CONSENSUS STATEMENT OF THE SPANISH SOCIETY OF INFECTIOUS DISEASES AND CLINICAL MICROBIOLOGY (SEIMC), THE SPANISH SOCIETY OF TROPICAL MEDICINE AND INTERNATIONAL HEALTH (SETMSI), 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.

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ABSTRACT

The Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Society of Tropical Medicine and International Health (SEMTSI), 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 references on which the 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.

KEY WORDS

Hydatidosis; Cystic echinococcosis; *Echinococcus granulosus*; Guidelines.

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

MoCaT: modified 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 & wait

WHO: World Health Organization

WHO-IWGE: WHO Informal Working Group on Echinococcosis

1. 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[1]. 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*[2]. 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[3]. Spain is considered a highly endemic area; the rate of transmission remains high but there is a variable geographical distribution[4-6]. The diagnosis of CE should be made according to the WHO criteria[7]. The management of CE is complex, and currently, despite WHO recommendations, there is no consensus on its management[7-9]. 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[10]. In recent years, the *watch and wait* (W&W) approach has been analysed in selected patients[11].

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 have therefore evaluated the available evidence-based data and made recommendations on the various aspects of the disease.

2. 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 (eg “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[12,13]. 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 (**Table 1**) and the AGREE standards[14]. 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.

3. NATURAL HISTORY

I. What is the natural history of CE?

As with other intermediate hosts, humans acquire the disease after the accidental ingestion of eggs, from water, food or fomites contaminated with the faeces of infected dogs or other canids (**Figure 1a**)[15]. The proteolytic action of the gastric enzymes breaks down the external layer of the egg (embryophore), releasing and activating the oncosphere (or hexacanth), which bears three pairs of hooks (**Figure 1b**). After hatching in the final sections of the small intestine (jejunum and ileum), the oncosphere uses its hooks to anchor into the intestinal microvilli. This mechanical action, combined with lysis of the surrounding tissue by the oncosphere's secretory glands, allows it to cross the small intestinal epithelium (**Figure 1c**) and reach the bloodstream[16,17].

The oncosphere reaches the liver via the portal vein, where it may be retained and develop into the larval stage of the parasite (metacestode or hydatid cyst) or cross the hepatic filter and reach the lungs. If it crosses this barrier, the oncosphere can disseminate via the systemic circulation and inhabit any other organ. This development of the metacestode is known as primary echinococcosis.

Once in the definitive organ, the conversion from oncosphere to larva (cyst) requires a series of cellular reorganisation processes that lead to the formation of several membranes[17]. The first of these membranes, the laminated layer, surrounds the parasitic larva and provides it with physical support, acting as a protective barrier with host immunomodulatory properties. Surrounding the laminated layer is the adventitious layer, which is fibrous and not of parasitic origin but generated from the host's cellular inflammatory response against the parasite (**Figure 2a**). The innermost membrane, known as the germinal (or proligerous) layer, constitutes the parasite itself[18]. During the development of the cyst, the innermost germinal layer made up of pluripotent undifferentiated proliferative cells forms cellular protrusions (daughter vesicles) which mature and form capsules; in their interior, the asexual process of budding takes place,

leading to the formation of protoscoleces (**Figure 2b**). The detachment of the daughter vesicles from the germinal layer creates daughter cysts (**Figures 2c and 2d**), which can rupture to form a sediment or hydatid sand that is commonly found inside fertile cysts. The central cavity of these is filled with a clear fluid (hydatid fluid) made up of a complex mix of water, lipoproteins, mineral salts and other organic compounds. Each protoscolex can potentially develop into a new adult worm if the cyst is ingested by a dog or other canid. The time required for a protoscolex to develop into a cyst is not fully known, but in humans it is estimated to be more than 10 months.

4. EPIDEMIOLOGICAL SITUATION AND ECONOMIC IMPACT

II. What is the epidemiological situation of CE in humans and animals?

Currently there is no consensus on the ideal epidemiological surveillance system for human CE. Seroprevalence studies have significant limitations[19] such as i) low sensitivity[20], ii) difficulty differentiating between contact with the disease and having the disease, iii) difficulty selecting a representative sample, and iv) increased cost of follow-up and repeated tests. Radiology-based prevalence studies have been conducted in several populations[21-26]. Such methods are highly sensitive but expensive. Registry-based studies are more common. Studies based on surgical cases could represent an effective tool although they underestimate the true extent of CE. Currently, under the auspices of the European Union, as part of the HERACLES project (Hyman cystic Echinococcosis ReseArch in CentraL and Eastern Societies)[27,28], a voluntary registry has been set up for groups who work actively with CE. This system provides a well-defined clinical record that allows a great deal of information to be extracted. However, this registry is not used everywhere, so it is difficult to know the precise epidemiology of CE, and it is based on the passive registration of confirmed cases, so it underestimates data on the population prevalence. Another possible registration system is that of hospital cases, from the analysis of the *minimum basic dataset*, which allows the study and estimation of the epidemiological situation of CE in a particular area and comparison of the results between different areas and/or over time. This could represent a tool for the study of this disease. The main limitations of this system are that it does not include patients diagnosed in private hospitals and clinics, or cases that do not require hospital admission[29]. Theoretically, registries that involve mandatory reporting should be the most effective, but they are affected by considerable under-reporting. Several factors contribute to this problem: i) clinics not knowing about the registry, ii) diagnostic doubt, and iii) the fact that diagnosis is incidental in a significant proportion of cases.

Spain, along with other Mediterranean countries, is considered a CE-endemic area[3]. The autonomous communities of Spain most affected by the disease are Aragon, Castilla La Mancha, Castile-León, the Valencian Community, Extremadura, and La Rioja, regions which are all characterised by a high concentration of sheep farms[6,30].

In 1982, human CE was included on the list of diseases with mandatory reporting, and cases were reported in this way until 1996. During this period, the annual incidence of the disease decreased from 2.5 cases per 100 000 population in 1985 to 1.0 per 100 000 population in 1996. This decrease was partly due to the implementation and continuation of CE control programs, particularly in regions where the disease represented a major veterinary public health problem[31]. Following the creation of the national epidemiological surveillance network in 1996, CE was then only reported in the autonomous communities in which the disease was endemic. This was the case until 2015, when reporting was made compulsory again throughout the whole of Spain.

During the period 2000-2015, the incidence rates of human CE remained relatively stable (0.24-0.54 cases per 100 000 population) with a slight decreasing trend (**Figure 3**). Small variations and even rises in the disease have been observed in certain years of the historical series; these changes are more evident at a regional level[4,32]. From an epidemiological perspective, this situation corresponds to the consolidation phase of the disease control programmes implemented in the 1980s and 1990s. However, it should be noted that in Spain the disease is still active, as demonstrated by the paediatric cases reported in Castile-León and the Basque Country[4,33].

Regarding animal CE, the disease has mandatory reporting in all slaughterhouses nationwide, where the finding of hydatid cysts requires the condemnation and destruction of the infected viscera[30]. The changes in the prevalence of the disease in livestock during the period 2005-2016 are shown in **Figure 4**. During this period, a slight but progressive decrease in the prevalence of the disease can be seen in cattle (0.3-0.7%), while the rates of infection in pigs and solipeds remained stable with levels below 0.1%. In sheep and goats, the prevalence of the disease was more variable, with isolated peaks and a rise in the rates between 2012-2016. This situation is similar to that described in humans, again reflecting the success of CE control campaigns. As slaughterhouses mainly deal with young animals, it is likely that the prevalence rates in adult animals would be higher. Despite the advances in the control of the disease, it is still transmitted in domestic cycles, probably via unregulated home slaughter and feeding domestic dogs with infected viscera. This highlights the importance of maintaining the disease prevention, control, and surveillance strategies that are underway both regionally and nationally. Finally, a sylvatic transmission cycle of the parasite has also been described, between

cervids and wild boar as the intermediate hosts and wolves as the main definitive host. Currently, it is unknown how often and to what extent any potential overlap occurs between domestic and sylvatic cycles of *E. granulosus*.

III. What is the economic cost of CE in Spain?

The estimated socioeconomic impact of CE in a particular region can be expressed in monetary and non-monetary terms[34]. If expressed in non-monetary terms, one of the indicators of the overall burden of the disease is disability-adjusted life years (DALY). It can be useful to compare the burden of disease between different regions and against other diseases; this can help prioritise resources and monitoring of interventions. However, this does not quantify the real economic cost of the disease; a more effective method is to perform a monetary estimation, which can also include the impact of the disease on the farming sector.

The assessment of the economic cost of a disease requires, firstly, detailed knowledge of its morbidity and mortality, making a distinction between infection (undiagnosed or asymptomatic carriers) and disease (symptomatic individuals). In the case of CE, the long asymptomatic period characteristic of the infection along with the considerable under-reporting of cases, prevents the exact determination of its incidence and prevalence. Therefore, any accurate calculation of the monetary cost of the disease should include estimates based on mathematical models that minimise the effects of these associated uncertainties[35].

The economic impact of human CE is the sum of the direct and indirect costs incurred due to the infection. The direct costs include those associated with diagnosis, surgical and/or pharmacological treatment, clinical care and hospitalisation. The main indirect cost is that resulting from the loss of productivity, for both symptomatic and asymptomatic individuals with the parasite. CE also represents a serious veterinary problem, affecting cattle, sheep, goats, and pigs. Here, the direct costs of the disease are those incurred from the condemnation of infected viscera from abattoirs, and the indirect costs are those resulting from the loss of productivity associated with the reduction in the rates of growth, fertility, and milk production in the affected livestock.

In 2005 alone, the total economic losses due to human and animal CE in Spain were estimated at close to 149 million euros[36]. The estimated total median cost of the human disease was 133 million euros when asymptomatic and/or undiagnosed individuals were included in the analysis, but 0.9 million euros when this population was excluded from the analysis. The large difference found between these two groups highlights the need for more accurate prevalence data on human CE, and improved techniques for

estimating productivity losses in asymptomatic or undiagnosed cases. Likewise, the economic impact of animal EC was estimated at 15.5 million euros, of which 15.3 million corresponded to indirect costs and 0.2 million to direct costs[36].

The quality of these estimations can be improved by replacing the official national data with local regional data from hospitals (humans) and abattoir condemnation records (livestock). This approach is feasible in small-scale studies and better reflects the epidemiological differences that exist between different geographical areas. With this approach, the cost of human and animal CE in the province of Álava in 2005 was estimated to range between 62 000 and 360 000 euros[33]. In an aim to combine the impact of the disease in humans (DALY, non-monetary estimation) with the losses due to the disease in animals (mainly cattle, monetary estimation), a modification of the DALY indicator, termed zDALY, was recently proposed[37]. This indicator estimates the burden of zoonotic diseases such as CE, thanks to the inclusion of an additional component that converts monetary losses from livestock disease into an animal loss equivalent (ALE). Thus, estimation of the zDALYs for CE in different countries indicates which sector suffers the greatest burden of disease in each country. For example, in Iran, it is mainly the livestock sector, while in Peru most of the burden is associated with human disease. It also allows a comparison of costs independently of the level of development of the country. Spain, with an economic impact from animal CE of 15.5 million euros, has an ALE (904) lower than, for example, Kyrgyzstan (5.5 million euros, ALE=4786), as the rate is adjusted when the gross national income per capita for each country is included. Independently of the indicators used, the data available clearly demonstrate that CE still causes substantial economic losses in Spain from both human and veterinary health.

IV. What are the main mechanisms of transmission and the at-risk groups?

The transmission of human CE is linked to the accidental ingestion of the eggs of *E. granulosus* sensu lato via the contamination of hands, water and food with the faeces of the definitive host (mainly dogs) and other carnivores. Such contamination, in endemic areas, is highly plausible considering that each worm produces thousands of eggs daily and that canids (and other definitive hosts) may be infected with hundreds of worms. In addition, the eggs are infectious from the moment they are released and remain infectious for months or even a year thanks to their resistant outer layer or embryophore that protects them from adverse environmental conditions (they are sensitive to dehydration and heat, but they can survive at sub-zero temperatures). Strictly speaking, humans are not pure intermediate hosts. In reality they are accidental or aberrant

intermediary hosts, as they do not play an important role in the life cycle of the parasite. Human-human transmission does not exist[38].

In the domestic cycle, sheep are the most common intermediate host, so it is unsurprising that the *E. granulosus* sensu stricto genotypes G1 (classically considered an ovine genotype) and G3 are responsible for most of the human cases worldwide (88%). Other genotypes, such as *E. canadensis* (G7) and *E. ortleppi* (G5) are also involved in human CE, but less frequently[39-41].

The role of wild hosts in the perpetuation of this disease must not be forgotten, though. For example, in Spain, the population of wild boar (whose carcasses may be eaten by dogs and wolves especially during hunting season, and who carry the G1 genotype) has doubled in recent years, potentially contributing to the transmission and spread of CE.

According to a systematic review[42], the main risk factors for acquiring CE are i) living in endemic rural areas in which dogs have access to offal and ii) owning a dog. In the review, no association was found between the ingestion of food and water contaminated with eggs, so it is thought that the risk of transmission of the disease via these traditionally accepted routes is not based on confirmed evidence and may be anecdotal. Other significant risk factors, such as sex (female) or age (older than 16 years) are variables that reflect intrinsic and sociocultural determinants of infection. The determinant *age* could be explained by the chronic nature of CE, which means that in many cases, a diagnosis is not made until years after the infection is acquired, while the determinant *female sex*, could be because in some developing rural endemic areas, it is the women who perform domestic tasks and feeding of animals, meaning a greater exposure to the parasite through contact with infected dogs[42].

From a *One Health* perspective[43], we cannot ignore the potential influence of environmental factors on the frequency and intensity or transmission and the distribution of the parasite, the indirect effects of which could generate changes in animal population dynamics, spatial overlap of competent hosts and creation of better conditions for egg survival[43].

5. CLINICAL FEATURES OF CE

V. What are the main clinical features?

Although there is a broad spectrum of CE signs and symptoms, the acute post-infection phase is always silent[44]. Only 50% of patients are symptomatic at the time of diagnosis[45]. This is partly due to the slow growth of the cyst (1-5 cm/year)[46,47], with possible latency periods of up to 50 years (mean 10 years)[46]. The size of the cysts can also vary substantially; those more than 10 cm are termed *giant* cysts[48]. Giant hydatid cysts occur

more often in the lung than in the liver, due to the elastic structure of the lung, which facilitates growth, and more often in children than in adults[49]. Infection is usually acquired in childhood, and generally presents in adulthood or is discovered incidentally (imaging studies performed for other reasons)[45]. The clinical manifestations of CE depend on many factors, among which are i) the *Echinococcus* genotype (for example G8 occurs preferentially in the lung and is slow-growing, while G6 has tropism for the brain[38]), ii) the organ affected, iii) the number of cysts, iv) the size of the lesions, v) the host immune response, and vi) the integrity of the cyst wall. **Table 2** describes the most common locations and their clinical features. In general, 40-80% of cysts occur in the liver[44,46,47,50-52](mainly in the right lobe), 10-30% occur in the lung[46,50-52], and those occurring in other organs (spleen[50,51,53,54], kidney and urinary tract[51,55,56], abdominal cavity[50,51,57], heart[58], brain[50,59-61], bone[44,51,62,63], subcutaneous tissue[64], muscle[65], and pancreas[66]) comprise around 4-20% of the total. 20% of cases are multi-organ disease. The most common symptoms are abdominal pain and dyspnoea[50,51]; pleural involvement may cause dry cough and chest pain as well as dyspnoea. Pleural cysts can break and cause massive pleural effusion[67]. Rarely, CE occurs in the ovaries (0.6-0.9%)[51,68]; when this happens the cysts are usually asymptomatic although they can produce pain, abdominal distension, menstrual abnormalities, intermenstrual bleeding, or infertility[68]. Other reported atypical locations include the thyroid and parathyroid, causing enlargement of the gland and compression of structures, causing pain, dyspnoea, respiratory distress, dysphonia, dysphagia, tracheal perforation, and even death due to allergic reactions[69,70]. Ocular involvement may affect the orbit, producing proptosis and diplopia[71], or may be subretinal, causing panuveitis[72]. In the adrenal glands, cysts can cause abdominal or lumbar pain, a palpable abdominal mass and even hypertension due to pressure on the gland[73,74]. There is no specific result on blood tests: 30% of patients have hypogammaglobulinaemia and eosinophilia[45,57]. The presence of leucocytosis suggests superinfection of the cyst. Liver involvement may be reflected by (moderately) raised transaminases, bilirubin, or alkaline phosphatase.

VI. What are the most common complications of CE?

When CE presents, it generally does so via three types of complications: i) mechanical, ii) infectious, and iii) immunological, and occasionally a combination thereof. None of these are specific, and all are potentially fatal[31,32].

