



# Enfermedades Infecciosas y Microbiología Clínica

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## Consensus statement

**Executive Summary of the Consensus Statement of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Society of Tropical Medicine and International Health (SEM-TSI), the Spanish Association of Surgeons (AEC), the Spanish Society of Pneumology and Thoracic Surgery (SEPAR), the Spanish Society of Thoracic Surgery (SECT), the Spanish Society of Vascular and Interventional Radiology (SERVEI), and the Spanish Society of Paediatric Infectious Diseases (SEIP), on the Management of Cystic Echinococcosis<sup>☆</sup>**



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**Abbreviations:** AE, alveolar echinococcosis; CE, cystic echinococcosis; CRP, C-reactive protein; CT, computed tomography; DALY, disability-adjusted life year; DNA, deoxyribonucleic acid; ERCP, endoscopic retrograde cholangiopancreatography; FDG, fluorodeoxyglucose; HF, hydatid fluid; LAMP, loop-mediated isothermal amplification of nucleic acid; MoC, aTmodified catheterisation technique; MR, magnetic resonance; PAIR, puncture, aspiration, injection and reaspiration; PAIRD, puncture, aspiration, injection, reaspiration and drainage; PET, positron emission tomography; PEVAC, modified percutaneous evacuation; RFA, radiofrequency ablation; Sen, sensitivity; Spe, specificity; VATS, video-assisted thoracoscopic surgery; W&W, watch and wait; WHO, World Health Organization; WHO-IWGE, WHO Informal Working Group on Echinococcosis.

<sup>☆</sup> The complete consensus statement is available as [Appendix A. Supplementary data](#).

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## ABSTRACT

The Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Society of Tropical Medicine and International Health (SEM-TSI), the Spanish Association of Surgeons (AEC), the Spanish Society of Pneumology and Thoracic Surgery (SEPAR), the Spanish Society of Thoracic Surgery (SECT), the Spanish Society of Vascular and Interventional Radiology (SERVEI), and the Spanish Society of Paediatric Infectious Diseases (SEIP) considered it pertinent to issue a consensus statement on the management of cystic echinococcosis (CE) to guide healthcare professionals in the care of patients with CE.

Specialists from several fields (clinicians, surgeons, radiologists, microbiologists, and parasitologists) identified the most clinically relevant questions and developed this Consensus Statement, evaluating the available evidence-based data to propose a series of recommendations on the management of this disease. This Consensus Statement is accompanied by the corresponding references on which these recommendations are based.

Prior to publication, the manuscript was open for comments and suggestions from the members of the SEIMC and the scientific committees and boards of the various societies involved.

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## Resumen ejecutivo de la Declaración de consenso de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC), la Sociedad Española de Medicina Tropical y Salud Internacional (SEM-TSI), la Asociación Española de Cirujanos (AEC), la Sociedad Española de Neumología y Cirugía Torácica (SEPAR), la Sociedad Española de Cirugía Torácica (SECT), la Sociedad Española de Radiología Vascul e Intervencionista (SERVEI) y la Sociedad Española de Infectología Pediátrica (SEIP) sobre el tratamiento de la equinococosis quística

## RESUMEN

La Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC), la Sociedad Española de Medicina Tropical y Salud Internacional (SEM-TSI), la Asociación Española de Cirujanos (AEC), la Sociedad Española de Neumología y Cirugía Torácica (SEPAR), la Sociedad Española de Cirugía Torácica (SECT), la Sociedad Española de Radiología Vascul e Intervencionista (SERVEI) y la Sociedad Española de Infectología Pediátrica (SEIP) han considerado pertinente la elaboración de una declaración de consenso sobre el tratamiento de la equinococosis quística (EQ) que sirva de ayuda al personal sanitario en la atención de pacientes con EQ.

Varios tipos de profesionales (médicos, cirujanos, radiólogos, microbiólogos y parasitólogos) han seleccionado las preguntas más clínicamente relevantes y han desarrollado esta Declaración de consenso, en la que evalúan los datos basados en la evidencia disponibles para proponer una serie de recomendaciones sobre el tratamiento de esta enfermedad. Esta Declaración de consenso se acompaña de la bibliografía correspondiente que fundamenta estas recomendaciones.

