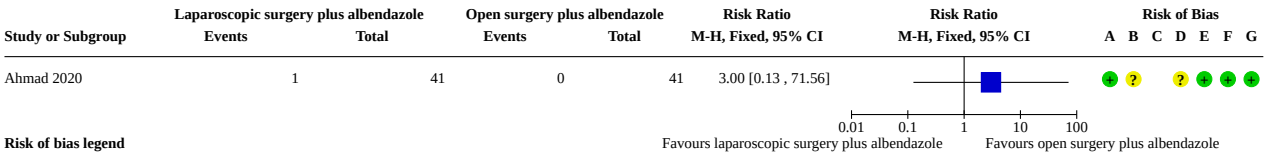
Footnotes

(1) Standard catheterization: 4 pain, 4 fever, 2 catheter dislodgement. PAIR: 4 pain, 6 fever, 2 angioneurotic oedema.

Comparison 2. Laparoscopic surgery plus albendazole versus open surgery plus albendazole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Recurrence	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.2 Complications of treatment	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.2.1 Major complications	2	142	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.13, 1.92]
2.2.2 Minor complications	2	142	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.02, 0.98]
2.3 Duration of hospital stay (days)	2	142	Mean Difference (IV, Random, 95% CI)	-1.90 [-2.99, -0.82]

Analysis 2.1. Comparison 2: Laparoscopic surgery plus albendazole versus open surgery plus albendazole, Outcome 1: Recurrence



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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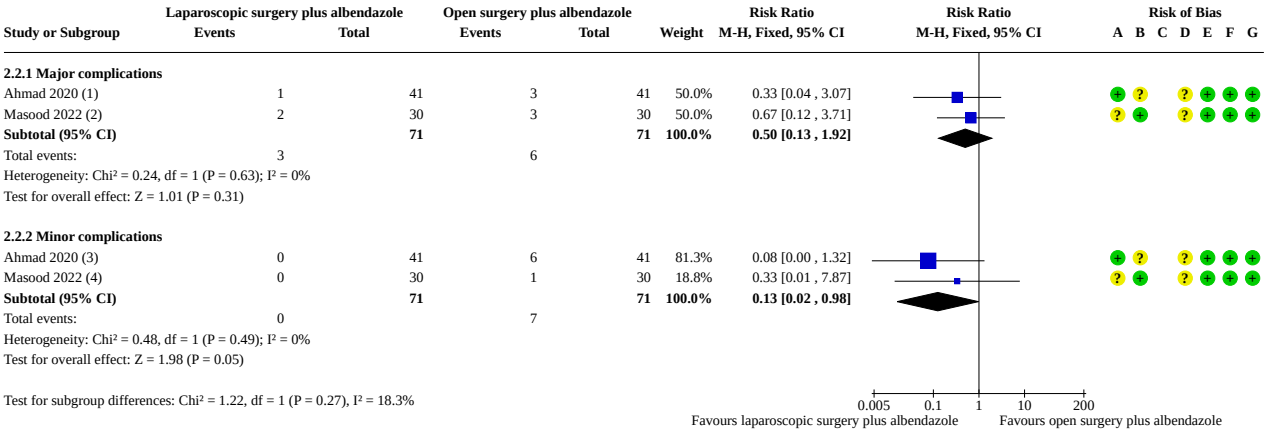
Analysis 2.2. Comparison 2: Laparoscopic surgery plus albendazole versus open surgery plus albendazole, Outcome 2: Complications of treatment



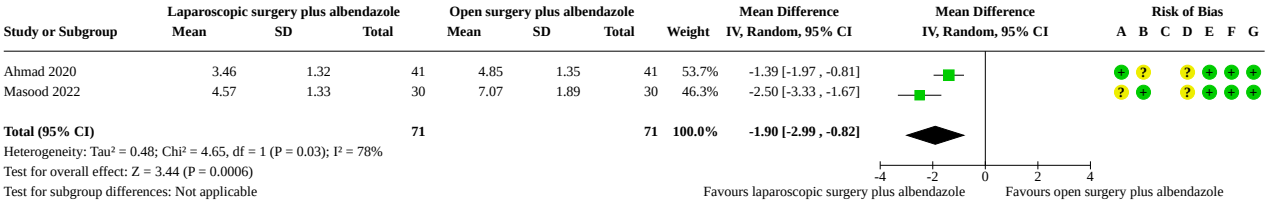
Footnotes

(1) Laparoscopic surgery group: 1 biliary fistula. Open surgery group: 3 biliary fistula.
(2) Laparoscopic surgery group: 1 cavity abscess, 1 atelectasis. Open surgery group: 2 bilary fistula, 1 atelectasis.
(3) Open surgery group: 6 abdominal wound infections.
(4) Open surgery group: 1 wound infection.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.3. Comparison 2: Laparoscopic surgery plus albendazole versus open surgery plus albendazole, Outcome 3: Duration of hospital stay (days)



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

ADDITIONAL TABLES

Table 1. World Health Organization cyst classification system

WHO cyst stage	Description of cyst stage
CE1	Unilocular fluid-filled cyst with pathognomonic signs being the visualization of the 'double wall sign' on ultrasound consisting of an outer hypoechoic and inner hyperechoic wall structure formed by the interfaces of the host-derived and parasitic-derived cyst wall layers.