Mechanical complications may relate to the pressure exerted on the infected organ, as well as the repercussions of a possible mass effect on adjacent tissues, depending on the number and size of cysts[75]. Expansion of hepatic CE can cause venous compression,

Budd-Chiari syndrome, portal vein thrombosis[76], or compression of the bile ducts, which can cause atrophy of hepatic segments or lobes[77]. Lesions in the hepatic parenchyma can also cause portal hypertension and/or ascites[78]. Fistulisation or rupture of the cyst, generally into the peritoneal or pleural cavities, can produce fever and, in the case of a pulmonary fistula, the cyst contents may be expelled via the bronchi or may be retained, remaining as a possible focus of bacterial or fungal infection[79]. Occasionally, a cyst can cause pulmonary embolism if it ruptures inside the vena cava[80]. If fistulisation occurs into the pericardial cavity, it can cause cardiac tamponade or pericarditis[81]. The most common complication of hepatic cysts (3-17%) is a biliary tract fistula[82], mainly to the right hepatic duct (55-60%), resulting in secondary cholangitis[83]. This may manifest as cholangitis and/or secondary sepsis as it causes abdominal pain, jaundice and fever. Rupture of hepatic cysts may occur in three ways: i) most commonly, as a communicating rupture with leakage of the cyst contents into the pericystic bile ducts (44-64%), ii) a contained rupture, with rupture and collapse of the endocyst after its contents have leaked to the pericyst, producing a “water lily sign” or “serpent sign” on CT, and iii) direct rupture[84], with release of vesicles into the bile ducts which can cause biliary obstruction. This complication can lead to spread of the infection to other organs and occurrence of new cysts in a shorter period of time[47], and to the development of anaphylactic reactions. When CE occurs in the spine, spinal cord compression is a possible complication; when it occurs in bone, pathological fracture may occur[85].

Infection represent another potential complication. Ruptured cysts can be colonised by bacteria, producing an abscess, which presents in the same way as any pyogenic abscess[50,52]. This is a common form of presentation (1-40%)[5386]. It is likely that superinfection originates in the organs adjacent to the CE (the bile tract or bronchial tree) or as a complication of a bacteraemia of any aetiology. The most commonly isolated bacteria are gram positive cocci and enterobacteria, both in the liver and the lungs. Severe sepsis and even death may occur[31]. The microorganism and the clinical features depend on the site of the CE. In patients with pulmonary CE, coinfection with *Aspergillus* spp. has been described, with a great clinical variability (from asymptomatic to symptoms of cough, haemoptysis, chest pain and fever)[50,54].

Lastly, the most common hypersensitivity reactions associated with CE are classical anaphylactoid reactions such as urticaria-angioedema, bronchial asthma and even circulatory collapse[55]. They occur in association with the release of antigenic material in up to 10% of all ruptures into the peritoneum[47]. Other reactions mediated by type III hypersensitivity mechanisms have also been described, with formation of circulating

immune complexes that may be deposited in different tissues. Renal involvement can lead to glomerulonephritis due to immune complex deposits[56]. Severe complications include anaphylactic reactions due to immune or hypersensitivity reactions[57]. In these cases, the most serious clinical features are the haemodynamic effects, the most common being shock (81%). Mouse models have been used to study the haemodynamic changes secondary to anaphylaxis of parasitic origin, finding, in the early phases, a redistribution of blood flow to the kidneys, central nervous system, liver and heart, with a reduced splanchnic blood flow. There then occurs a reduction in cardiac output, peripheral perfusion, heart rate and peripheral resistance[58]. The risk of anaphylactic shock and CE dissemination is highest after cyst rupture, although this has also been observed, in rare cases, after a PAIR procedure[87]. Rarely, symptoms of immune-mediated reactions such as bronchospasm, membranous nephropathy, and even anaphylaxis, may occur without any cyst complications having occurred[38]. Dermatological manifestations occur in a high percentage of patients. The most common are urticaria, followed by flushing and angioedema[55,59,60]. On occasion, these symptoms may even precede haemodynamic changes by years[61].

VII. Is CE a direct cause of mortality? What are the main risk factors associated?

Currently, CE is considered a benign disease, with a moderate morbidity. However, studies on CE-associated mortality are scarce and do not have conclusive results[31,134]. Studies carried out in different geographical areas have reported very heterogeneous figures, although most of them demonstrate that there is a mortality directly attributable to CE and/or its complications[31,32].

A study conducted in South America[88] reported a case fatality rate of 2.9% (7% in Brazil, 0.7% in Chile)[88]. In Spain, two studies of hospitalised patients found fatality rates of 1.6% and 1.9%[6,89], being lower in patients with pulmonary involvement and higher in those with liver or other organ involvement. Another Spanish study[90] found an overall fatality rate of 31%, although in none of the cases was it directly attributable to the CE. The mortality rates from various studies range between 0.008-3.1/100 000 population-year[89,91,92]. Mechanical complications have been described as the main cause of mortality, followed by infectious, and less frequently, allergic complications[31]. Multiple factors associated with increased mortality have been analysed, such as educational level, urban residency, and being an immigrant. However, the most consistently associated factor is advanced age[90-92]. No study has found increased mortality based on

sex, cyst location or any particular treatment[90-92]. Finally, it is important to highlight the low mortality associated with elective surgery[135,136].

6. CLASSIFICTION OF CYSTIC ECHINOCOCCOSIS

VIII. What is the WHO classification of CE? Is it representative of cyst viability?

The current WHO classification was introduced in 2003 (**Table 3**), and describes 6 stages that are based on the ultrasound characteristics of the cysts to define activity[93]. There is a good correlation between the ultrasound classification and the viability of the cysts: in general, CL, CE1 and CE2 are considered active, CE3 (CE3a and CE3b) are considered transitional, and CE4 and CE5 are considered inactive[93]. The WHO classification helps in decision-making on the management of the disease, although the final decision on treatment is determined by several factors including but not limited to i) the patient characteristics, ii) the number of cysts, iii) the location and iv) the presence of complications. The gold standard to determine cyst viability is assessing the ability of the cyst contents to proliferate in the peritoneal cavity of a mouse. Other methods to confirm cyst viability are i) histopathological examination of the cyst wall and the germinal layer, ii) examination of the cyst contents with conventional microscopy to observe the presence, integrity and motility of protoscoleces or the presence of other parts of the parasite, and iii) analysis of the metabolites of the cyst contents (for example, using magnetic resonance [MR] spectroscopy). A 2008 study by Hosch et al[94] analysed the viability of cysts of different WHO stages, comparing microscopy against MR spectroscopy, and found that MR spectroscopy obtained a higher viability for active cysts and lower viability for transitional cysts. However, the patients in the study had received treatment with albendazole prior to surgery, which probably slightly affected the results obtained.

7. DIAGNOSIS OF CE

IX. What are the WHO diagnostic criteria for CE? What are the most commonly used tools in the diagnosis of CE?

In 1985, the WHO Informal Working Group on Echinococcosis (WHO-IWGE) was set up, and in 2010 a consensus statement was issued, which set out diagnostic criteria for CE[7] (**Table 4**). Diagnosis of CE is confirmed by the presence of the parasite (protoscolex) on microscopy of the cyst contents or histological sample[7]. As this evidence is difficult to obtain, in everyday practice the diagnosis is based on three pillars: i) the clinical features, ii) microbiology and iii) imaging. The clinical features and standard blood tests are nonspecific, as mentioned in previous sections of this document. The most commonly

used microbiology tests are serological techniques, with variable results; it should be borne in mind that a negative result does not rule out infection. If samples of the cyst can be obtained, it is recommended to aspirate a sample of cystic fluid for direct microscopy. Several different stains are used to determine the presence of the parasite and its viability. Lastly, molecular diagnosis using gene amplification techniques is currently limited to research centres and some tertiary level centres[95]. The use of common imaging techniques such as X-ray, CT and MR is described in later sections of the document.

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

Serological methods are used to support the ultrasound and clinical diagnosis of CE, as they have some limitations. Classical techniques that use hydatid fluid (HF) as an antigen source are gradually being replaced by the use of purified, recombinant antigens and/or peptides, in an attempt to avoid the disadvantages associated with HF, such as variable sensitivity depending on the purification systems and the sources (ovine, bovine, human, etc), and the low specificity due to cross reaction with other parasites. At present, serological methods primarily use synthetic or purified derivations of the two main *E. granulosus* antigens, Ag5 and AgB:

i) Ag5is a highly immunogenic glycoprotein; the recombinant antigens produced to date (rAg5 and rAg5-38) have a lower antigenicity[96]. Therefore, most of the new tests involving this antigen use the purified native form.

Ii) AgB is a thermostable oligomeric lipoprotein formed of five subunits: AgB/1, EgAgB/2, EgAgB/3, EgAgB/4, and EgAgB/5, of which the first four are expressed in metacestodes while AgB/5 is only expressed in the adult parasite. In addition, the human and bovine forms have differential expression, AgB/1 being the most expressed in the human form[97-99]. The different subunits have notable differences in their diagnostic application. In one study of 146 patients with CE, the diagnostic sensitivities of the subunits AgB/1, AgB/2 and AgB/4 were higher (83.1%, 62.9% and 75.8%, respectively) than those obtained with the subunits AgB/3 and AgB/5 (29.0% and 41.1%)[100]. But in a comparative study using ELISA, with six different recombinant antigens (two derived from AgB (AgB/1 and AgB/2) and four others (EgcMDH, EgCaBP2, EgAFFPf and EgAFFPt), the recombinants derived from AgB showed better results. In particular, rAgB/2 gave the best diagnostic values. It gave different values when CE had been confirmed surgically - 92.6% sensitivity and 99.5% specificity in a study of 58 patients - or clinically - 73.2% sensitivity and 80.0% specificity in a study of 71 patients[101]. In another recent analysis, with a series of 148 patients with CE, both recombinant antigens (AgB/1 and AgB/2) showed similar sensitivities in active-transitional cysts (85.1% and 84.5%, respectively) with different

specificities (97.1% and 83.9%)[102]. In addition, the use of a construct (Ag2B2t) made of a double tandem repeat of the original recombinant protein AgB/2 improves the diagnostic values of ELISA, with a sensitivity of 97.6%[103].

One of the first fast assays, based on a combination of crude native antigens and partially purified antigens was a dot immunogold filtration assay (DIGFA). The technique uses *E. granulosus* hydatid fluid extracts (EgCF and AgB), *E. granulosus* protoscolex extract (EgP) and an *E. multilocularis* metacestode antigen (Em2). The sensitivity of this method was higher when used in a hospital setting (93%) than in the field (71.8%)[104].

The first fast diagnosis system to use immunochromatogaphy (ICT) used HF as an antigen, with a sensitivity of 96.2%. Later, other ICT tests were developed that used a mixture of purified AgB and Ag5 (VIRapid® Hydatidosis; Sen=69-74.1%, Spe=96-100%), recombinant AgB (ADAMU-CE; Sen=71.7%, Spe=100%), or recombinant AgB1 (HYDrapid; Sen=64%, Spe=100%), with similar sensitivities (with the exception of ADAMU-CE) to those obtained with a commercial ELISA (RIDASCREEN®) and with better specificity. Therefore the rapid diagnostic techniques have a diagnostic utility similar to conventional ELISA techniques in the diagnosis of hepatic CE[105-107].

In general, recombinant antigen and purified antigen techniques have a high specificity in healthy patients, and a much higher specificity than those that use HF in patients with other parasitoses. However, they still show cross-reactivity in patients with alveolar echinococcosis (AE) and cysticercosis. As a general rule, the sensitivity of the technique is higher in cases of multiple cysts than single cysts, independently of the antigen used. Lastly, all the techniques (conventional tests and rapid tests) have a low diagnostic sensitivity in cases of inactive cysts[108,109].

Recommendations

- Currently, conventional and rapid diagnostic tests have a low diagnostic sensitivity in the case of inactive cysts. (**A-I**).
- Classical techniques are gradually 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**).

X. Do cyst characteristics such as location, number, and stage affect the accuracy of the diagnosis?

The location, number and developmental stage of the cysts are determining factors that affect the accuracy of CE diagnosis. *E. granulosus* larvae can cause lesions in any part

of the body. Serological tests such as ELISA, indirect haemagglutination and latex agglutination determine the immunological response to the infection. These techniques are used when there is an initial suspicion or to support ultrasound diagnosis and have different sensitivity depending on the location of the cysts, with lower sensitivity for pulmonary (50-60%) than hepatic cysts (85-98%). These traditional figures for sensitivity have been contested in recent studies that found a similar sensitivity in different locations when other factors were accounted for.

Sensitivity is higher in patients with multiple cysts (reaching 90-100%) than those with only one cyst[19,110,111], whether hepatic or pulmonary. This difference becomes more evident when comparing complicated versus uncomplicated cases[103,112].

Another variable that affects the diagnostic value of serological methods is the developmental stage of the cysts. In all the series studied (**Table 5**), the antibody detection rate was higher in patients with active-transitional cysts (CE1, CE2, CE3a, and CE3b), with a mean sensitivity of 86.7%, than in patients with inactive or calcified cysts (CE4 and CE5), with a considerably lower mean sensitivity of 44%. This is probably because the inactive cysts release no or minimal quantities of antigen, reducing the stimulation of the patient's immune response and consequently the production of antibodies. Furthermore, the use of purified and recombinant antigens has enabled confirmation that the expression of some immunodominant antigens varies with disease progression, a known limiting factor in the serological diagnosis of CE. Therefore, depending on the antigen used, some techniques are more useful than others for the diagnosis of certain stages. Immunoproteomic studies with serum from patients with all developmental stages of CE (from CE1 to CE5) suggest that the AgB isoforms should not be used in the initial or chronic stages of the disease, during which they are hardly expressed. However, these isoforms have other features that should be taken into account, revealed on individual analysis of their diagnostic utility. A construct of AgB2 (Ag2B2t) has shown quite acceptable sensitivity, albeit lower than that of Ag5, for inactive cases (**Table 5**), with the advantage that the AgB constructs can be easily synthesised as recombinants while maintaining their diagnostic properties. Another example is AgB1, which could be used in combined assays as a marker of cyst viability, to differentiate biologically nonviable inactive cysts from biologically viable inactive cysts that may require treatment and/or follow-up[102,103,113,114].

Regarding the specificity of diagnostic techniques, one of the major problems is that most of the tests include only healthy subjects as the controls, so the values obtained are higher than the real values. Only some assays measure other parasitic and common nonparasitic cystic diseases that can interfere in the differential diagnosis of CE.

We can conclude that the current antibody detection systems that use purified and recombinant antigens have a higher specificity than those that use hydatid fluid, with a similar sensitivity depending on the technique. However, antibody detection is fully determined by the number and developmental stage of cysts, which determines both the release and the differential expression of the antigens. Therefore, the detection of a single molecule is not useful in the serological diagnosis of CE; combinations of the previously described antigens should be used. Furthermore, markers of early infection, cyst viability, disease progression, and cure need to be identified.

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

When evaluating the utility of molecular methods in the diagnosis of CE, we must differentiate between i) diagnostic techniques based on molecular methods, such as serological diagnosis with recombinant antigens and ii) molecular techniques proper such as PCR and its variants (RT-PCR, q-PCR, LAMP, etc). Molecular techniques with recombinant antigens are gaining ground as more reliable tools in the serological diagnosis of CE. In the second category (molecular techniques proper), there are multiple PCR techniques and derivatives that allow molecular differentiation between CE and AE, as well as genotyping, although this diagnostic application is limited to patients who undergo interventions (surgery or aspiration) where DNA can be extracted from the samples taken. Molecular characterisation of genotypes should be performed in humans wherever possible, not only because it is essential for accurate epidemiological surveillance, but also because of the different tropism of each genotype. In one study involving sequencing of clinical samples, it was found that, although the more common genotypes in humans (G1/G3, G6 and G7) usually inhabit the liver, each type has different tendencies. The G7 genotype infects almost exclusively the liver (98.6%) while the G1 genotype combines hepatic (54.6%) with pulmonary involvement in a high percentage of cases (19.6%). The G6 genotype, in addition to infecting the liver (54.3%) and lungs (25.7%), has a higher tropism for the central nervous system (12.9%)[115].

Genotyping of human cases is essential for the standardisation and validation of the new serological tools that use recombinant antigens, as some parasitic genotypes do not express certain antigen subunits. It is therefore recommended that, regardless of whether there is a firm diagnosis according to other methods (imaging and/or additional tests), molecular genotyping should be performed after surgery or aspiration, using the clinical samples taken. The development of new, noninvasive, easy-to-use techniques opens new avenues in the study of biomarkers. An example is the use of a breath test in the diagnosis of CE. The chemical analysis of exhaled breath identifies different

compounds between patients with CE and AE and between these groups and healthy controls[116]. However, its trial did not include patients with other parasitoses or other diseases in which the levels of these compounds could be altered, so larger studies are needed to determine its clinical application.

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**).

XI. What are the imaging techniques of choice in CE of the liver, lungs, and other locations?

The choice of diagnostic imaging technique in CE depends on factors such as i) the location of the disease, ii) the stage, and iii) the resources available. **Table 6** shows the most common techniques and their indications. Conventional plain X-ray is usually the first technique used in many situations, with CE being found incidentally; it is also useful in CE of the lung and bone. It may show linear calcifications surrounding the cyst(s), if calcified.

Ultrasound is the main technique and that which provides the most information in CE of the liver[117]. It also permits staging of the cyst[118], which is important in treatment decisions. Ultrasound is the best technique to detect the membranes and “hydatid sand” in the cysts[119]. Ultrasound is also the technique of choice for other abdominal locations[117] (renal, splenic, peritoneal, etc.), and for pulmonary CE with cysts in contact with the pleura[120], or locations that are accessible with ultrasound such as the orbits, muscles, soft tissues, etc. In cardiac CE, echocardiography is a very useful technique. Ultrasound is also considered the most appropriate investigation for monitoring the efficacy of surgery, percutaneous intervention, and anthelminthic treatment. Although there are several different classification systems, the most widely used is that suggested by the WHO-IWGE, which is based on that developed by Gharbi[121] (**Table 3**).