Antes de su publicación, el manuscrito estuvo abierto a comentarios y sugerencias de los miembros de la SEIMC y de los comités científicos y juntas directivas de las diferentes sociedades implicadas.

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### Palabras clave:

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## Introduction and rationale

Cystic echinococcosis (CE) or hydatid disease is a zoonosis caused by the tapeworm *Echinococcus granulosus* sensu lato; dogs are the definitive hosts, and humans are an accidental intermediate host. Due to its impact in terms of morbidity, its higher prevalence in developing areas, and the lack of investment in research, echinococcosis is included on the World Health Organization's (WHO) list of *Neglected Tropical Diseases*. Although CE has a worldwide distribution, most human cases are concentrated in South America, North and East Africa, the Middle East, and countries in Central and Western Asia. In Europe, it is particularly prevalent in Mediterranean countries such as Greece, Italy and Portugal.

Spain is considered a highly endemic area; the rate of transmission remains high but there is a variable geographical distribution. The diagnosis of CE should be made according to the WHO criteria. The management of CE is complex, and currently, despite WHO recommendations, there is no consensus on its management. Essentially, there are three categories of treatment, which are often used in combination: (i) surgery, (ii) percutaneous techniques, and (iii) antiparasitic drugs.

The management varies considerably depending on (i) the patient characteristics, (ii) the features of the cyst, and (iii) the resources available at the health care facility. Currently, the treatment of choice is surgery, although several alternative techniques are available. The PAIR technique (puncture, aspiration, injection

and reaspiration) has been introduced and can be used instead of surgery in selected cases. The usefulness of other methods such as modified catheterisation (MoCaT), modified percutaneous evacuation (PEVAC), immune therapies, chemo-radioisotope therapy, and radiofrequency ablation (RFA) must be compared in the future. Antiparasitic drugs, mainly benzimidazoles as monotherapy or in combination with other drugs such as praziquantel, generally have secondary role: they are mainly used in patients who are not candidates for surgery, to reduce the risk of anaphylaxis, dissemination, and/or postoperative recurrence, although they have also shown promising results as an initial curative therapy in specific situations. In recent years, the *watch and wait* (W&W) approach has been analysed in selected patients.

CE therefore remains an ongoing problem that generates intense debate regarding its optimal treatment.

#### *Aims of the consensus statement*

The aim of this Consensus Statement is to provide the best possible evidence on the management of CE. Numerous different specialists involved in the management of patients with CE evaluated the available evidence-based data and made recommendations on the various aspects of the disease.

#### **Methods**

##### *Overall methodology of the statement*

A systematic review of the literature was carried out to evaluate data on the epidemiology, clinical features, diagnosis and treatment options of CE. Twenty-three PICO (patient, intervention, comparison and outcome) questions were identified, as well as 17 additional questions. These questions were distributed among the different members of the group for evaluation. A PubMed search was performed for the dates 1968 to December 2018 for articles in English or Spanish with the following search terms: “Hydatidosis”, “Hydatid cyst”, “Hydatid disease”, “Cystic Echinococcosis” and “*Echinococcus granulosus*” associated with each of the items explored (e.g. “surgery”, “treatment”, “cure”, “relapse”, “recurrence”, “albendazole”, “praziquantel”). This search was complemented with a review of Medline and the Cochrane Database of Systematic Reviews using the key terms “Hydatidosis”, “Hydatid cyst”, “Hydatid disease”, “Cystic Echinococcosis” and “*Echinococcus granulosus*”. The search was performed according to the PRISMA criteria. It was first reviewed by the collaborators and then by the text coordinator. A total of 438 publications were selected, with duplicate or irrelevant publications being eliminated. Queries regarding the selection of specific references for each question may be directed to the authors responsible. The recommendations are based on the SEIMC international criteria for consensus guidelines and the AGREE standards. The coordinator and the authors of the article issued an edition of the consensus statement, which was made available on the SEIMC website from 9-30 May 2019 for external review. The document was also reviewed by the scientific committees of the various scientific societies involved. All the authors have approved the content of the document and the final recommendations.

#### *Definitions*

*Cure* refers to the eradication of an *E. granulosus* infection and may occur spontaneously or with treatment. Given the recurrent nature of the infection, the term *cure* is only used in cases in which there is no recurrence of infection after a long follow-up period. This follow-up period should be at least 5–10 years.