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Table 1. World Health Organization cyst classification system *(Continued)*

CE2	Fluid-filled cyst containing daughter cysts, with 'septated' appearance on ultrasound formed by the presence of avascular inner sept-like structures deriving from the adjacent daughter cyst walls, which constitute the pathognomonic features of this stage.
CE3a	Unilocular fluid-filled cyst with pathognomonic signs being the visualization on imaging of the detached parasitic layer fluctuating in the fluid content and being avascular, thin and regular in all sections.
CE3b	Cyst with complex content encompassing ≥ 1 daughter cysts in an avascular matrix where the pathognomonic 'ball of wool' signs of stage CE4 is visible on imaging.
CE4	Cyst with solid avascular content where detached parasitic layers are visible as hypoechoic folded structures, depicting the pathognomonic 'ball of wool' appearance.
CE5	Cyst with CE4 features and egg-shell wall calcification.

Table adapted from Brunetti 2010.

Table 2. Gharbi cyst stage reclassification into the WHO stage classification

Gharbi classification	WHO classification
I	CE1
II	CE3a
III	CE2

We reclassified the Gharbi cyst stages into the World Health Organization (WHO) cyst classification system using the reported cyst characteristics within the study.

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials

2023, Issue 5

#1 ((hydatid or hydatic) AND (liver or hepatic or cyst* or disease*))

#2 MeSH descriptor: [Echinococcus] explode all trees

#3 MeSH descriptor: [Echinococcosis] explode all trees

#4 (hepatic or liver) AND hydatid*

#5 echinococc*

#6 (hepatic hydatidosis or liver hydatidosis)

#7 #1 or #2 or #3 or #4 or #5 or #6

MEDLINE (PubMed)

((echinococcosis[MeSH Major Topic]) AND (((drug therapy[MeSH Subheading]) OR (randomized[Title/Abstract] OR placebo[Title/Abstract] OR randomly[Title/Abstract] OR trial[Title/Abstract] OR groups[Title/Abstract])) OR ((randomized controlled trial[Publication Type]) OR (controlled clinical trial[Publication Type]))) AND ((humans[Filter]))) OR ((((drug therapy[MeSH Subheading]) OR (randomized[Title/

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Abstract] OR placebo[Title/Abstract] OR randomly[Title/Abstract] OR trial[Title/Abstract] OR groups[Title/Abstract])) OR ((randomized controlled trial[Publication Type]) OR (controlled clinical trial[Publication Type]))) AND (("hydatic liver"[Title/Abstract] OR "hydatic cyst*"[Title/Abstract] OR "hydatic disease*"[Title/Abstract]) OR ("hydatid liver"[Title/Abstract] OR "hydatid cyst*"[Title/Abstract] OR "hydatid disease*"[Title/Abstract])) AND ((humans[Filter])))

Web of Science Core Collection

CPCI-S, SCI-EXPANDED

#3 #1 AND #2

#2 random* or "controlled trial" or double blind* or single blind* (Topic) or randomized controlled trial (Topic) or placebo (Topic)

#1 ((hydatid or hydatic) and (liver or hepatic or cyst* or disease*)) (Topic) or echinococc* (Topic)

WHO Global Index Medicus

tw:((tw:(((hydatid OR hydatic) AND (liver OR hepatic OR cyst* OR disease*)))) OR (tw:(echinococcosis)) AND (tw:(randomized OR randomised OR clinical trial)))

ClinicalTrials.gov

Interventional Studies | Echinococcus

Interventional Studies | Echinococcosis

WHO ICTRP

Echinococc*

CONTRIBUTIONS OF AUTHORS

All authors made substantial contributions to the conception or design of the work, and wrote the review protocol, which is published on PROSPERO (CRD42023421407).

RK and FT screened the search results, extracted data and assessed risk of bias in included studies.

RK, FT and LU contributed to examining the data, writing the review and critically appraising the review for important intellectual content.

All authors approved the final version prior to publication and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DECLARATIONS OF INTEREST

RK: no relevant interests; works as a General Practitioner.

LU: no relevant interests; works as a health professional at the Ministry of Health, Río Negro Province, Argentina; affiliated to the World Association of Echinococcosis.

FT: no relevant interests; has published opinions in medical journals relevant to the interventions in the work; consultant on cystic echinococcosis.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK

  Department of Clinical Sciences

External sources

- Foreign, Commonwealth, and Development Office (FCDO), UK

  Project number 300342-104

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title from 'Treatment of cystic echinococcosis (hydatid disease)' to 'Treatment of uncomplicated hepatic cystic echinococcosis (hydatid disease)' to ensure the review population was clearer.

We planned to undertake subgroup analyses of participant age and cyst size. This was not possible due to the limited number of studies and data concerning age and cyst size were unable to be disaggregated in the included studies.

We planned to conduct sensitivity analyses with praziquantel included compared to excluded in case of an additive or synergistic effect; however, no studies included praziquantel.

We planned to conduct sensitivity analyses of summary assessments of the risk of bias, including studies that were at low risk of bias. All included studies had a low risk of bias; these analyses were not required to be undertaken.

INDEX TERMS

Medical Subject Headings (MeSH)

*Albendazole [therapeutic use]; Anthelmintics [therapeutic use]; Anticestodal Agents [therapeutic use]; Bias; Combined Modality Therapy [methods]; *Echinococcosis, Hepatic [complications] [surgery] [therapy]; *Praziquantel [therapeutic use]; *Randomized Controlled Trials as Topic; Recurrence

MeSH check words

Adolescent; Adult; Child; Humans; Middle Aged

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