When there are limitations to ultrasound, for example in obese patients, those with abdominal distension, or previous surgery, CT and MR are indicated. They are the techniques of choice for extra-abdominal or subdiaphragmatic locations, in bone,

multiple, or complicated lesions with fistulas or abscesses, and as a form of presurgical assessment[122].

CT is very sensitive to the presence of calcium and can determine the internal structure of the cyst when it is extensively calcified and therefore not amenable to ultrasound[123]. However, it has a worse correlation to cyst staging. Nonetheless, extrahepatic cysts have a very variable appearance as this is determined by the host's reaction to the cyst, so it can be difficult to determine the stage unequivocally and even to diagnose CE.

MR is the technique of choice in intracranial and central nervous system disease, and for assessing possible cyst complications, mainly cystobiliary fistulas[124]. MR also has a higher sensitivity for differentiating fluid areas deep within lesions[94]. MR spectroscopy can be used to determine the viability of the intracystic parasite[125,126]. **Figure 5** shows images obtained with the different radiological techniques.

XII. Are nuclear medicine techniques useful in the diagnosis of echinococcosis?

There is little evidence on the use of nuclear medicine techniques in CE. A high uptake of fluorodeoxyglucose (FDG) usually equates to cyst complication, due to rupture, infection, or both. Usually there is peripheral uptake of the tracer and a central area with absence of uptake[127]. There is no clear evidence that intact cysts show increased metabolic activity and therefore uptake of FDG[128]. Therefore, currently, neither nuclear medicine techniques such as PET-CT, nor other radiological techniques allow a clear, unequivocal determination of cyst activity, viability or progression[129]. The most significant limitation for the use of CT-PET is the repeated administration of FDG[130]. Currently, the dual technique PET-MRI is coming into use. It has a lower radiation dose and better correlation with staging than ultrasound, but it is not yet routinely available in clinical practice[131].

8. FUNDAMENTALS OF CYSTIC ECHINOCOCCOSIS MANAGEMENT

XIII. What are the main principles and objectives of CE treatment?

The main principles of CE treatment are the complete eradication of the parasite and prevention of recurrence, with the aim of reducing morbidity and mortality[47]. In general, management should aim to preserve the function of the organ or system affected. Currently there are three active treatment modalities for the management of CE: i) open or laparoscopic surgery, ii) percutaneous techniques, and iii) pharmacological treatment. In many patients these treatment approaches are combined. Lastly, iv) the W&W strategy may be considered, depending on the patient and cyst stage[8,132-138]. The choice of treatment is not standardised; it is based on multiple factors including i) cyst size and location, ii) disease stage, iii) complications, iv) patient comorbidities, and v) medical

team experience and available resources. Thus, for an optimal treatment approach, the creation of multidisciplinary units, with clinicians, surgeons, radiologists, and other professionals is recommended for the management of this disease. Ideally, patients would be referred to regional or national referral centres. **Figure 6** shows a possible algorithm for the overall management of CE.

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

There is no solid evidence to determine the best follow-up schedule for CE, as each case is unique in terms of signs and symptoms, progress, and response to treatment, among other factors. The frequency and format of follow-up depends on the patient's clinical status, the type and location of cyst and the type of therapeutic intervention performed. Theoretically, follow-up should be long-term: at least 3-5 years, with no established maximum duration. In some patients, follow-up should be indefinite. CE5 cysts (and probably uncomplicated CE4 cysts) that are slow to progress do not require follow-up[138]. CE3b cysts should be assessed on an individual basis[11], while other CE stages should be followed up, unless the patient's clinical condition does not allow it. **Figure 7** shows a possible follow-up schedule. Follow-up is generally based on ultrasound and other imaging tests (CT and/or MR) initially every 6 months, then annually once clinically stable. Questions 21 and 22 describe additional tests that should be performed.

Recommendations

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

9. SURGICAL TREATMENT OF CYSTIC ECHINOCOCCOSIS

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

Surgery remains the definitive curative treatment for CE with large, active, symptomatic or complicated cysts. A variety of techniques have been described, but there is no consensus on which is the best[139]. To obtain the best surgical results, an individualised approach is crucial[140,141]. This will depend on factors such as i) the organ affected, ii) the number of cysts, iii) the presence or absence of cystobiliary communications, iv) potential bacterial superinfection, and v) intracyst haemorrhage. All surgical strategies should have two main objectives: i) removal of the cysts, and ii) obliteration of the cavity[140]. **Table 7** shows the most common surgical techniques. Open surgery is the most accepted surgical procedure for treating hepatic CE, especially in complicated cases[139,142], and is the mainstay of treatment for large, active, symptomatic and/or

complicated cysts: i) CE 2-CE 3b, ii) cysts > 5 cm, iii) cysts with multiple daughter vesicles, iv) infected cysts, v) cysts communicating with the biliary tree, and vi) cysts exerting a mass effect on adjacent organs[126,139].

The relative contraindications for surgery are i) patients who are not fit for surgery due to their general status or associated comorbidities, ii) multiple cysts, iii) difficult-to-access cysts (in central liver segments or close relation to the main portal branches or main hepatic branches), and iv) very small or partially or completely calcified cysts[143].

Recommendations

- Surgery 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, ii) cysts > 5 cm, iii) cysts with multiple daughter cysts, iv) infected cysts, v) cysts communicating with the biliary tree, and vi) cysts exerting 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, and iii) very small, difficult-to-access, or partially or completely calcified cysts. (**B-II**).

5. What are the best and most frequently used surgical techniques in hepatic CE? Are classical surgical techniques still the techniques of choice? What is the preferred strategy in hepatic CE: radical or conservative surgery?

Surgery should be adapted to the patient, their anatomy, the surgeon's experience and the hospital facilities. It is not clear which treatment option is the safest and most effective. The ideal approach should be simple, with complete resection of the cyst without rupture. Every effort should be made to protect the peritoneal cavity and avoid intraoperative cyst leakage with the use of gauze and compresses soaked in scolicidal solution.

Anatomical liver resection, total cysto-pericystectomy and open or partial cystectomy with or without omentoplasty are the most frequently used surgical techniques, the first two being understood as radical and the second as conservative surgery. Omentoplasty is effective for preventing complications in conservative surgery in hepatic CE[140].

The classical techniques, understood as nonradical or conservative techniques, have facilitated the management of CE in hospitals that do not have hepatobiliarypancreatic surgery units, as they are less complex techniques that generally need less time and are

safe. However, the rates of recurrence (4-25%) and postoperative complications (6-47%) tend to be higher than those of radical techniques[126,139,141,143-147]. Radical surgery refers to the removal of the cyst along with the pericystic membrane, and may even include liver resection[126]. These procedures must be performed by surgeons who have experience in hepatobiliarypancreatic surgical centres[143]. As stated above, radical surgery has the advantages of having fewer postoperative compilations and lower recurrence rates (0-3%), but a high intraoperative risk (0-26%) for what is still considered a benign disease[139,143,144]. In highly experienced centres, an “almost total” cystectomy is considered a radical technique. This variant is of great use in cysts close to hepatic vascular structures, and also has a low rate of complications.

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 cysto-pericystectomy 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 risk of associated 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 and elective surgery in terms of complications or recurrence rate?

There is no consensus on which surgical technique has the lowest rate of complications. Recurrences usually occur due to the failure to completely remove the endocysts and/or their dissemination during surgery. Therefore, extra care must be taken during the surgical act to prevent such dissemination[126].

Radical or conservative surgery has a complication rate of 3-25% and a recurrence rate of 2-40%. Both rates tend to differ depending on the location and size of the cyst, the surgeon’s experience and the chosen treatment[126,146,148-152].

The most common complication of hepatic CE is infection and communication with the biliary tract. Contact between the cyst and the biliary tract is observed in 3-7% of cases[82,126]. There is a direct association between the size of the cyst and the probability of biliary tract involvement. An increase in bilirubin and alkaline phosphatase levels and a cyst diameter of more than 10.5 cm may suggest occult cystobiliary communication[153]. Occult rupture is seen in approximately 10-37% of cases[143]. If intrabiliary rupture is suspected, standard imaging techniques (ultrasound, MR, and CT) and even endoscopic retrograde cholangiopancreatography (ERCP) may be used. If there is preoperative evidence of a cyst opening to the biliary tract, ERCP sphincterotomy before surgery reduces the postoperative risk of an external fistula[154]. The reported incidence of rupture into the peritoneal cavity is approximately 10-16%[143]. Intraperitoneal rupture can occur during surgery or PAIR treatment. Trauma can be another cause of intraperitoneal leakage. Morbidity (12-63%) and mortality (0-12%) are high after intraperitoneal rupture[143,150-152,155,156].

Several techniques (omentoplasty, introflexion, capitonnage [closure in layers of the space occupied by the cyst], external drainage and synthetic fibrin) have been described to prevent postoperative complications caused by the presence of a residual cavity after conservative surgery[145], but only omentoplasty has been shown to be effective in preventing complications after conservative surgery[145].

Laparoscopy has been shown to be a safe and technically feasible technique[139,144]. The first laparoscopic surgery for CE was described in 1992[157]. As with other diseases, appropriate patient selection is essential. The position of laparoscopic surgery within the management of hepatic CE is yet to be defined[145]. Patients may be poor candidates for surgery if they have i) cysts located deep in the liver parenchyma, ii) cysts located in posterior lobes, near the vena cava, or multiple cysts (>3), and iii) cysts with calcified walls. Laparoscopic surgery can offer some advantages such as i) better aesthetic results, ii) shorter hospital stay, iii) less postoperative pain, iv) lower rate of surgical site infection, and v) lower rate of complications that conventional procedures due to better control of the residual cavity and local recurrence[144]. The possible limitations of laparoscopic treatment include i) a significant learning curve, ii) risk of intraoperative cyst leakage, iii) difficult-to-control haemorrhage[144], iv) increased risk of intraoperative leakage due to increased pressure within the cyst[126].

There are few studies focusing on emergency surgery in CE; most publications relate to isolated cases, so only limited conclusions can be drawn. In general, urgent surgery for CE is due to complications of the disease. The most common mechanical complication that requires urgent intervention is obstructive jaundice. In selected cases and depending on the situation, it is advisable to perform preoperative MR-cholangiography

or ERCP, to assess the relationship of the cyst to the biliary structures. Another less common complication is the combined mechanical and immunoallergic complication caused by the spontaneous rupture of the cyst, which can cause anaphylactic shock when the cyst contents come into contact with the abdominal cavity. This complication requires the patient to be admitted to an intensive care unit as well as complicating the surgical procedure itself. It also produces peritoneal seeding of the protoscoleces. Bacterial superinfection of CE is another common complication that requires early treatment.

Recommendations

- Appropriate patient selection is essential for successful laparoscopic surgery. The laparoscopic approach is safe and technically feasible. (**C-III**).
- Laparoscopic surgery may offer some advantages such as i) shorter hospital stay, ii) less postoperative pain and iii) lower rate of surgical site infection. It may be appropriate in selected cases of hepatic CE. (**C-III**).
- Patients may not be candidates for surgery if they have multiple (>3), calcified, or deep cysts, cysts in posterior lobes, or cysts near the vena cava. (**C-III**).

7. What are the most frequently used surgical techniques in pulmonary CE?

The main objective of surgical treatment of pulmonary disease is the complete removal of the cyst, minimising resection of the parenchyma[158-161]. Cysto-pericystectomy is the technique of choice to enable preservation of lung tissue. In this technique, the cyst is resected and possible air leaks to open bronchioles are closed[158-160]. In cases in which there is associated destruction of lung parenchyma (complicated or abscessed cysts), the surgical team should perform the minimum lung resection required to ensure the complete removal of the affected parenchyma, which sometimes requires anatomical resection[162,163]. Capitonnage, which was classically recommended when performing cysto-pericystectomy, has not been demonstrated to reduce postoperative air leakage[162]. Suitable approaches are thoracotomy and video-assisted thoracoscopy (VATS). In centres with experience, both have comparable results but VATS has a lower morbidity, and is therefore the recommended technique[164-167]. Patients with cysts in the right hemithorax, mainly in the lower lobe with associated cysts in the superior hepatic lobes, may be treated via independent thoracic and abdominal approaches or by thoracophrenolaparotomy. Percutaneous techniques are not recommended in pulmonary CE due to the high risk of rupture of the cysts and secondary contamination[168].

Recommendations

- Cysto-pericystectomy is the surgical technique of choice in pulmonary CE. (**C-II**).

- Only the minimum pulmonary resection necessary should be performed in cases with associated pulmonary destruction or nonviable parenchyma (complicated or abscessed cysts). (**C-II**).
- When performing cysto-pericystectomy, capitonnage has not been demonstrated to reduce postoperative air leakage. (**C-II**).
- For the surgical approach, thoracotomy and VATS have comparable results, but VATS has a lower morbidity and is therefore the recommended technique. (**B-II**).
- Patients with disease in the right lower lobe associated with cysts in superior 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. What are the efficacy and complications of the surgical techniques in pulmonary CE?

Following pulmonary surgery for CE, the rate of complications ranges between 0.5-2.3%[165,169-174], with a recurrence rate reaching 3.3%[169,175-179]. The complication rate is higher with thoracotomy than with VATS[164-167,169]. Patients who have undergone intervention for complicated cysts have a higher incidence of postoperative complications[170,175]. The most prevalent complications are i) prolonged air leak, ii) wound infection, iii) pneumonia, and iv) empyema.

Mortality reaches 5.4%[171,176,177,180], and is not related to cyst size or complications[171].

Recommendations

- Surgery is one of the best treatment options for pulmonary CE. It is associated with a low morbidity and mortality. (**C-II**).
- Patients who undergo intervention for complicated cysts have more postoperative complications. (**C-II**).

9. What is the best approach in difficult-to-access hepatic or pulmonary locations?

From a surgical perspective, all hepatic segments are theoretically accessible. Difficulties arise due to factors such as i) the size of the cyst, ii) the liver segment affected, and iii) the relationship to important structures (bile duct, great vessels and adjacent organs). These cases should be assessed on an individual basis, with further imaging studies if necessary (CT, MR-cholangiography, ERCP) to visualise the anatomical relationship of the cyst and evaluate the best surgical option. Usually a chemotherapeutic treatment is prescribed before surgery. Hepatobiliary fistulas with thoracic spread can be managed surgically via a low thoracotomy with resection of the bile-destroyed lung

and reconstruction with biological materials[167,168,181]. Conservative management of these fistulas has also been described, by draining bile to prevent it from passing to the chest and therefore facilitate the spontaneous closure of the fistula[182,183].

For difficult-to-access pulmonary sites, VATS or thoracotomy allows access to the entire lung, chest wall, anterior and posterior mediastinum, and pericardium. In cases in which the cyst is in a difficult-to-access area of the parenchyma, resection of the affected lung may be required. In most cases of cardiac cysts, access via midline sternotomy and extracorporeal circulation is required[184,185].

Recommendations

- From a surgical perspective, all liver segments are accessible. (**C-III**).
- Hepatobiliary fistulas with thoracic spread can be managed surgically via a low thoracotomy with resection of the bile-destroyed lung and reconstruction with biological materials. (**C-III**). They can also be managed conservatively, via the drainage of bile, which facilitates spontaneous closure of the fistula. (**C-III**).
- VATS and thoracotomy both provide access to the entire lung. (**C-III**).
- Most cases of cardiac CE are treated surgically via midline sternotomy and extracorporeal circulation. (**C-III**).

10. How should multi-organ CE be managed?

Multi-organ involvement is usually the result of simultaneous haematogenous spread to several organs after primary infection, although it can also be due to endovascular spread, or secondary seeding in cavities after surgery, after spontaneous microrupture, or contiguous spread. It occurs in less than 10% of cases of CE and has been described in all ages[158,186-200]. In one series of 84 cases of multi-organ CE, the most common site was lung and liver (49.9%), followed by both lungs (30.9%), both lungs and liver (10.7%), heart and lung (3.6%), both lungs, liver and spleen (1.2%), lung and spleen (1.2%), liver, spleen and pancreas (1.2%), and liver, spleen and kidney (1.2%)[186]. In all patients with CE, the possibility of multi-organ involvement, particular the hepatopulmonary combination, should be considered. Therefore, in patients with hepatic CE it is recommended to perform simple chest X-ray or better yet a CT of the chest, and in patients with pulmonary CE an abdominal ultrasound or CT is recommended[186]. Disseminated CE can be confused with metastatic cancer, although patients generally remain in good general health with CE. In such cases, MR and PET-CT with 18F-FDG can be useful[201,202]. The approach to multi-organ CE should be individualised and depends on factors such as i) cyst location(s), ii) cyst size, iii) cyst number, and iv) the clinical status of the patient. Usually, the treatment of multi-organ CE rests on surgery

and antiparasitic medication, although surgery is not always possible[7,75,203-210]. Pharmacological treatment prior to surgery with albendazole and/or praziquantel is prescribed to minimise the risk of dissemination. If the disease is very extensive and affecting end-organs, and there is reasonable doubt as to whether complete resection is possible, the surgical team may consider the use of strategies such as PAIR, which in selected cases has better results than classical surgery. When multi-organ involvement affects both hemithoraces, the possible approaches are VATS, sequential bilateral thoracotomy, or midline sternotomy[173]. In cases of concurrent right lower pulmonary lobe and superior hepatic segment(s) involvement, thoracophrenolaparotomy may be considered[184]. Some authors advocate this approach, reporting a similar rate of complications[173], while others demonstrate a lower morbidity with thoracotomy or VATS and laparotomy or laparoscopy at a later stage[165,184].