*Complicated CE* is CE that presents with symptoms caused by the CE, often secondary to a mechanical, infectious or allergic process or a combination thereof.

*Multi-organ CE* affects more than one organ simultaneously.

*Multiple CE* is the presence of two or more lesions in the same organ.

*Secondary CE* refers to new cysts that occur after the rupture of a cyst (primary cyst), spontaneously or following surgery or trauma.

*Atypical location* refers to CE outside the liver or lungs.

*Persistence* refers to the non-eradication of *E. granulosus* infection in relation to a non-eradication therapy or a watch and wait (W&W) approach.

*Local recurrence* is the recurrence of a primary cyst at the same site after treatment with a curative intention. This can occur months to years later due to primary dissemination of the protoscoleces or secondary to cyst rupture, which may be spontaneous, traumatic, or accidental during surgery.

*Distal recurrence* is the occurrence of cysts in new sites after treatment with a curative intention. This can occur months to years later due to primary dissemination of protoscoleces or secondary to cyst rupture, which may be spontaneous, traumatic, or accidental during surgery.

*Reinfection* refers to a new cyst that is unrelated to the original infection.

*Watch and wait*, as implied, the strategy of waiting and observing the patient.

#### 1. *What serological methods are available and how accurate are they in the diagnosis of CE?*

##### **Recommendations**

- Currently, conventional and rapid diagnostic tests have a low sensitivity in the case of inactive cysts (**A-I**).
- Classical techniques are progressively being replaced with the use of purified, recombinant antigens and/or peptides. At present, mainly purified or synthetic antigens derived mostly from *E. granulosus* Ag5 and AgB are used (**A-I**).
- Most recombinant antigen and purified antigen techniques are highly specific. However, they can show cross-reactivity with alveolar echinococcosis and cysticercosis. They are usually more sensitive in multiple CE (**A-I**).

#### 2. *Are molecular methods useful in the diagnosis of CE? Do the new parasitological tools help in the diagnosis?*

##### **Recommendations**

- Molecular techniques may be helpful in the future for the diagnosis of CE, but they are still in the process of optimisation (**A-I**).
- Genotyping can help in the management of patients with CE and is essential in the standardisation and validation of the new serological tools that use recombinant antigens (**A-I**).
- In the future, minimally invasive techniques such as exhaled breath tests may be used to assist in the diagnosis (**C-III**).

#### 3. *What is the best follow-up schedule for CE?*

##### **Recommendations**

- The optimal follow-up schedule for CE has not yet been established (**C-III**).
- Theoretically, follow-up should be long: at least 3–5 years, with no established maximum duration; in some patients, follow-up should be indefinite (**B-III**).

#### 4. *Surgical indications in hepatic CE: when and how?*

##### **Recommendations**

- Surgical is generally the treatment of choice and should be assessed on an individual basis (**A-II**).
- Open surgery is the most accepted procedure for the treatment of hepatic CE, especially in complicated cases (**B-II**).
- Surgery is the mainstay of treatment for large, active, symptomatic or complicated cysts: (i) CE 2-CE 3b cysts, (ii) cysts

- >5 cm, (iii) cysts with multiple daughter cysts, (iv) infected cysts, (v) cysts that communicate with the biliary tree, and (vi) cysts that exert a mass effect on adjacent organs (B-II).
- The relative contraindications for surgery are (i) patients who are unsuitable for surgery due to their general status or associated comorbidities, (ii) multiple cysts, (iii) very small, difficult-to-access cysts that are partially or completely calcified (B-II).
5. *What are the best and most frequently used techniques in hepatic CE? Are classical surgical techniques still the techniques of choice? What is the preferred strategy in hepatic CE: radical surgery or conservative treatment?*
- Recommendations**
- The surgical techniques used should be those that are appropriate for the patient, their disease, and the setting in which the operation will be performed. As far as possible, surgery should aim to minimise complications and recurrences (B-II).
  - Wherever possible, radical techniques are preferable to conservative techniques (B-II).
  - Anatomical liver resection, total cystopericystectomy and open or partial cystectomy with or without omentoplasty are the most frequently used surgical techniques (B-II).
  - The ideal approach should be simple, with complete resection of the cyst without rupture. All efforts should be made to protect the peritoneal cavity and avoid intraoperative cyst leakage (B-II).
  - Conservative procedures are safe and less complex than radical procedures, although the associated risk of morbidity and recurrence may be higher (B-II).
6. *In hepatic CE, how effective are surgical techniques and what are their complications? Does laparoscopic surgery have any benefit over traditional surgical techniques? Are there any differences between urgent surgery and elective surgery in terms of complications or recurrence rate?*
- Recommendations**
- Appropriate patient selection is essential for successful laparoscopic surgery. A laparoscopic approach is safe and technically feasible (C-III).
  - Laparoscopic surgery has some advantages such as (i) shorter hospital stay, (ii) less postoperative pain, and (iii) lower rate of surgical site infection, and can be used in selected cases of hepatic CE (C-III).
  - Patients with deep cysts, cysts in posterior lobes, near the vena cava, multiple (>3) cysts or calcified cysts may not be candidates for laparoscopic surgery (C-III).
7. *What are the most frequently used surgical techniques in pulmonary CE?*
- Recommendations**
- Cystopericystectomy is the surgical technique of choice in pulmonary CE (C-II).
  - In cases with associated lung damage or non-viable parenchyma (complicated cysts and abscesses), the minimum pulmonary resection necessary should be performed (C-II).
  - Capitonage associated with cystopericystectomy has not been demonstrated to reduce postoperative leakage (C-II).
  - Surgical approaches via thoracotomy and VATS have comparable outcomes, although VATS has a lower morbidity, and is therefore the recommended technique (B-II).
  - Patients with cystic disease in both the right lower lobe and in upper hepatic lobes may be treated via independent thoracic and abdominal approaches or via thoracophrenolaparotomy (D-III).
  - Percutaneous techniques are not recommended in pulmonary CE due to the high risk of cyst rupture and secondary dissemination (B-II).
8. *In pulmonary CE, how effective are surgical techniques and what are the possible complications?*
- Recommendations**
- Surgery is one of the best treatment options for pulmonary CE. It has a low rate of associated morbidity and mortality (C-II).
  - Patients who undergo surgery for complicated cysts have a higher incidence of postoperative complications (C-II).
9. *What is the best approach for difficult-to-access hepatic and pulmonary sites?*
- Recommendations**
- From a surgical perspective, all hepatic segments are theoretically accessible (C-III).
  - Hepatobiliary fistulas with thoracic spread can be managed surgically via a low thoracotomy with resection of the area of bile-damaged lung and reconstruction with biological materials (C-III). They can also be managed conservatively, by draining the bile, which encourages spontaneous closure of the fistula (C-III).
  - VATS or thoracotomy allows access to the whole lung (C-III).
  - Most cases of cardiac CE are treated surgically via a midline sternotomy and using extracorporeal circulation (C-III).
10. *What is the management of patients with multi-organ CE?*
- Recommendations**
- For any patient with CE, the possibility of multi-organ involvement, especially hepatopulmonary, must be borne in mind. Patients with hepatic CE should have a simple chest X-ray or a chest CT, and patients with pulmonary CE should have an abdominal ultrasound or CT (B-II).
  - A standardised medical treatment regimen has not yet fully established. When medical treatment is the only option, it should be prolonged, or even indefinite (avoiding stopping treatment) (B-III).
  - If the disease is very extensive and there is reasonable doubt about the possibility of complete resection, PAIR and/or chemotherapy may be considered (C-III).
  - In patients with multiple bilateral cysts, a sequential bilateral approach or a midline sternotomy may be used (D-III).
  - If the upper hepatic segments and right pulmonary lobes are affected, the surgical team may consider thoracophrenolaparotomy, or a sequential independent approach via thoracotomy or VATS and laparotomy or laparoscopy (C-II).
11. *How should patients with atypical location CE be managed?*
- Recommendations**
- In patients from endemic areas with cystic lesions, CE must be considered in the differential diagnosis (A-I).
  - All patients with suspicion of extrahepatic CE should have a CT of the chest and abdomen (A-III).
  - Wherever surgical techniques allow it, the treatment of choice for atypical location CE is surgery (B-I).
  - In splenic CE, although splenectomy is curative, conservative surgery is preferable; splenectomy should be reserved for patients with large cysts in the centre or close to the splenic hilum (A-II).
  - Anthelmintic treatment must be given for at least 2 weeks before and for up to 3 months after surgery (B-III).
  - In renal CE, laparoscopic surgery can be a safe and effective option (B-III).
  - If nephrectomy is performed, the largest possible amount of parenchyma should be preserved; total nephrectomy should be reserved for cysts on non-functioning kidneys, large cysts

(occupying the entire parenchyma) or those with signs of infection (**B-II**).