If surgery is to be performed, some authors suggest it be done in two stages, prioritising the treatment of cysts complicated with infections, fistulas or haemorrhages, those with pulmonary location (due to risk of rupture during general anaesthetic), and larger cysts[186]. Other authors, however, advocate single-stage surgery, provided the patient's condition allows it[75]. Cases treated with minimally-invasive surgery have been described[211]. When medical treatment is the only option, it is recommended that it be continued long-term, even indefinitely (avoiding stopping treatment), although there is little evidence for this recommendation[7]. Some authors also suggest the possibility of combined treatments with albendazole and praziquantel, or even with a third drug for several months[189,193,194,197].

Recommendations

- In all patients with CE, the possibility of multi-organ involvement, particularly the hepatopulmonary combination, should be considered. Patients with hepatic CE should undergo a plain chest X-ray or CT chest, and patients with pulmonary CE should undergo an abdominal ultrasound or CT. (**B-II**).
- There is no established regimen for medical treatment. When medical treatment is the only option, it should be prolonged and even indefinite (avoid stopping treatment). (**B-III**).
- If the disease is very extensive and there is reasonable doubt as to whether complete resection will be possible, PAIR and/or pharmacological therapy 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 disease affects superior hepatic segments and the right lung, thoracophrenolaparotomy or an independent approach via thoracotomy or VATS with laparotomy or laparoscopy at a later stage may be considered. (**C-II**).

11. How should patients with atypical location CE be managed?

Atypical locations of CE are those outside the liver and lungs. The frequency of the organs affected varies depending on the patient series consulted. Splenic, renal, musculoskeletal, central nervous system and cardiovascular locations are among the most frequent of the atypical locations.

Splenic involvement is described in 0.6-4% of published series[64,212] and is usually associated with involvement of other organs[213]. It is usually asymptomatic, although it can cause symptoms from local compression, superinfection, intracyst haemorrhage or due to rupture into the peritoneal cavity[214]. Surgical treatment should be conservative, with splenectomy reserved for centrally-located or large cysts[215]. In one literature review, no significant differences in recurrence rate were found between those treated with conservative or radical surgery[216]. Techniques such as simple drainage, partial cystectomy with or without external drainage and segmental splenectomy have been used. Percutaneous puncture and drainage using a large-gauge catheter is associated with a higher rate of bacterial superinfection than the PAIR technique using a fine needle[217]. In the absence of data on antiparasitic treatment, the recommendations should the same as for hepatic CE.

Renal CE occurs in 1-3% of cases[64,212], and can remain silent for years. The clinical features, when they present, include low back pain, flank discomfort, and dysuria, with or without haematuria[218-220]. The cysts are usually single cysts, located in the renal cortex, and renal function is usually unaffected[220]. 10-20% of patients with renal involvement excrete daughter vesicles in the urine (hydatiduria)[221]. The sensitivity of the serological techniques is up to 92%[218,219,222,223]. Ultrasound allows identification and classification of the lesions according to WHO-IWGE criteria,[133] but CT gives better visualisation of the cyst walls, a more reliable diagnosis on the presence of infection, and can better differentiate between renal abscesses and tumours[218,219,224,225]. It is therefore recommended that all patients undergo a preoperative CT. There are no conclusive data on treatment, but antiparasitic treatment, PAIR, minimally-invasive surgery, laparoscopic surgery, open surgery, and even nephrectomy have all been used[225-237].

Cardiovascular location is very uncommon (1-2%) but serious. The typical form is a solitary cyst (60-80% of cases) located in the left ventricle (55-60%), right ventricle (15%), both atria (5-7%), interventricular septum (5-9%), pericardium (8%), or great vessels[238]. The presentation includes symptoms of myocardial ischaemia (with raised

troponin and CK-MB), conduction disorders (inverted T-waves, ST-segment depression, ventricular ectopics, bundle branch block or complete block, and supraventricular tachycardias), heart failure (with raised NT-ProBNP), mechanical valve abnormalities and recurrent syncope[58,238-245]. Intramyocardial fistulas with acute and chronic bleeding, pericardial tamponade, and endocarditis have all been described. There may be associated systemic symptoms of the disease such as fever or cough, and less frequently, weight loss and fatigue[238-242]. If rupture occurs, it may lead to an anaphylactic reaction, pulmonary embolism with right heart failure, or arterial emboli to the brain, aorta or extremities[243-245]. Extracardiac CE co-exists in up to 80% of cases[58]. Serological techniques have a very high sensitivity, The most frequently used diagnostic imaging techniques are echocardiography, CT and MR[94,246-254]. Echocardiography (transthoracic or transesophageal) is the technique of choice given its availability, high sensitivity, high resolution, and ability to simultaneously analyse the haemodynamic effects[58,248,249]. The most characteristic finding is of fluid-filled nodules (possibly containing daughter vesicles) which must be differentiated from echo-dense, solid cardiac nodules that could be confused with primary tumours. MR better differentiates the fluid content of the cysts[94,251-254]. Treatment should be led by an experienced multidisciplinary team and is based on surgical removal of the cyst. Surgery is high-risk (generally involving extracorporeal circulation) and has an associated mortality of 10-12%, particularly due to postoperative complications such as systemic or pulmonary emboli, pericardial dissemination, and sepsis[58,255]. Local instillation of hypertonic saline (20-30%) is recommended, with the aim of preventing recurrence[255-257]. Intraoperative transthoracic echocardiography may be used, to allow better localisation of cysts, better differentiation of myocardial tissue, and identification of small cysts[257]. Antiparasitic treatment is not recommended before surgery, as it could weaken the cyst wall and predispose to cyst rupture[58]. Treatment with albendazole for at least 3-4 months after surgery appears to reduce the risk of recurrence[58,238,243,258]; it is used for a longer duration or even indefinitely in cases of endovascular rupture with pulmonary seeding[58].

Cysts occur in the central nervous system in 1-2% of CE cases; this location is more common in children and young adults (60-93%) and is very serious[259-262]. The cysts may occur as primary cysts or secondary to haematogenous spread from a cardiac focus. Between 6-63% have concomitant involvement of another organ. Most often, the territory of the middle cerebral artery is affected, especially the parietal lobes, although any vascular area may be affected, and extradural, intraventricular, and meningeal involvement have all been described[259-266]. The most common signs and symptoms are headache (83%), papilloedema (77%), vomiting (66%), hemiparesis (38%), seizures (33%), visual disturbances (27%), ataxia (11%), facial paralysis (5%), and even

psychiatric disorders[267-269]. Serological techniques have a very low sensitivity[259-276]. CT of the head shows spherical cystic images with very well-defined borders, with a similar density to cerebrospinal fluid, without surrounding oedema and with minimal or no uptake of contrast; only 1% of cysts appear calcified[270-273]. MR better defines the lesions and shows round images with low signal on T1 and high signal on T2, without enhancement after the injection of contrast medium[270]. The differential diagnosis includes all types of cystic lesions including tumours (cystic astrocytoma), infection (abscesses, neurocysticercosis) and congenital lesions (arachnoid cyst, epidermoid cyst). The treatment of choice consists of the intact removal of the cyst, using the Dowling technique[273-282]. Craniotomy is performed, the tunica adventitia is opened, and a catheter is introduced between the cyst wall and the brain parenchyma. Saline irrigation enables the intact removal of the germinal layer and its contents with gravity. The concern is rupture of the cyst during surgery, as it is associated with high rates of recurrence and mortality. If rupture occurs, the contents of the cyst should be aspirated and the area irrigated copiously with hypertonic saline. Rupture occurs in up to 25.6% of cases, while other complications (parenchymal haemorrhage, pneumocephalus, subdural haematoma) occur in 9.5-20% of operations, with local recurrence rates of 9.5-19% and a mortality of 10-12%[264,276-282]. Inoperable, recurrent, or ruptured cysts are treated with a prolonged course[277,283,284].

CE of the bone occurs in 1.6-3% of cases and most commonly affects the vertebrae (45%), followed by the pelvis (14%), femur (10%) tibia (10%), ribs (6%), skull (4%), humerus and fibula (2%)[285,286]. In vertebral disease, lumbar is more common than thoracic involvement (although as there are more thoracic vertebrae, overall more thoracic vertebrae are affected)[287]. Bone involvement is more common in isolation (83%) than with multi-organ involvement. Most bone cysts are asymptomatic until pathological fracture. The presence of local or diffuse pain, difficulty walking, and cutaneous fistulas have been described. The symptoms of vertebral involvement are back pain, nerve compression or spinal cord compression in the form of paraparesis, sphincter involvement or nerve root pain. Paraplegia is one of the most serious complications of vertebral echinococcosis, occurring in up to 75% of cases in which vertebral fracture occurs[288-294]. The prognosis of intradural hydatidosis appears to be better than that of extradural, paraspinal, or vertebral hydatidosis. CE of the bone is associated with high rates of recurrence (15-48%) according to whether the surgery is radical or not, with frequent sequelae in the form of persistent pain, fractures, paraplegia, and various disabilities. Due to the lack of a fibrous capsule in the bone, serological techniques are very sensitive. Plain X-ray, CT and MR are the imaging techniques of choice for diagnosis, with MR being the most valuable. The characteristic image is an expansive,

osteolytic lesion with cortical thinning and contiguous spread to adjacent soft tissues, most often located in the metaphysis when involving the long bones[118,286,287,295-297]. The main differential diagnoses are benign and malignant tumours, osteomyelitis, and fibrous dysplasia. In the case of vertebral lesions, the differential diagnosis includes vertebral tuberculosis and infectious spondylitis, although the intervertebral disc is not involved. A high index of suspicion is required to avoid diagnostic puncture of the cyst, due to the subsequent risk of dissemination and anaphylaxis. The treatment of choice is surgery[286-295], although it is not always possible due to the potential functional repercussions. Surgery must remove the affected bone and at least 1-2 cm of surrounding healthy bone, and include intraoperative irrigation with scolicidal solution[292,294,298-302]. In the case of vertebral involvement, the main objective is to decompress the spinal cord and stabilise the spine, since radical surgery in this location is often technically impossible[287]. When the pelvis is affected, radical surgery is almost impossible; occasionally, hemipelvectomy is performed[292,301]. Often, surgery requires the use of fixation materials or polymethacrylate cement (which could help avoid recurrence as the temperature reached when it hardens would kill the parasite)[303-305]. Although it is unclear whether there is an effect on the risk of recurrence, prolonged and even indefinite treatment with albendazole is nonetheless recommended[291,294]. The use of radiotherapy as an adjuvant, with cumulative doses of between 25-60 Gy, has been suggested, but results are difficult to interpret[306].

Recommendations

- In patients from endemic areas who have cystic lesions, CE should be considered in the differential diagnosis. (**A-I**).
- All patients with suspicion of extrahepatic CE should undergo a CT of the chest and abdomen. (**A-III**).
- Wherever technically possible, surgery is the treatment of choice for CE of atypical location (**B-I**).
- Although splenectomy is curative in splenic CE, the use of conservative surgery is preferable; splenectomy should be reserved for patients with large cysts located centrally or near the splenic hilum. (**A-II**).
- Anthelminthic treatment should be given for at least two weeks before intervention and for 3 months afterwards. (**B-III**).
- In renal CE, laparoscopic surgery can be a safe and effective option. (**B-III**).

- If nephrectomy is performed, the aim should be to preserve the most parenchyma possible, reserving total nephrectomy for cysts on nonfunctioning kidneys, large cysts (occupying the entire parenchyma) of 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 cyst wall destruction and consequent rupture. (**B-I**).
- The treatment of choice in cerebral CE consists of the intact removal of the lesion using the Dowling technique. (**B-I**).
- In CE of the bone, surgery should involve removal of the affected bone and at least 1-2 cm of surrounding healthy bone and intraoperative irrigation with scolicidal solution in the form of hypertonic saline. (**B-I**).

10. TREATMENT OF CYSTIC ECHINOCOCCOSIS WITH IMAGE-GUIDED INTERVENTIONAL TECHNIQUES

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

Since the mid-1980s, new radiological techniques have been introduced for the treatment of CE. One of the most relevant is PAIR[307], which is increasing used, often in place of surgery, although surgery remains the treatment of choice for most situations (**Table 8**).

The formal indication for PAIR is based mainly on CL, CE1, and CE3a categories of cysts with a size of between 5-10 cm. It is performed using ultrasound-guided or CT-guided puncture of the cysts to place an intracyst catheter of variable gauge, though which as much of the contents as possible are aspirated. Next, a scolicidal solution is instilled, up to one third of the volume of the fluid extracted[308], the most commonly used solutions being 95% ethanol or hypertonic saline (15-30%). After 10-30 minutes, the contents of the cyst are reaspirated. If necessary, the procedure is repeated several times until clean fluid is obtained. Other techniques based on PAIR have been developed, such as PAIRD (puncture, aspiration, injection, reaspiration and drainage), in which a drainage catheter is inserted and kept in until the output from the cyst falls below 10 mL daily. It is used for CE1 and CE3a cysts larger than 10 cm (although there are authors who use PAIRD in cysts smaller than 10 cm[309]). Another variant is the D-PAI technique (percutaneous double puncture, aspiration and injection of ethanol), in which the cyst is completely emptied and refilled to 50-60% of the volume with ethanol, which is not reaspirated. After 3-7 days, the procedure is repeated[310].

All the techniques described are effective for unilocular cysts, but they do not have the same efficacy in multilocular cysts or those with a solid component. Such cysts have a greater tendency to recurrence as it is difficult to evacuate the content and the cyst is compartmentalised, which means viable parts are left behind. Other techniques have been developed for the percutaneous treatment of these types of cysts, such as percutaneous evacuation (PEVAC), which allows treatment of cysts with biliary communication[311], the modified catheterisation technique (MoCaT), and the dilatable multi-function trocar (DMFT)[312]. These techniques are based on evacuating all the contents of the cyst including the laminated and germinal layers. However, the morbidity and mortality of these techniques is higher than PAIR and similar to surgery, and there are not enough studies to allow a conclusion on their true efficacy, so their current use is limited[308].

With the aim of reducing hospital stay, techniques such as the Örmeci technique are being developed. This uses a smaller (22G) Chiba needle[308]. For each centimetre of cyst diameter, 3 times this value (as volume) is aspirated (eg, for a 7 cm diameter cyst, 21 mL would be aspirated), and the aspirated volume is replaced with the same volume of a combination of two thirds 95% alcohol and one third Aethoxysklerol (polidocanol)[308]. Five minutes after the injection, the needle is removed and the patient is observed for 2 hours in case of possible complications (essentially allergic reactions). The patient is discharged home if there are no complications. Other percutaneous treatment efforts exist, such as radiofrequency ablation[313].

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. How are image-guided interventional techniques usually performed?

Percutaneous techniques must be performed by professionals with experience in image-guided drainage to minimise the risks of cyst dissemination or complications affecting the biliary tree, urinary tract, or other structures. In general, PAIR (**Figure 8**) has been

demonstrated to be safe and effective, should be performed under sedation or general anaesthetic, and should have a surgical team available for the management of potential complications[314]. The procedure should be performed in an interventional suite with a resuscitation team available in case of possible anaphylactic reactions. Prior to the intervention, the possibility of a complicated cyst should be excluded. Communication with the biliary tract must be excluded given the risk of chemical sclerosing cholangitis. Therefore, before instilling the scolicidal liquid, it is usually standard to perform cystography with a 50:50 mixture of contrast and saline in the cavity to exclude direct communication with the biliary tract. If communication is detected, the scolicidal infusion must be stopped. Prior to the procedure, it can be useful to perform MR-cholangiography[7]to assess the intrahepatic biliary tract and the presence of possible cyst fistulas. The rapid determination of intracyst bilirubin levels during the procedure can be helpful in indicating the presence of a communication between the cyst and the biliary tract[314].

Depending on the cyst characteristics, particularly the size, ultrasound-guided puncture may be performed using a needle (PAIR) or a drainage catheter (PAIRD). The route should be chosen to ensure there is healthy liver between the cyst and the liver capsule, as puncture of the cyst via a route adjacent to the liver capsule would increase the risk of dissemination. At this point, approximately 10-15 mL of the cyst contents should be aspirated and assessed for the presence of scoleces. If scoleces are observed, the procedure is continued. If parasites are not seen and determination with antigens is negative, the clinical and epidemiological features should be evaluated: if they are highly orientative, the procedure should be continued; if not, it should be discontinued. After determining the absence of communication with the bile tract, the scolicidal agent is administered[315]. A volume of approximately one third of the aspirated volume is administered. After 15 minutes, the cyst is reaspirated.

Recommendations

- Percutaneous treatments must be performed in an intervention suite with resuscitation support, anaesthetic sedation, and a surgical team on stand-by. (**C-III**).
- To avoid complications, communication between the cyst and the biliary, renal, or respiratory tracts must be excluded (**C-III**).

14. What is the best scolicidal agent?

Although a variety of substances have been used as scolicidal agents, including silver nitrate, iodopovidone, thymol, plant extracts, albendazole, chlorhexidine, hot water (50-60ºC), hydrogen peroxide, 95% ethanol, hypertonic saline (concentrations between 15-

30%), and others[316], the optimal scolicidal agent has not yet been identified. The ideal scolicidal agent should meet a series of requisites: i) highly-scolicidal, ii) fast acting, iii) widely available, iv) cheap, and iv) minimal side effects[317]. At present, the two most frequently used agents are hypertonic saline solution (at least 20% concentration) and ethanol (95%)[315], since at lower concentrations they lose their scolicidal efficacy[318]. One important difference between the two is that 95% alcohol has a greater sclerosing activity on the cyst wall than saline at the concentrations stated[312]. However, saline is safer if nearby vascular structures are punctured, or if there is a high risk of complications[319]. The most serious side effects of these two agents are anaphylactic reactions and chemical sclerosing cholangitis (if cystobiliary fistulas are present or develop)[320], so the presence of such fistulas should be ruled out prior to the intervention.

Recommendations

- At present, there is no ideal scolicidal agent. Ethanol (95%) and hypertonic saline (minimum 20% concentration) are the scolicidal agents of choice, as they are widely available, have a good scolicidal activity and are cheap. Their use is limited by their side effects, including chemical sclerosing cholangitis and anaphylactic reactions. (**B-III**).
- Before using alcohol or hypertonic saline as scolicidal agents, the presence of cystobiliary fistulas must be excluded. (**B-III**).

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

The factors that determine treatment choice are i) type of cyst, ii) size of cyst, iii) location of cyst, and iv) presence or absence or complications[7].

Percutaneous techniques can be used in pregnant patients and in children older than 3 years, but the preoperative use of benzimidazoles in these situations should be evaluated on an individual basis[321,322].

PAIR is indicated in i) CL, CE1 and CE3a cysts between 5-10 cm, ii) infected cysts, iii) multiple cysts (if they are all accessible for puncture), iv) postoperative recurrence, and v) after failed medical treatment. The modified technique with insertion of a drainage catheter (PAIRD) can be performed in CL, CE1 and CE3a cysts larger than 10 cm. In CE2 and CE3b cysts, there is more evidence supporting surgery[323], although techniques such as MoCaT or PEVAC may be used in patients who are unsuitable for or refuse surgery[323].

The contraindications for the use of percutaneous techniques include i) uncooperative patients, ii) cysts in difficult-to-access locations (eg spinal, cerebral, cardiac), iii) calcified

cysts, and iv) cysts that communicate with the biliary tree, peritoneum, bronchi, or urinary tract. The efficacy of PAIR in hepatic CE varies according to the series consulted, from 88-100%, with a recurrence rate of 1.6-10.9%[308]. There is insufficient evidence for the other techniques (in CE2 and CE3b), although the reported efficacy is always below 40%[323]. In general, the rate of complications is low. Anaphylaxis occurs in 0.3% of procedures and the mortality is practically zero[308].

Recommendations

- PAIR is indicated for cysts measuring 5-10 cm in stage CE, CE1 and CE3a, and in the case of multiple accessible cysts, infected cysts, postoperative recurrence, and failed medical treatment. (**B-III**).
- The modified technique with insertion of a drainage catheter (PAIRD) can be performed in CL, CE1 and CE3a cysts larger than 10 cm. (**B-III**).
- In CE2 and CE3b, there is a stronger indication for surgery, although the modified techniques (MoCaT or PEVAC) may be performed if the patient is not suitable for or refuses surgery. (**C-III**).
- Percutaneous techniques can be used in pregnant patients and in children younger than 3 years old. (**B-III**).

11. MEDICAL TREATMENT OF CE

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

Initially, pharmacological treatment was recommended for patients with inoperable disease and for patients with multi-organ CE. Subsequently, several studies suggested that pharmacological treatment could be an alternative to surgery in uncomplicated cysts[132], and an adjuvant to surgical/percutaneous treatment for the prevention of secondary cysts. Albendazole should be started at least 4 days before an intervention (the WHO suggests 4-30 days before) and continued for at least 1 month after the intervention.

In general, pharmacological treatment is not recommended for stages CE4-5[7]. **Table 9** shows the key studies evaluated. Mebendazole was one of the first drugs used in the treatment of CE. Most of the information on this drug comes from case series and observational studies. These studies had a low number of patients (from 7 to 85), and the most frequently used dose was 40-50 mg/kg/day divided into 3 doses (the dosage recommended by the WHO), with a highly variable duration (from 1 to 55 months, the most common being 3-6 months); in addition, in some cases the treatment was continuous and in others it was cyclical with rest periods. In general, the drug had a good safety profile. The criteria for response to treatment were very different and the follow-

up times were highly variable, which makes comparison difficult[324-331]. One observational study showed that the response rate was dose-dependent with better responses at higher doses of mebendazole and with prolonged treatment[284]. Another study found no differences in the response to treatment when comparing continuous treatments against cyclical treatment with treatment breaks[332]. One study of patients who underwent surgery found that perioperative treatment with mebendazole reduced the percentage of live scoleces obtained during surgery[333].

Albendazole was introduced at the beginning of the 1980s. The dose recommended by the WHO is 10-15 mg/kg/day divided into 2 doses (the usual dose for adults is 400 mg every 12 hours), to be taken with fatty foods to increase the bioavailability[8,133]. Since then, it has gradually replaced mebendazole, due to its advantages which include lower dosage and better intestinal absorption. In general, treatment can be given in several cycles (1-6) with breaks of 10-14 days or continuously for 3-6 months. Complete resolution of cysts is achieved in less than 50% of patients on medical treatment[8,133-135]. One study suggested that larger cysts respond more slowly to treatment[134].

i) Studies on albendazole versus placebo[334,335]:

Stojkovic et al[132] collected data on 711 patients with 1308 cysts. They found that after 1-2 years of treatment with benzimidazoles, 50-75% of active C1 cysts were classified as inactive/resolved, compared with 30-50% of CE2 and CE3 cysts. However, 25% of cysts were reactivated 1.5-2 years after having initially responded, and multiple recurrences were observed. This study suggests that smaller active cysts in stage CE1 have the best response[132]. Two studies compared albendazole versus placebo[334,335], both analysing response to treatment (cure, improvement, no response, worsening) as an outcome variable. In both studies, the proportion of radiological improvement/cure was higher in the albendazole group than in the placebo group.

ii) Studies comparing albendazole versus mebendazole:

Some studies have analysed treatment with albendazole alone[136,334-337]or in combination with mebendazole[331,338,339]. Two studies specifically compared the efficacy of albendazole with that of mebendazole. The first was a prospective observational study of 337 patients, in which they compared degenerative changes observed on ultrasound during post-treatment follow-up: these were greater in patients treated with albendazole (80% versus 50.6%)[340]. The second was a randomised clinical trial of 448 patients. Treatment was given for 3-6 months, and follow-up ranged from 1-14 years, with a higher percentage of degenerative changes in the albendazole group (82.2% versus 56.1%), but the percentage of recurrences was the same[339]. The outcome variables were the viability of the protoscoleces and of the cysts (intact/dead and viable/nonviable) and the response to treatment (cure, improvement, no response, worsening). A recent meta-

analysis also evaluated which benzimidazole was most effective in the treatment of CE[10], and found better results with albendazole than with mebendazole: albendazole has a better bioavailability and can reach higher serum concentrations (with a peak concentration at approximately 4 hours and a half-life of 6-15 hours)[341]. However, the main problem with albendazole is its somewhat variable penetration of the cyst.

iii) Studies comparing surgery/PAIR versus surgery/PAIR plus benzimidazoles[10,136,331,334-338,342]:

A recent meta-analysis[10] demonstrated that antiparasitic treatment with benzimidazoles improves efficacy compared to surgery/PAIR alone[10,132,343,344]. However, there was insufficient data to determine the best time to start anthelminthic treatment, or the dose or duration of treatment. The most frequently used treatment regimens for preoperative albendazole range from 1 day to 3 months before surgery and continue for 1-3 months after surgery. The results are inconclusive in terms of whether longer treatment (>3 months) is more effective than shorter treatment[334,345].

The additional benefit of very long treatment courses (>6 months) is marginal for most patients, although in clinical practice they are routinely given to patients with multiple or inoperable CE. **Figure 9** shows a possible algorithm for the management of symptomatic or complicated CE.

Recommendations

- Pharmacological treatment is recommended for inoperable, multi-organ CE and as an adjuvant to percutaneous or surgical treatment. (**B-II**).
- Pharmacological treatment is not recommended for CE4-5. (**B-III**).
- There are insufficient data to determine the optimal duration, frequency and dose of treatment. (**B-II**).
- Benidazoles are useful drugs in CE, and albendazole is the drug of choice. (**A-I**).
- Surgery or PAIR combined with anthelminthics before and/or after the procedure gives better results. (**A-I**).
- The recommendations on timing of pre- and post-intervention treatment ranges from 1 day to 3 months before and 1 to 3 months after. (**B-II**).
- The additional benefit obtained with more than 6 months of anthelminthic treatment is marginal for most patients, although it is often given in patients with multiple or inoperable CE. (**B-II**).

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

Praziquantel is another antiparasitic used in the treatment of CE, obtained through the *foreign medicines* programme. It can be obtained with reasonable delivery times, so its availability should not present an obstacle to its use. Combined treatment with albendazole and praziquantel may be considered in the three medical situations in which pharmacological treatment is used in CE: i) prior to surgery or percutaneous intervention, ii) after surgery or percutaneous intervention, and iii) as an alternative to surgery.

One of the difficulties in recommending a suitable prescribing regimen for combination treatment is that multiple regimens have been used[346-354]. Currently, the most frequently used regimen consists of a dose of 10-50 mg/kg/day of praziquantel, for highly variable durations. Most studies that assess the efficacy of combination treatment are based on cyst viability, which means that the treatment is usually administered before an intervention. The sterilising effect of the combination may be superior to monotherapy, but a reduction in recurrence has not been demonstrated[355-357]. In addition, a longer treatment duration appears to be associated with greater reduction in cyst viability. The duration and dose of combined treatments are not well defined, but at least 4 weeks of combined treatment is recommended prior to an intervention[148,357,358]. Combination medical therapy after an intervention, however, can reduce the risk of dissemination and recurrence, especially if leakage occurs. However, there is no evidence to indicate that this is superior to the use of albendazole monotherapy[10,353-357,359]. The duration of treatment in this situation is not well defined. The use of combined therapy with albendazole and praziquantel as the mainstay of treatment may have some benefit in patients who have had treatment failure or poor disease control with albendazole alone. There is some experience with prolonged use (more than 24 months).

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, or iii) as an alternative to surgery. (**C-II**).
- Combination treatment with albendazole and praziquantel prior to an intervention reduces cyst viability. 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 cyst viability. (**C-II**).
- The duration and dose of combination treatment are not well established, but it is recommended to start it at least 4 weeks before an intervention. (**C-II**).

- Combined anthelminthic treatment after an intervention may reduce the risk of dissemination and recurrence, especially if leakage occurs. (**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 duration and dose of combination therapy are not well established. (**C-II**).

18. Are there any other safe and effective anthelminthic treatments?

The efficacy of different formulations of albendazole in CE has been evaluated, essentially in preclinical studies, using in vitro and in vivo animal models[360]. Only two clinical studies have evaluated newer albendazole formulations. One prospective observational study of 212 patients with hepatic CE treated with an emulsion of albendazole orally had a mean cure rate of 75%, obtaining the best results with a dose of 12.5 mg/kg/day for 9 months. One retrospective study of 110 patients treated with liposomal albendazole and 108 patients treated with conventional albendazole found a higher cure rate in the first group[361,362].

Other drugs have been used in a small number of patients and described in case series. Flubendazole was given to 8 patients at a dose of 50 mg/kg/day, with a good response in only 1 patient[331]. Two patients were treated with thiabendazole at a dose of 50 mg/kg/day for 3 years without a clear response[363]. Finally, one study described 7 cases of CE that had failed to respond to medical-surgical treatment and which were treated with a combination of nitazoxanide (a dose of 500 mg/12 hours) and albendazole, for 3-24 months; improvement was observed in 3 patients[364].

Recommendations

- Besides albendazole and praziquantel, there are other drugs that have been used in the treatment of CE, all with an acceptable safety profile. (**B-III**).
- Other drugs, such as nitazoxanide and thiabendazole, may have some efficacy in CE. (**B-III**).

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

The W&W strategy is based on the premise that the natural history of CE may be sufficient for the control and/or resolution of the disease (13-25% of cases of hepatic CE may resolve spontaneously without treatment)[336,365-368]. Numerous epidemiological studies support this approach[138,366,367,369-377]. **Table 10** describes the key studies on this topic.

One of the main drawbacks of this approach is that currently there is no imaging or laboratory technique that can determine cyst viability with complete reliability[129]. Cysts in stage CE1 may degenerate spontaneously, while those in stages CE4 and CE5 considered "inactive" may occasionally increase in size and progress, although generally they tend to remain stable over time. Various consensus statements and expert recommendations on the management of CE have supported the W&W approach[7,23,378-380], leading to its increasing use in asymptomatic uncomplicated patients with hepatic CE4 and CE5[381]. In addition, new observational studies support this strategy and coincide in showing that, in the immunocompetent population with CE4 and CE5 cysts, only a very small percentage of patients (0-6%)[138,370,372,377,382,383]develop reactivation to a previous stage (in most cases to CE3b). There is, therefore, a vast majority of patients in these stages who would benefit from conservative management, avoiding the side effects of medication and the complications related to surgery, and also reducing costs. There is very little evidence on a W&W approach in other situations. Although it has been suggested as a possible option in asymptomatic patients with uncomplicated hepatic cysts in stage CE3b[11], the sample size and limitations of the study in question mean that recommendations cannot be made. Data on inactive cysts in other locations or in immunosuppressed populations are even more scarce or practically non-existent, and do not allow recommendations to be made. Given the biological plausibility[94,129]and the extrapolation of the existing data, this strategy could be considered on an individual basis according to the location and the patient characteristics. The patient should be informed of the risks and benefits of this strategy and of the different alternatives, which become more relevant in the case of inactive cysts. This includes the possibility of having no complications for several years, the difficulties of establishing an accurate prognosis based on the evidence available, the possible alternative treatment options and the potential complications of these, and the risk of severe complications, including death[137,379]. Follow-up of these patients is important and should be long-term. Losing patients to follow-up is a common problem in most patient groups[11,372,382]. Most reactivations occur during the first few years of follow-up. While further studies are awaited, continuing follow-up for at least 3-5 years seems appropriate and prudent[7,11,378,379,382], although some authors recommend extending this period to 10 years[381,384].

Recommendations

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

12. SPECIAL SITUATIONS

XIV. Are there any particular considerations for immunosuppressed patients?

In immunocompetent patients, the specific cellular immune response appears to play an important role in host defence mechanisms, possibly contributing to the death of the parasite[385]. The association between immunosuppression and echinococcosis is clearly described in the case of *E. multilocularis*[386], while in CE the description is limited to isolated cases[387-402]. Therefore, it is not possible to draw definitive conclusions or make recommendations. However, in comparison with immunocompetent patients, it appears that i) serology is more often negative; ii) benzimidazoles can interact with other medications that undergo oxidative metabolism by cytochrome P450 (CYP3A4)[403,404], for example, ritonavir considerably increases levels of albendazole sulfoxide, and albendazole increases cyclosporin levels by up to 30%; and iii) the clinical progress is similar, although the prognosis depends on the underlying disease.

XV. What particular considerations are there for CE in special patient groups such as pregnant women or children?

The incidence of CE during pregnancy is very low. It is estimated that there is one case of CE per 20 000-30 000 pregnancies in endemic areas. In our setting, the diagnosis should be suspected particularly if the pregnant patient comes from an endemic country[405]. Pregnancy constitutes an additional risk in CE. The reduction in cellular immunity during pregnancy may lead to faster growth of cysts. In addition, the increase in pressure caused by the gravid uterus may predispose to or cause cyst rupture. Likewise, the pressure of a space-occupying cyst could induce premature labour. Surgical treatment of hepatic CE in the late stages of pregnancy could result in cyst rupture and induce labour. Cyst rupture during labour can cause an anaphylactic reaction and even death for the mother and fetus[406], so all precautions must be taken and treatment planned. Diagnosis of CE during pregnancy is not easy. The nonspecific abdominal discomfort of pregnancy can mask the symptoms of CE[407]. Ultrasound is the ideal investigation during pregnancy, particularly in the first trimester. CT provides more information but should be avoided during pregnancy; MR may be considered as a good alternative. Most hepatic cysts are single and are discovered incidentally or due to a complication. Treatment with albendazole has risks of teratogenicity and embryotoxicity, and it is not recommended to be given during the first trimester of pregnancy given that the risk of miscarriage is highest; this risk decreases after weeks 16-18. The second trimester is the best time for intervention as fetal morphogenesis is complete, the placenta has a good functional capacity and the size of the uterus does not interfere too

much with surgery. However, the treatment approach depends on multiple factors that must be carefully considered. The W&W approach may be a viable option in certain situations.