- Echocardiography is the technique of choice for the diagnosis of cardiac CE, due to its wide availability, high sensitivity, high resolution and its ability to simultaneously analyse the haemodynamic effects (**B-II**).
- In cardiac CE, antiparasitic treatment prior to surgery can increase the risk of damage to the cyst wall and of cyst rupture (**B-I**).
- The treatment of choice in cerebral CE is excision of the cyst intact, using the Dowling technique (**B-I**).
- In CE of the bone, surgery should remove the affected bone and at least 1–2 cm of surrounding healthy bone; intraoperative irrigation should be performed with a scolicedal solution of hypertonic saline (**B-I**).

12. *What type of image-guided interventional techniques are currently used?*

#### Recommendations

- PAIR is a safe and effective technique in selected patients (CE1 and CE3a) (**B-II**).
- For CE1 and CE3a cysts larger than 10 cm, a PAIRD drainage catheter is required (**B-III**).
- Percutaneous techniques are effective for unilocular cysts, but they do not have the same efficacy in multilocular cysts or those with solid components. For such cysts, techniques such as PEVAC, MoCaT and DMFT have been developed (**C-III**).
- There is insufficient evidence on the modified techniques for the treatment of CE2 and CE3b cysts, which also have a higher morbidity and mortality; therefore, they are indicated in patients who are not suitable for or refuse surgery (**C-III**).

13. *What is the usual procedure for image-guided interventional techniques?*

#### Recommendations

- Percutaneous techniques must be performed in an intervention suite with life support, anaesthetic sedation, and a surgical team on stand-by (**C-III**).
- To avoid complications, communication between the cysts and the biliary, renal, or bronchial tree must be excluded (**C-III**).

14. *What is the best scolicedal solution?*

#### Recommendations

- Currently there is no perfect scolicedal agent. Ethanol (95%) and hypertonic saline solution (minimum 20% concentration) are the scolicedal agents of choice, since they are widely available, have good scolicedal activity, and are cheap. Their use is limited by their side effects such as chemical sclerosing cholangitis and anaphylactic reactions (**B-III**).
- Before using ethanol or hypertonic saline solution as scolicedal agents, the presence of cysto-biliary fistulas must be ruled out (**B-III**).

15. *What are the indications for each of the image-guided interventional techniques? How effective is percutaneous interventional treatment?*

#### Recommendations

- PAIR is indicated for cysts between 5 and 10 cm that are stage CL, CE1 or CE3a, and for accessible multiple cysts, infected cysts, postsurgical recurrence or after failed medical treatment (**B-III**).
- The modified technique with insertion of a drainage catheter (PAIRD) can be performed in CL, CE1 and CE3a cysts greater than 10 cm (**B-III**).
- In type CE2 and CE3b cysts, surgery is indicated, although modified techniques (MoCaT or PEVAC) can be performed if the patient is not suitable for or refuses surgery (**C-III**).

- Percutaneous techniques can be used in pregnant women and in children older than 3 years (**B-III**).

16. *What factors influence the choice of antiparasitic treatment? Which, when, how and for how long? Assessment of safety and efficacy.*

#### Recommendations

- Pharmacological treatment is recommended for inoperable or multi-organ CE and as an adjunct to percutaneous treatment or surgery (**B-II**).
- Pharmacological treatment is not recommended for CE4–5 (**B-III**).
- There are insufficient data to establish the optimum dose, frequency, and duration of treatment (**B-II**).
- Benzimidazoles are useful drugs in CE, albendazole being the drug of choice (**A-I**).
- Better results are achieved when surgery or PAIR are combined with anthelmintics given before and/or after the procedure (**A-I**).
- Recommendations on duration of treatment prior to intervention range from 1 day to 3 months, and for after the intervention, from 1 to 3 months (**B-II**).
- The additional benefit obtained from more than 6 months of anthelmintic treatment is marginal for most patients, although it is often given in patients with multiple or inoperable CE (**B-II**).

17. *Is combined anthelmintic treatment with albendazole and praziquantel better than treatment with albendazole alone?*

#### Recommendations

- Combined treatment with albendazole and praziquantel may be considered in the three medical situations in which pharmacological treatment is used: (i) prior to interventional treatment, (ii) after interventional treatment, and (iii) as an alternative to surgery (**C-II**).
- Combined treatment with albendazole and praziquantel before an interventional procedure reduces the viability of the cysts. The sterilising effect of the combination may be superior to that of monotherapy (**C-II**).
- A longer duration of combined treatment appears to be associated with a greater reduction in the viability of the cysts (**C-II**).
- Treatment dose and duration are not well defined, but it is recommended to give at least 4 weeks of combined treatment prior to intervention (**C-II**).
- Combined anthelmintic treatment after an intervention may reduce the risk of dissemination and recurrence, especially if leakage has occurred (**C-II**).
- The use of combined medical treatment may have some benefit in patients with (i) disseminated disease, (ii) previous treatment failure, (iii) poor disease control on monotherapy, or (iv) when surgery is contraindicated. The dose and duration of combination therapy are not well established (**C-II**).

18. *Are there any other safe and effective anthelmintic treatments?*

#### Recommendation

- In addition to albendazole and praziquantel, other drugs have been used in the treatment of CE, all with an acceptable safety profile (**B-III**).
- Drugs such as nitazoxanide and thiabendazole may have some efficacy in CE (**B-III**).

19. *In which patients is a watch and wait strategy recommended?*

#### Recommendations

- The W&W strategy is suggested for the management of patients with asymptomatic uncomplicated hepatic cysts in stages CE4 and CE5 (**B-III**).
- The follow-up of these patients is important and should be long-term, for at least 3–5 years (**C-III**).

20. *What follow-up is needed after a therapeutic procedure: which patients, how, and for how long? What are the most useful tools?*

**Recommendations**

- Initial follow-up should assess early complications of surgery or percutaneous intervention; late complications and recurrence should be assessed at a later date (**B-II**).
- The duration of follow-up should be individualised according to the patient, disease, and the available resources. It should last at least 3 years, although in certain patients it may be extended indefinitely (**B-II**).
- In hepatic CE, follow-up should routinely involve ultrasound (**B-II**). In other locations, CT and/or MR may be used depending on availability (**B-II**).

21. *Is serology useful in post-treatment follow-up?*

**Recommendation**

- Serology results must be interpreted with caution in the follow-up of patients with CE. Occasionally, a reduction in the titres can be associated with cure, and an increase can be associated with a recurrence (**B-III**).
- In patients who have undergone intervention, complete antigen detection techniques are not useful for follow-up (**C-II**).
- In patients with stage CE1–CE3a cysts who have undergone intervention with curative intent, detection of antibodies against AgB2t and Ag2B2t can be useful for follow-up, as it can differentiate active infection from cure (**B-II**).

22. *Are radiological methods useful in post-treatment follow-up?*

**Recommendations**

- Ultrasound is the technique of choice for the follow-up of disease in the liver, abdomen, soft-tissues, and lungs with cysts in contact with the pleura, and any location that is accessible with ultrasound (**B-II**).
- If there are limitations to ultrasound, CT and MR can be used for follow-up, particularly MR as it limits radiation doses (**C-III**).

- When it is difficult to determine the activity of the cyst, imaging techniques should be complemented with blood tests (**C-III**).

23. *What measures can be taken to prevent CE?*

**Recommendations**

- Any measure against CE should be aimed at interrupting the life cycle of the parasite. Interventions can be aimed at the definitive host and/or the intermediate host (**A-I**).
- Interventions aimed at the definitive host are essential, as the main risk factors in acquiring CE are linked to dogs, which represent the most common primary source of infection in humans (**A-III**).

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**Conflicts of interest**

The authors declare no conflict of interest.

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**Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.eimc.2019.10.015](https://doi.org/10.1016/j.eimc.2019.10.015).