In Spain, CE in children is uncommon. Although most paediatric cases occur in immigrants, autochthonous cases are reported[4,405]. Suspicion should be higher in children from the southern cone of South America, certain areas of sub-Saharan Africa, rural areas, and circumstances of close contact with dogs fed with organs[408,409]. In young children and infants, cyst growth is faster than in adults. In children, CE usually presents as a single cyst, although up to one third of cases may be multiple cysts. Central nervous system involvement is particularly common in children. 50-75% of intracranial cysts are found in paediatric patients[408,409]. 10% have CE in other locations. The clinical features and diagnosis are similar to in adults. The choice of surgical and/or percutaneous (possible in those older than 3 years old) technique depends on the same factors as in adults. As in adults, the treatment of choice is albendazole, from one month pre-surgery to 3-6 months post-surgery. Combination treatment is described in previous sections[350]. Complications are common (25-30%) and range from cyst rupture to bronchopulmonary fistula, pneumothorax, abscesses and secondary bacteraemia[408,409]. With appropriate treatment, the mortality is usually very low.

13. FOLLOW-UP AND EVALUATION OF TREATMENT

XVI. Is recurrence common? What factors affect recurrence? Are there any special considerations for the management of recurrences?

Despite surgical advances, recurrence remains one of the main problems with CE[410]. The incidence varies, ranging from 0-22%. **Table 11** summarises the key studies on CE recurrence. The risk appears to be greatest in cases of[45,411-413] i) active cysts (stages CE1-CE2 of the WHO classification), ii) large cysts (>7 cm), iii) multiple cysts, iv) cysts in the lungs, v) cysts in liver segments II-III, and vi) when postoperative complications occur. In addition, the expertise of the surgeon and the surgical technique used are key factors in predicting recurrence: the rate is higher in cases where the cyst has ruptured during surgery and if the surgical technique used is partial cystectomy rather than total cysto-pericystectomy. If laparoscopic surgery is performed, peritoneal recurrence is 5-6 times higher[45,411-418].

Figure 10 shows a possible algorithm for the management of recurrence. Treatment with albendazole for 1-6 months (starting one week before surgery) appears to reduce recurrence[415-417]. Early diagnosis of recurrence is difficult, given the natural history of CE and the difficulties in interpreting serology and imaging. The management of recurrence

should be individualised to the patient and the details of the recurrence, usually the complication rates are the same as in primary disease.

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

There is no standardised post-procedure follow-up, and the subject remains debated. Issuing recommendations is difficult given the lack of cost-effectiveness studies on CE follow-up. Theoretically, after any intervention, all patients should be followed up, although the follow-up should be individualised depending on the patient and the resources available. During follow-up, initially patients should be assessed for early complications of the surgery or intervention performed, with at least one follow-up at one month after the intervention[419]. Later, the patient should be assessed for possible late complications and recurrence, and follow-up may be extended for years or even indefinitely.

The best-established follow-up is that of hepatic CE. Most authors agree on the need for regular follow-up with ultrasound after surgery or percutaneous intervention and to monitor the efficacy of anthelminthic treatment[415,417]. In general, CT has a higher sensitivity and specificity (75-89%) than ultrasound (60%) for the diagnosis of recurrence[415,417]. In other locations, follow-up is not so well established and is often done using CT or MR (to reduce the radiation dose). The duration of follow-up is not well established and ranges from 3-5 years or even lifelong[45].

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 depending on the patient, the 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 is usually with ultrasound. (**B-II**). In other locations, CT and/or MR may be used, depending on the resources available. (**B-II**).

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

Several studies have evaluated the usefulness of serological techniques in the follow-up of CE. The most commonly used techniques include enzyme-immunoassay, haemagglutination, immunoblot and more recently, immunochromatographic techniques, which generally focus on the detection of antibodies against purified whole antigens (HF, protoscolex soluble antigen) and recombinant antigens (AgB, AgB2t,

Ag2B2t, AgPEg29, Ag5 and others) as well as using different immunoglobulin types and isotypes (IgM, IgE, total IgG, and IgG4)[368,420-425].

In general, in the follow-up of patients with CE, the serological results should be interpreted with caution due to limitations of their evidence, such as i) the small number of patients, ii) the follow-up time, which is often short compared to the life of the cestode, iii) the lack of homogeneity and reproducibility among studies, iv) the initial low diagnostic sensitivity (more pronounced with the purified recombinant antigens than with whole antigens, especially in stage 4 and 5 cysts), v) the persistence of high titres in postoperative patients, especially in techniques that use whole antigens, which means recurrence cannot be detected in postoperative patients[426-429]. However, some studies have associated reduction in titres with cure[368], and an increase in titres with recurrence[415].

Of all the tests, those based on detection of antibodies against AgB2t and Ag2B2t can be of some use in patients who were initially seropositive, with the test becoming negative in patients with a good response to treatment after the second to fourth year post-treatment[425].

Consequently, there is still no gold-standard technique for the follow-up of CE; biomarkers for the clinical follow-up of CE remain to be identified. Lastly, one study on differential gene expression in tissues of patients with calcified and uncalcified cysts found differences between the two, indicating that the low expression of the genes LGALS4 and ASAH1 in patients with calcified CE cysts could be a potential biomarker indicative of disease cure[430].

Recommendations

- In the follow-up of patients with CE, serological results must be interpreted with caution. Occasionally, a decrease in titres may be associated with cure, and an increase, with recurrence. (**B-III**).
- In patients who have undergone an intervention, detection using whole antigens is not useful for follow-up. (**C-II**).
- In patients with CE1-CE3a who have undergone intervention with curative intent, the detection of antibodies against AgB2t and Ag2B2t can be useful for follow-up, as they can differentiate between active infection and cure. (**B-II**).

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

Generally, follow-up for hepatic, abdominal, soft tissue, and lung (in contact with pleura) locations is performed with ultrasound, given the innocuous nature of this technique in all locations accessible with ultrasound. It should be noted that, as the WHO-IWGE classification is based on ultrasound, there is a good correlation between cyst

morphology and cyst activity[121]. If the cyst location is not accessible with ultrasound (due to a poor acoustic window, obesity, abdominal distension, previous surgery or impossible visualisation), MR should be used to limit the dose of radiation with CT. MR also correlates better than CT with the staging of CE[140,225]. Sometimes, there is not a good correlation between cyst appearance and cyst activity, so additional blood tests should also be performed to determine cyst activity[431].

Recommendations

- Ultrasound is the technique of choice for the follow-up of hepato-abdominal cysts, soft tissue cysts, lung cysts in contact with the pleura, and all locations that are accessible with ultrasound. (**B-II**).
- If there are limitations to ultrasound, CT and MR can be used for follow-up, with preference for MR to limit the dose of radiation. (**C-III**).
- Imaging techniques should be complemented with laboratory tests when it is difficult to determine cyst activity. (**C-III**).

14. VACCINATION AND CONTROL

XVII. Is there an effective vaccine for humans?

Currently there is no commercially available vaccine against human CE. This is mainly due to the limited advances that have taken place in this field, for reasons including i) the difficulties intrinsic to the development of effective vaccination strategies in a relatively complex organism with a high genetic diversity, ii) the differential expression of genes according to the stage of development, and iii) a variable host immune response. However, a series of molecules have been identified, mainly somatic antigens and excretion/secretion antigens, which can induce an increased immunoprotective response in in vitro and in vivo experimental models (**Table 12**). Among the main candidates for vaccines against CE are EG95, a recombinant antigen obtained from the parasite oncosphere that also has a variable expression in protoscoleces and adult worms[432]. The vaccine based on this antigen can induce up to 98% protection against the parasite in vaccinated sheep, as demonstrated in field studies carried out in Argentina and Australia[433]. However, recent research has revealed that the efficacy of this vaccine can vary depending on the genetic variant of *E. granulosis* that is causing the infection[39,434]. Other molecules with a promising immunogenic capacity are Eg31 (a fibrous protein belonging to the paramyosin family that can induce cytokine production in cell cultures in contact with protoscoleces of the parasite), EgDf1 (a highly immunogenic fatty acid binding protein), and Eg14-3-3 (a protein essential to many cell

differentiation processes). All these molecules have been produced as recombinant antigens and trialled in vaccinated mice, although to date the level of immunoprotection in experimental infections has only been assessed for EG95 (in sheep orally infected with oncospheres) and Eg14-3-3 (in mice intraperitoneally infected with protoscoleces). Currently, new approaches are being adopted to develop new vaccines and improve the currently available vaccines. These include the search for more immunogenic epitopes (such as synthetic peptides tested individually or in combination), the potentiation of the immune response using more efficient adjuvants, and the search for new routes of administration (eg nanoparticles). Likewise, new technologies, such as bioinformatic tools based on in silico analysis to predict the therapeutic value of specific molecules are making significant contributions[435,436]. However, this knowledge and research needs to be transferred to the human setting, where there remains much to be done. Well-designed and well-conduced clinical trials are required to provide solid evidence on the immunogenicity of these vaccines in humans, as well as their safety, tolerability, efficacy and efficiency.

23. What measures can be taken to prevent CE?

The effective control of CE requires a detailed knowledge of the routes of transmission of the disease and the risk factors that predispose to transmission. The parasite ecology of *E. granulosus* is particularly complex as a result of its high genetic diversity and the large number of animals that can act as intermediate hosts (sheep, goats, cattle, and pigs) or definitive hosts (dogs, wolves, and other canids). The fact that *E. granulosus* can be perpetuated through domestic, peri-domestic and sylvatic cycles represents an added complication in the control of the disease. Other factors to consider are environmental and climatic aspects and those associated with human behaviour and interventions[42].

Any method to be used against CE should be aimed at interrupting the life cycle of the parasite. Thus, potential interventions may focus on either the definitive host (mainly dogs) or the intermediate host[437].

Interventions aimed at the definitive host are essential, as in Spain, contact with infected dogs is considered the main risk factor for acquiring CE. Such measures should include i) regular anthelminthic treatment, ii) eradication of stray dogs, iii) control of the size of canine populations, iv) vaccination of dogs in endemic areas, v) compulsory de-worming of dogs travelling to or from endemic areas and vi) legislation that regulates these measures.

The focus of interventions aimed at the intermediate host differ for livestock or humans. For livestock, the following interventions should be carried out: A) *General interventions*,

aimed at livestock susceptible to disease transmission, in the form of: i) actively looking for cysts in infected organs during veterinary inspection of abattoirs, ii) improvements in the hygiene measures in abattoirs, iii) condemnation and destruction of infected organs, iv) collection and destruction of dead animals, v) veterinary control of domestic slaughter, and vi) legislation that regulates these measures. B) *Specific interventions*, applicable to animals such as sheep, which have a more active and significant role in the disease transmission, in the form of: i) vaccination of sheep (antigen EG95) and ii) slaughter of older sheep. These should be carried out in conjunction with the general interventions.

Regarding interventions aimed at the intermediate accidental host (humans), education is paramount in increasing awareness of this disease and its transmission. Finally, we cannot forget that the implementation of interventions requires knowledge of the real situation of CE in Spain, which is currently underestimated. The creation of a national register of cases has been proposed, to help prioritise the control measures that should be taken[438].

Recommendations

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

Figure and table legends

Figures

Figure 1. Initial stages of development of *Echinococcus granulosis* in an intermediate host. **A**) Egg (30–40 μm); **B**) Oncosphere or hexacanth; **C**) Oncosphere anchored in intestinal brush border, beginning to penetrate the mucosa. Image reproduced with permission from M. Conchedda, Universitá degli Studi di Cagliari, Monserrato, Italy.

Figure 2. Hydatid cyst morphology. **A**) An intact unilocular cyst; **B**) A dissected unilocular cysts containing hydatid fluid and daughter vesicles or capsules attached to the germinal layer; **C**) Multilocular cyst with an incision showing daughter cysts inside it; **D**) Daughter cysts with cyst walls of varying thickness. Images reproduced with permission from M. Conchedda, Universitá degli Studi di Cagliari, Monserrato, Italy.

Figure 3. Human CE cases (presented as cases per 100 000 population) for the period 2000-2015 reported to the System of Mandatory Reportable Diseases of the Spanish

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References

1. Jenkins DJ, Romig T, Thompson RCA. Emergence/re-emergence of Echinococcus spp.--a global update. International Journal for Parasitology. 2005;35(11-12):1205-19.

2. WHO.www.who.org

3. Grosso G, Gruttadauria S, Biondi A, Marventano S, Mistretta A. Worldwide epidemiology of liver hydatidosis including the Mediterranean area. World journal of gastroenterology : WJG. 2012;18(13):1425-37.

4. Lopez-Bernus A, Belhassen Garcia M, Alonso-Sardón M, Carpio-Perez A, Velasco-Tirado V, Romero-Alegria A, et al. Surveillance of Human Echinococcosis in Castilla-Leon (Spain) between 2000-2012. Torgerson PR, editor. PLoS Neglected Tropical Diseases. Public Library of Science; October 2015;9(10):e0004154.

5. Lopez-Bernus A, Belhassen Garcia M, Carpio-Perez A, Luis PDV, Romero-Alegria A, Velasco Tirado V, et al. Is cystic echinoccocosis re-emerging in western Spain? Epidemiology and Infection [Internet]. 21 March 2015;:1–9. Accessed via: http://www.techset.co.uk/epds/techsetepds/techepds.aspx?gid=03/21/20155:51:54PM0AD&whoami=Author&Journal=HYG&jid=HYG

6. Herrador Z, Siles-Lucas M, Aparicio P, López-Vélez R, Gherasim A, Gárate T, et al. Cystic Echinococcosis Epidemiology in Spain Based on Hospitalization Records, 1997-2012. Torgerson PR, editor. PLoS Neglected Tropical Diseases. Public Library of Science; August 2016;10(8):e0004942.

7. Brunetti E, Kern P, Vuitton DA, Writing Panel for the WHO-IWGE. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Tropica. 2010;114(1):1–16.

8. Guidelines for treatment of cystic and alveolar echinococcosis in humans. WHO Informal Working Group on Echinococcosis. Vol. 74, Bulletin of the World Health Organization. World Health Organization; 1996. pp. 231-42.

9. Vuitton DA. The WHO Informal Working Group on Echinococcosis. Coordinating Board of the WHO-IWGE. Parassitologia. December 1997;39(4):349-53.

10. Velasco-Tirado V, Alonso-Sardón M, Lopez-Bernus A, Romero-Alegria A, Burguillo FJ, Muro A, et al. Medical treatment of cystic echinococcosis: systematic review and meta-analysis. BMC Infectious Diseases. BioMed Central; 5 July 2018;18(1):306.

11. Rinaldi F, De Silvestri A, Tamarozzi F, Cattaneo F, Lissandrin R, Brunetti E. Medical treatment versus «Watch and Wait» in the clinical management of CE3b echinococcal cysts of the liver. BMC Infectious Diseases. BioMed Central Ltd; 2014;14(1):492.

12. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA

statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. 2009. p. e1000100.

13. Urrútia G, Bonfill X. [PRISMA declaration: a proposal to improve the publication of systematic reviews and meta-analyses]. Medicina clínica. 9 October 2010;135(11):507-11.

14. agreecollaboration.org [Internet]. [cited 6 October 2018]. Accessed via: http://www.agreecollaboration.org

15. Eckert J, Deplazes P. Biological, Epidemiological, and Clinical Aspects of Echinococcosis, a Zoonosis of Increasing Concern. Clinical Microbiology Reviews. 2004;17(1):107-35.

16. Bortoletti G, Gabriele F, Conchedda M. Natural history of cystic echinococcosis in humans. Parassitologia. December 2004;46(4):363-6.

17. Holcman B, Heath DD, Shaw RJ. Ultrastructure of oncosphere and early stages of metacestode development of Echinococcus granulosus. International Journal for Parasitology. August 1994;24(5):623-35.

18. Holcman B, Heath DD. The early stages of Echinococcus granulosus development. Acta Tropica. 1 April 1997;64(1-2):5–17.

19. Siracusano A, Bruschi F. Cystic echinococcosis: progress and limits in epidemiology and immunodiagnosis. Parassitologia. June 2006;48(1-2):65-6.

20. Lopez-Bernus A, Belhassen García M, Carpio-Perez A, Perez Del Villar L, Romero-Alegria A, Velasco Tirado V, et al. Is cystic echinoccocosis re-emerging in western Spain? Epidemiology and Infection. 8 April 2015;:1–7.

21. Shambesh MA, Craig PS, Macpherson CN, Rogan MT, Gusbi AM, Echtuish EF. An extensive ultrasound and serologic study to investigate the prevalence of human cystic echinococcosis in northern Libya. American Journal of Tropical Medicine and Hygiene. March 1999;60(3):462-8.

22. Macpherson CNL, Kachani M, Lyagoubi M, Berrada M, Shepherd M, Fields PF, et al. Cystic echinococcosis in the Berber of the Mid Atlas mountains, Morocco: new insights into the natural history of the disease in humans. Annals of tropical medicine and parasitology. 2004;98(5):481-90.

23. Larrieu E, Frider B, del Carpio M, Salvitti JC, Mercapide C, Pereyra R, et al. [Asymptomatic carriers of hydatidosis: epidemiology, diagnosis, and treatment]. Revista panamericana de salud pública = Pan American journal of public health. 2000;8(4):250-6.

24. Apt W, Pérez C, Galdamez E, Campano S, Vega F, Vargas D, et al. [Echinococcosis/hydatidosis in the VII Region of Chile: diagnosis and educational intervention]. Revista panamericana de salud pública = Pan American journal of public health. January 2000;7(1):8–16.

25. Harandi MF, Moazezi SS, Saba M, Grimm F, Kamyabi H, Sheikhzadeh F, et al. Sonographical and serological survey of human cystic echinococcosis and analysis of risk factors associated with seroconversion in rural communities of Kerman, Iran. Zoonoses Public Health. Blackwell Publishing Ltd; December 2011;58(8):582-8.

26. Yang YR, Craig PS, Vuitton DA, Williams GM, Sun T, Liu TX, et al. Serological prevalence of echinococcosis and risk factors for infection among children in rural communities of southern Ningxia, China. Tropical medicine & international health : TM & IH. Blackwell Publishing Ltd; August 2008;13(8):1086-94.

27. Tamarozzi F, P R, F G, Mariconti M, GJ N, F R, et al. RIEC (Registro Italiano Echinococcosi Cistica) the first prospective registry of cystic echinococcosis with an European future. Eurosurveillance. 29 March 2015.

28. heracles-fp7.eu [Internet]. [cited 29 March 2015]. Accessed via: http://www.heracles-fp7.eu

29. Carmena D, Benito-Pérez de Mendiola A, Sánchez-Serrano LP. Reporting of human cystic echinococcosis in Spain: how effective is the epidemiological surveillance system? Enfermedades

infecciosas y microbiologia clinica. February 2010;28(2):135-6.

30. Echinococcus granulosus infection in Spain. April 2008;55(3):156-65.

31. Jiménez S, Pérez A, Gil H, Schantz P, Ramalle E, Juste R. Progress in control of cystic echinococcosis in La Rioja, Spain: decline in infection prevalences in human and animal hosts and economic costs and benefits. Acta Tropica. 2002;83(3):213-21.

32. Lopez-Bernus A, Belhassen Garcia M, Prieto-Vicente AJ, Alonso-Sardón M, Carpio-Perez A, Velasco-Tirado V, et al. [Epidemiological update of hydatid disease in hospitals in the public health system of Extremadura (2003-2012)]. Enfermedades infecciosas y microbiologia clinica. 25 July 2015.

33. Carabin H, Balsera-Rodríguez FJ, Rebollar-Sáenz J, Benner CT, Benito A, Fernández-Crespo JC, et al. Cystic Echinococcosis in the Province of Álava, North Spain: The Monetary Burden of a Disease No Longer under Surveillance. Torgerson PR, editor. PLoS Neglected Tropical Diseases. Public Library of Science; August 2014;8(8):e3069.

34. Carabin H, Budke CM, Cowan LD, Willingham AL, Torgerson PR. Methods for assessing the burden of parasitic zoonoses: echinococcosis and cysticercosis. Trends in Parasitology. July 2005;21(7):327-33.

35. Torgerson PR. Economic effects of echinococcosis. Acta Tropica. February 2003;85(2):113-8.

36. Benner C, Carabin H, Sánchez-Serrano LP, Budke CM, Carmena D. Analysis of the economic impact of cystic echinococcosis in Spain. Bulletin of the World Health Organization. January 2010;88(1):49–57.

37. Torgerson PR, Rüegg S, Devleesschauwer B, Abela-Ridder B, Havelaar AH, Shaw APM, et al. zDALY: An adjusted indicator to estimate the burden of zoonotic diseases. One Health. June 2018;5:40-5.

38. Agudelo Higuita NI, Brunetti E, McCloskey C. Cystic Echinococcosis. Kraft CS, editor. Journal of clinical microbiology. American Society for Microbiology Journals; March 2016;54(3):518-23.

39. Alvarez Rojas CA, Romig T, Lightowlers MW. Echinococcus granulosus sensu lato genotypes infecting humans--review of current knowledge. International Journal for Parasitology. January 2014;44(1):9–18.

40. Laurimäe T, Kinkar L, Moks E, Romig T, Omer RA, Casulli A, et al. Molecular phylogeny based on six nuclear genes suggests that Echinococcus granulosus sensu lato genotypes G6/G7 and G8/G10 can be regarded as two distinct species. Parasitology. Cambridge University Press; 21 May 2018;3:1–9.

41. Kinkar L, Laurimäe T, Acosta-Jamett G, Andresiuk V, Balkaya I, Casulli A, et al. Distinguishing Echinococcus granulosus sensu stricto genotypes G1 and G3 with confidence: A practical guide. Infection, genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases. October 2018;64:178-84.

42. Possenti A, Manzano-Román R, Sánchez-Ovejero C, Boufana B, La Torre G, Siles-Lucas M, et al. Potential Risk Factors Associated with Human Cystic Echinococcosis: Systematic Review and Meta-analysis. Flisser A, editor. PLoS Neglected Tropical Diseases. Public Library of Science; November 2016;10(11):e0005114.

43. Atkinson J-AM, Gray DJ, Clements ACA, Barnes TS, McManus DP, Yang YR. Environmental changes impacting Echinococcus transmission: research to support predictive surveillance and control. Glob Chang Biol. Wiley/Blackwell (10.1111); March 2013;19(3):677-88.

44. Armiñanzas C, Gutiérrez-Cuadra M, Fariñas MC. [Hydatidosis: epidemiological, clinical, diagnostic and therapeutic aspects]. Rev Esp Quimioter. June 2015;28(3):116-24.

45. Velasco-Tirado V, Romero-Alegria A, Belhassen Garcia M, Alonso-Sardón M, Esteban-Velasco C, Lopez-Bernus A, et al. Recurrence of cystic echinococcosis in an endemic area: a retrospective study. BMC Infectious Diseases. BioMed Central; 27 June 2017;17(1):455.

46. A systematic review of the literature on cystic echinococcosis frequency worldwide and its associated clinical manifestations. June 2013;88(6):1011-27.

47. Nunnari G, Pinzone MR, Gruttadauria S, Celesia BM, Madeddu G, Malaguarnera G, et al. Hepatic echinococcosis: clinical and therapeutic aspects. World journal of gastroenterology : WJG. 2012;18(13):1448-58.

48. Usluer O, Ceylan KC, Kaya S, Sevinc S, Gursoy S. Surgical management of pulmonary hydatid cysts: is size an important prognostic indicator? Tex Heart Inst J. Texas Heart Institute; 2010;37(4):429-34.

49. Kanat F, Turk E, Aribas OK. Comparison of pulmonary hydatid cysts in children and adults. ANZ J Surg. Wiley/Blackwell (10.1111); October 2004;74(10):885-9.

50. Sarkar S, Roy H, Saha P, Sengupta M, Sarder K, Sengupta M. Cystic echinococcosis: A neglected disease at usual and unusual locations. Trop Parasitol. January 2017;7(1):51-5.

51. Al-Jawabreh A, Ereqat S, Dumaidi K, Nasereddin A, Al-Jawabreh H, Azmi K, et al. The clinical burden of human cystic echinococcosis in Palestine, 2010-2015. Macpherson CNL, editor. PLoS Neglected Tropical Diseases. Public Library of Science; July 2017;11(7):e0005717.

52. Colombe S, Togami E, Gelaw F, Antillon M, Fuentes R, Weinberger DM. Trends and correlates of cystic echinococcosis in Chile: 2001-2012. Tamarozzi F, editor. PLoS Neglected Tropical Diseases. Public Library of Science; September 2017;11(9):e0005911.

53. Prieto M, Marquina T, Mifsut P, Moreno T. [Splenic hydatidosis: 5 cases of this location]. Enfermedades infecciosas y microbiologia clinica. October 2011;29(8):634-5.

54. Culafić DM, Kerkez MD, Mijac DD, Lekić NS, Ranković VI, Lekić DD, et al. Spleen cystic echinococcosis: clinical manifestations and treatment. Scand J Gastroenterol. 2010;45(2):186-90.

55. Gupta A, Gupta J, Devkaran B, Gupta A. Primary renal echinococcosis with gross hydatiduria. BMJ Case Rep. BMJ Publishing Group Ltd; 24 August 2017;2017:bcr–2017–220502.

56. Bellil S, Limaiem F, Bellil K, Chelly I, Mekni A, Haouet S, et al. [Descriptive epidemiology of extrapulmonary hydatid cysts: a report of 265 Tunisian cases]. Tunis Med. February 2009;87(2):123-6.

57. Geramizadeh B. Isolated Peritoneal, Mesenteric, and Omental Hydatid Cyst: A Clinicopathologic Narrative Review. Iran J Med Sci. Shiraz University of Medical Sciences; November 2017;42(6):517-23.

58. Díaz-Menéndez M, Pérez-Molina J-A, Norman FF, Pérez-Ayala A, Monge-Maillo B, Fuertes PZ, et al. Management and outcome of cardiac and endovascular cystic echinococcosis. Garcia HH, editor. PLoS Neglected Tropical Diseases. Public Library of Science; January 2012;6(1):e1437.

59. Chen S, Li N, Yang F, Wu J, Hu Y, Yu S, et al. Medical treatment of an unusual cerebral hydatid disease. BMC Infectious Diseases. BioMed Central; 5 January 2018;18(1):12.

60. Duransoy YK, Mete M, Selçuki M. [Cerebral cystic echinococcosis in the light of our experience]. Turkiye Parazitol Derg. 2013;37(4):277-81.

61. Khan MM, Shah M, Khan AA, ur Rehman R, Ayub S, Ahmad A, et al. CLINICAL FEATURES AND OUTCOME ANALYSIS OF INTRACRANIAL HYDATID CYSTS. J Ayub Med Coll Abbottabad. January 2016;28(1):39–43.

62. Tapia E O, Vidal T A, Bellolio J E, Roa S JC. [Bone hydatidosis: report of five patients and review of the literature]. Revista médica de Chile. November 2010;138(11):1414-21.

63. Gezercan Y, Ökten AI, Çavuş G, Açık V, Bilgin E. Spinal Hydatid Cyst Disease. World Neurosurg. December 2017;108:407-17.

64. Salamone G, Licari L, Randisi B, Falco N, Tutino R, Vaglica A, et al. Uncommon localizations of hydatid cyst. Review of the literature. G Chir. CIC Edizioni Internazionali; July 2016;37(4):180-5.

65. Tekin R, Avci A, Tekin RC, Gem M, Cevik R. Hydatid cysts in muscles: clinical manifestations, diagnosis, and management of this atypical presentation. Revista da Sociedade Brasileira de Medicina Tropical. SBMT; September 2015;48(5):594-8.

66. Ahmed Z, Chhabra S, Massey A, Vij V, Yadav R, Bugalia R, et al. Primary hydatid cyst of pancreas: Case report and review of literature. Int J Surg Case Rep. 2016;27:74-7.

67. Mardani P, Karami MY, Jamshidi K, Zadebagheri N, Niakan H. A Primary Pleural Hydatid Cyst in an Unusual Location. Tanaffos. National Research Institute of Tuberculosis and Lung Disease; 2017;16(2):166-9.

68. Alonso García ME, Suárez Mansilla P, Mora Cepeda P, Bayón Álvarez E, Alvarez Colomo C, González Martín JI. Ovarian hydatid disease. Arch Gynecol Obstet. Springer Berlin Heidelberg; May 2014;289(5):1047-51.

69. Eken H, Isik A, Balci G, Firat D, Cimen O, Soyturk M. A Rare Case of Isolated Cystic Hydatid of Thyroid Gland. Medicine. March 2016;95(10):e2929.

70. Arora VK, Chopra N, Singh P, Venugopal VK, Narang S. Hydatid cyst of parotid: Report of unusual cytological findings extending the cytomorphological spectrum. Diagn Cytopathol. Wiley-Blackwell; September 2016;44(9):770-3.

71. Fallahi Motlagh M, Janghi Aghdam H, Fallahi Motlagh B. Primary Orbital Hydatid Cyst: A Case Report. Acta Med Iran. August 2017;55(8):530-2.

72. Guo C, Zhu R, Qiu J, Zhu L, Yang L. Subretinal echinococcosis: a case report. BMC Ophthalmol. BioMed Central; 5 October 2017;17(1):185.

73. Akçay MN, Akçay G, Balik AA, Böyük A. Hydatid cysts of the adrenal gland: review of nine patients. World Journal of Surgery. Springer-Verlag; January 2004;28(1):97-9.

74. Mahmoudi A, Maâtouk M, Noomen F, Nasr M, Zouari K, Hamdi A. [Hydatid cyst of the adrenal: about a case]. Pan Afr Med J. 2015;21:272.

75. Dziri C, Haouet K, Fingerhut A, Zaouche A. Management of cystic echinococcosis complications and dissemination: where is the evidence? World Journal of Surgery. June 2009;33(6):1266-73.

76. Akbulut S, Yilmaz M, Kahraman A, Yilmaz S. Budd-Chiari syndrome due to giant hydatid cyst: a case report and brief literature review. J Infect Dev Ctries. 15 June 2013;7(6):489-93.

77. Karabulut K, Ozden I, Poyanli A, Bilge O, Tekant Y, Acarli K, et al. Hepatic atrophy-hypertrophy complex due to Echinococcus granulosus. J Gastrointest Surg. March 2006;10(3):407-12.

78. San Juan López C, Lázaro Sáez M, Barrientos Delgado A, Casado Martín M, Hallouch Toutouh S, Vega Sáenz JL. Portal hypertension as a complication of hepatic hydatidosis. Gastroenterología y hepatología. 26 February 2018.

79. Moro P, Schantz PM. Echinococcosis: a review. International Journal of Infectious Diseases. 2009;13(2):125-33.

80. Toumi O, Salem R, Jabra SB, Abdesslem G, Noomen F, Hamdi AA. Pulmonary Embolism as a Rare Complication of Liver Hydatid Cyst: Report of Two Cases. Iran J Med Sci. Shiraz University of Medical Sciences; March 2018;43(2):214-7.

81. Martín-Herrero F, Cruz I, Muñoz L. Hepatic hydatid cyst rupturing into pericardial cavity. Heart. BMJ Publishing Group Ltd; October 2006;92(10):1536-6.

82. Kumar R, Reddy SN, Thulkar S. Intrabiliary rupture of hydatid cyst: diagnosis with MRI and hepatobiliary isotope study. Br J Radiol. British Institute of Radiology; March 2002;75(891):271-4.

83. Atli M, Kama NA, Yuksek YN, Doganay M, Gozalan U, Kologlu M, et al. Intrabiliary rupture of a hepatic hydatid cyst: associated clinical factors and proper management. Arch Surg. November 2001;136(11):1249-55.

84. Alexiou K, Mitsos S, Fotopoulos A, Karanikas I, Tavernaraki K, Konstantinidis F, et al. Complications of Hydatid Cysts of the Liver: Spiral Computed Tomography Findings. Gastroenterology Res. August 2012;5(4):139-43.

85. Monge-Maillo B, Olmedo Samperio M, Pérez-Molina J-A, Norman F, Mejía CR, Tojeiro SC, et al. Osseous cystic echinococcosis: A case series study at a referral unit in Spain. Tamarozzi F, editor. PLoS Neglected Tropical Diseases. Public Library of Science; February 2019;13(2):e0007006.

86. Ergüney S, Tortum O, Taspinar AH, Ertem M, Gazioğlu E. [Complicated hydatid cysts of the liver]. Annales de chirurgie. 1991;45(7):584-9.

87. Neumayr A, Troia G, de Bernardis C, Tamarozzi F, Goblirsch S, Piccoli L, et al. Justified concern or exaggerated fear: the risk of anaphylaxis in percutaneous treatment of cystic echinococcosis-a systematic literature review. Brooker S, editor. PLoS Neglected Tropical Diseases. Public Library of Science; June 2011;5(6):e1154.

88. Pavletic CF, Larrieu E, Guarnera EA, Casas N, Irabedra P, Ferreira C, et al. Cystic echinococcosis in South America: a call for action. Revista panamericana de salud pública = Pan American journal of public health. 21 August 2017;41:e42.

89. Belhassen Garcia M, Romero-Alegria A, Velasco-Tirado V, Alonso-Sardón M, Lopez-Bernus A, Alvela-Suárez L, et al. Study of Hydatidosis-Attributed Mortality in Endemic Area. Sim RB, editor. PloS one. 14 March 2014;9(3):e91342.

90. Amado-Diago CA, Gutiérrez-Cuadra M, Armiñanzas C, Arnaíz de Las Revillas F, Gómez-Fleitas M, Fariñas MC. Echinococcosis: A 15-year epidemiological, clinical and outcome overview. Revista clínica española. October 2015;215(7):380-4.

91. Martínez P. [Characterization of human hydatidosis mortality: Chile, 2000-2010]. Revista chilena de infectología : órgano oficial de la Sociedad Chilena de Infectología. Sociedad Chilena de Infectología; February 2014;31(1):7–15.

92. Bristow BN, Lee S, Shafir S, Sorvillo F. Human echinococcosis mortality in the United States, 1990-2007. PLoS Neglected Tropical Diseases. 2012;6(2):e1524.

93. WHO Informal Working Group. International classification of ultrasound images in cystic echinococcosis for application in clinical and field epidemiological settings. Acta Tropica. February 2003;85(2):253-61.

94. Hosch W, Junghanss T, Stojkovic M, Brunetti E, Heye T, Kauffmann GW, et al. Metabolic viability assessment of cystic echinococcosis using high-field 1H MRS of cyst contents. NMR Biomed. Wiley-Blackwell; August 2008;21(7):734-54.

95. Kern P, Frosch P, Helbig M, Wechsler JG, Usadel S, Beckh K, et al. Diagnosis of Echinococcus multilocularis infection by reverse-transcription polymerase chain reaction. Gastroenterology. August1995;109(2):596–600.

96. Lorenzo C, Last JA, González-Sapienza GG. The immunogenicity of Echinococcus granulosus antigen 5 is determined by its post-translational modifications. Parasitology. Cambridge University Press; November 2005;131(Pt 5):669-77.

97. Oriol R, Williams JF, Pérez Esandi MV, Oriol C. Purification of lipoprotein antigens of Echinococcus granulosus from sheep hydatid fluid. American Journal of Tropical Medicine and Hygiene. July 1971;20(4):569-74.

98. Lightowlers MW, Liu DY, Haralambous A, Rickard MD. Subunit composition and specificity of the major cyst fluid antigens of Echinococcus granulosus. Mol Biochem Parasitol. December 1989;37(2):171-82.

99. Monteiro KM, Cardoso MB, Follmer C, da Silveira NP, Vargas DM, Kitajima EW, et al. Echinococcus granulosus antigen B structure: subunit composition and oligomeric states. Ito A, editor. PLoS Neglected Tropical Diseases. 2012;6(3):e1551.

100. Jiang L, Zhang Y-G, Liu M-X, Feng Z. Analysis on the reactivity of five subunits of antigen B family in serodiagnosis of echinococcosis. Experimental Parasitology. May 2012;131(1):85–91.

101. Virginio VG, Hernández A, Rott MB, Monteiro KM, Zandonai AF, Nieto A, et al. A set of recombinant antigens from Echinococcus granulosus with potential for use in the immunodiagnosis of human cystic hydatid disease. Clinical and experimental immunology. Wiley-Blackwell; May 2003;132(2):309-15.

102. Pagnozzi D, Tamarozzi F, Roggio AM, Tedde V, Addis MF, Pisanu S, et al. Structural and Immunodiagnostic Characterization of Synthetic Antigen B Subunits From Echinococcus granulosus and Their Evaluation as Target Antigens for Cyst Viability Assessment. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 3rd ed. 17 April 2018;66(9):1342-51.

103. Hernandez-Gonzalez A, Santivañez S, Garcia HH, Rodríguez S, Muñoz S, Ramos G, et al. Improved serodiagnosis of cystic echinococcosis using the new recombinant 2B2t antigen. Zhang W, editor. PLoS Neglected Tropical Diseases. Public Library of Science; 2012;6(7):e1714.

104. Feng X, Wen H, Zhang Z, Chen X, Ma X, Zhang J, et al. Dot immunogold filtration assay (DIGFA) with multiple native antigens for rapid serodiagnosis of human cystic and alveolar echinococcosis. Acta Tropica. February 2010;113(2):114-20.

105. Wang J-Y, Gao C-H, Steverding D, Wang X, Shi F, Yang Y-T. Differential diagnosis of cystic and alveolar echinococcosis using an immunochromatographic test based on the detection of specific antibodies. Parasitology Research. Springer Berlin Heidelberg; October 2013;112(10):3627-33.

106. Tamarozzi F, Covini I, Mariconti M, Narra R, Tinelli C, De Silvestri A, et al. Comparison of the Diagnostic Accuracy of Three Rapid Tests for the Serodiagnosis of Hepatic Cystic Echinococcosis in Humans. Hirayama K, editor. PLoS Neglected Tropical Diseases. February 2016;10(2):e0004444.

107. Vola A, Tamarozzi F, Noordin R, Yunus MH, Khanbabaie S, De Silvestri A, et al. Preliminary assessment of the diagnostic performances of a new rapid diagnostic test for the serodiagnosis of human cystic echinococcosis. Diagn Microbiol Infect Dis. September 2018;92(1):31-3.

108. Jiao W, Fu C, Liu W-L, Wang Y, Gao C-H, Chai J-J. [Diagnostic potential of five natural antigens from Echinococcus granulosus in the patients of cystic echinococcosis with different clinical status]. Zhongguo ji sheng chong xue yu ji sheng chong bing za zhi = Chinese journal of parasitology & parasitic diseases. April 2014;32(2):116-22.

109. Tamarozzi F, Mariconti M, Covini I, Brunetti E. [Rapid diagnostic tests for the serodiagnosis of human cystic echinococcosis]. Bulletin de la Société de pathologie exotique (1990). Lavoisier; February 2017;110(1):20–30.

110. Siles-Lucas MM, Gottstein BB. Molecular tools for the diagnosis of cystic and alveolar echinococcosis. Tropical medicine & international health : TM & IH. June 2001;6(6):463-75.

111. Ito A, Craig PS. Immunodiagnostic and molecular approaches for the detection of taeniid cestode infections. Trends in Parasitology. September 2003;19(9):377-81.

112. Santivañez SJ, Arias P, Portocarrero M, Rodríguez S, Gonzalez AE, Gilman RH, et al. Serological diagnosis of lung cystic hydatid disease using the synthetic p176 peptide. Clin Vaccine Immunol. American Society for Microbiology; June 2012;19(6):944-7.

113. Mariconti M, Bazzocchi C, Tamarozzi F, Meroni V, Genco F, Maserati R, et al. Immunoblotting with human native antigen shows stage-related sensitivity in the serodiagnosis of hepatic cystic echinococcosis. The American journal of tropical medicine and hygiene. The American Society of Tropical Medicine and Hygiene; January 2014;90(1):75-9.

114. Ahn C-S, Cai H, Kim J-G, Han X, Ma X, Bae Y-A, et al. An Echinococcus multilocularis Antigen B3 Proteoform That Shows Specific Antibody Responses to Active-Stage Alveolar Echinococcosis. Gilligan PH, editor. Journal of clinical microbiology. American Society for Microbiology Journals; October 2015;53(10):3310-7.

115. Cucher MA, Macchiaroli N, Baldi G, Camicia F, Prada L, Maldonado L, et al. Cystic echinococcosis in South America: systematic review of species and genotypes of Echinococcus granulosus sensu lato in humans and natural domestic hosts. Tropical medicine & international health : TM & IH. Wiley/Blackwell (10.1111); February 2016;21(2):166-75.

116. Welearegay TG, Diouani MF, Österlund L, Borys S, Khaled S, Smadhi H, et al. Diagnosis of Human Echinococcosis via Exhaled Breath Analysis: A Promise for Rapid Diagnosis of Infectious Diseases Caused by Helminths. Journal of Infectious Diseases. 16 July 2018;28:239.

117. Macpherson CNL, Milner R. Performance characteristics and quality control of community based ultrasound surveys for cystic and alveolar echinococcosis. Acta Tropica. February 2003;85(2):203-9.

118. Pedrosa I, Saíz A, Arrazola J, Ferreirós J, Pedrosa CS. Hydatid disease: radiologic and pathologic features and complications. Radiographics. Radiological Society of North America; May 2000;20(3):795–817.

119. Lewall DB. Hydatid disease: biology, pathology, imaging and classification. Clinical radiology. December 1998;53(12):863-74.

120. Fortia El M, Gatit El A, Bendaoud M. Ultrasound wall-sign in pulmonary echinococcosis (new application). Ultraschall Med. © Georg Thieme Verlag KG Stuttgart · New York; December 2006;27(6):553-7.

121. Gharbi HA, Hassine W, Brauner MW, Dupuch K. Ultrasound examination of the hydatic liver. Radiology. May 1981;139(2):459-63.

122. Azizi A, Blagosklonov O, Lounis A, Berthet L, Vuitton DA, Bresson-Hadni S, et al. Alveolar echinococcosis: correlation between hepatic MRI findings and FDG-PET/CT metabolic activity. Abdominal Imaging. Springer US; January 2015;40(1):56–63.

123. Polat P, Kantarci M, Alper F, Suma S, Koruyucu MB, Okur A. Hydatid disease from head to toe. Radiographics. Radiological Society of North America; March 2003;23(2):475–94–quiz536–7.

124. Coşkun A, Oztürk M, Karahan OI, Erdogan N, Işin S, Güleç M. Alveolar echinococcosis of the liver: correlative color Doppler US, CT, and MRI study. Acta Radiol. August 2004;45(5):492-8.

125. McManus DP, Gray DJ, Zhang W, Yang Y. Diagnosis, treatment, and management of echinococcosis. BMJ. 11 July 2012;344:e3866.

126. Mihmanli M, Idiz UO, Kaya C, Demir U, Bostanci O, Omeroglu S, et al. Current status of diagnosis and treatment of hepatic echinococcosis. World J Hepatol. Baishideng Publishing Group Inc; 8 October 2016;8(28):1169-81.

127. Kumar NS, Barve K, Joshi J, Basu S. Incidental Diagnosis of an Asymptomatic Hydatid Cyst Through Low-Grade 18F-FDG Uptake in the Peripheral Rim. J Nucl Med Technol. Society of Nuclear Medicine; December 2015;43(4):292-4.

128. Kadam SG, Basu S, Joshi JM. Doughnut sign on FDG-PET scan in a ruptured lung hydatid cyst. Indian J Chest Dis Allied Sci.July 2012;54(3):185-7.

129. Gottstein B, Wang J, Blagosklonov O, Grenouillet F, Millon L, Vuitton DA, et al. Echinococcus metacestode: in search of viability markers. Parasite (Paris, France). 2014;21(Suppl 11):63.

130. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. The New England journal of medicine. 29 November 2007;357(22):2277-84.

131. Wehrl HF, Wiehr S, Divine MR, Gatidis S, Gullberg GT, Maier FC, et al. Preclinical and Translational PET/MR Imaging. J Nucl Med. Society of Nuclear Medicine; 1 June 2014;55(Supplement 2):11S–18S.

132. Stojkovic M, Zwahlen M, Teggi A, Vutova K, Cretu CM, Virdone R, et al. Treatment response of cystic echinococcosis to benzimidazoles: a systematic review. Carabin H, editor. PLoS Neglected Tropical Diseases. Public Library of Science; 2009;3(9):e524.

133. International classification of ultrasound images in cystic echinococcosis for application in clinical and field epidemiological settings. February 2003;85(2):253-61. Accessed via: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=12606104&retmode=ref&cmd=prlinks

134. Todorov T, Vutova K, Donev S, Ivanov A, Katzarov K, Takov D. The types and timing of the degenerative changes seen in the cysts during and after benzimidazole treatment of cystic echinococcosis. Annals of tropical medicine and parasitology. October 2005;99(7):649-59.

135. Vuitton DA. Benzimidazoles for the treatment of cystic and alveolar echinococcosis: what is the consensus? Expert Review of Anti-infective Therapy. Taylor & Francis; March 2009;7(2):145-9.

136. Bildik N, Cevik A, Altintaş M, Ekinci H, Canberk M, Gülmen M. Efficacy of preoperative albendazole use according to months in hydatid cyst of the liver. Journal of clinical gastroenterology. March 2007;41(3):312-6.

137. Velasco-Tirado V, Romero-Alegria A, Pardo-Lledias J, Alonso-Sardón M, Lopez-Bernus A, Sampedro JQ, et al. Management of cystic echinococcosis in the last two decades: what have we learned? Transactions of the Royal Society of Tropical Medicine and Hygiene. 1 May 2018;112(5):207-15.

138. Lissandrin R, Tamarozzi F, Mariconti M, Manciulli T, Brunetti E, Vola A. Watch and Wait Approach for Inactive Echinococcal Cyst of the Liver: An Update. The American journal of tropical medicine and hygiene. The American Society of Tropical Medicine and Hygiene; August 2018;99(2):375-9.

139. Keong B, Wilkie B, Sutherland T, Fox A. Hepatic cystic echinococcosis in Australia: an update on diagnosis and management. ANZ J Surg. January 2018;88(1-2):26–31.

140. Pakala T, Molina M, Wu GY. Hepatic Echinococcal Cysts: A Review. J Clin Transl Hepatol. Xia & He Publishing Inc; 28 March 2016;4(1):39–46.

141. Symeonidis N, Pavlidis T, Baltatzis M, Ballas K, Psarras K, Marakis G, et al. Complicated liver echinococcosis: 30 years of experience from an endemic area. Scand J Surg. 10 ed. SAGE PublicationsSage UK: London, England; 2013;102(3):171-7.

142. Sokouti M, Sadeghi R, Pashazadeh S, Abadi SEH, Sokouti M, Rezaei-Hachesu P, et al. A systematic review and meta-analysis on the treatment of liver hydatid cyst: Comparing laparoscopic and open surgeries. Arab J Gastroenterol. September 2017;18(3):127-35.

143. Sözüer E, Akyuz M, Akbulut S. Open surgery for hepatic hydatid disease. International surgery. The International College of Surgeons, World Federation of General Surgeons and Surgical Specialists, Inc; November 2014;99(6):764-9.

144. Tuxun T, Zhang J-H, Zhao J-M, Tai Q-W, Abudurexti M, Ma H-Z, et al. World review of laparoscopic treatment of liver cystic echinococcosis--914 patients. Int J Infect Dis. Elsevier; July 2014;24:43–50.

145. Gomez I Gavara C, López-Andújar R, Belda Ibáñez T, Ramia Ángel JM, Moya Herraiz Á, Orbis Castellanos F, et al. Review of the treatment of liver hydatid cysts. World J Gastroenterol. 7 January 2015;21(1):124-31.

146. Aydin U, Yazici P, Onen Z, Ozsoy M, Zeytunlu M, Kiliç M, et al. The optimal treatment of hydatid cyst of the liver: radical surgery with a significant reduced risk of recurrence. Turk J Gastroenterol. March 2008;19(1):33-9.

147. Tagliacozzo S, Miccini M, Amore Bonapasta S, Gregori M, Tocchi A. Surgical treatment of hydatid disease of the liver: 25 years of experience. American journal of surgery. 2011;201(6):797–804.

148. Gollackner B, Längle F, Auer H, Maier A, Mittlböck M, Agstner I, et al. Radical surgical therapy of abdominal cystic hydatid disease: factors of recurrence. World Journal of Surgery. June 2000;24(6):717-21.

149. Buttenschoen K, Carli Buttenschoen D. Echinococcus granulosus infection: the challenge of surgical treatment. Langenbecks Arch Surg. September 2003;388(4):218-30.

150. Pang Q, Jin H, Man Z, Wang Y, Yang S, Li Z, et al. Radical versus conservative surgical treatment of liver hydatid cysts: a meta-analysis. Front Med. Higher Education Press; June 2018;12(3):350-9.

151. Ramia JM, Serrablo A, Serradilla M, Lopez-Marcano A, la Plaza de R, Palomares A. Major hepatectomies in liver cystic echinococcosis: A bi-centric experience. Retrospective cohort study. Int J Surg. June 2018;54(Pt A):182-6.

152. He Y-B, Yao G, Tuxun T, Bai L, Li T, Zhao J-M, et al. Efficacy of radical and conservative surgery for hepatic cystic echinococcosis: a meta-analysis. Int J Clin Exp Med. e-Century Publishing Corporation; 2015;8(5):7039-48.

153. Kilic M, Yoldas O, Koc M, Keskek M, Karakose N, Ertan T, et al. Can biliary-cyst communication be predicted before surgery for hepatic hydatid disease: does size matter? American journal of surgery. November 2008;196(5):732-5.

154. Galati G, Sterpetti AV, Caputo M, Adduci M, Lucandri G, Brozzetti S, et al. Endoscopic retrograde cholangiography for intrabiliary rupture of hydatid cyst. American journal of surgery. February 2006;191(2):206-10.

155. Akcan A, Akyildiz H, Artis T, Ozturk A, Deneme MA, Ok E, et al. Peritoneal perforation of liver hydatid cysts: clinical presentation, predisposing factors, and surgical outcome. World Journal of Surgery. 10 ed. June 2007;31(6):1284-91.

156. Sözüer EM, Ok E, Arslan M. The perforation problem in hydatid disease. American Journal of Tropical Medicine and Hygiene. May 2002;66(5):575-7.

157. Katkhouda N, Fabiani P, Benizri E, Mouiel J. Laser resection of a liver hydatid cyst under videolaparoscopy. Br J Surg. June 1992;79(6):560-1.

158. Doğan R, Yüksel M, Cetin G, Süzer K, Alp M, Kaya S, et al. Surgical treatment of hydatid cysts of the lung: report on 1055 patients. Thorax. BMJ Publishing Group; March 1989;44(3):192-9.

159. Burgos R, Varela A, Castedo E, Roda J, Montero CG, Serrano S, et al. Pulmonary hydatidosis: surgical treatment and follow-up of 240 cases. Eur J Cardiothorac Surg. December 1999;16(6):628–34–discussion634–5.

160. Halezeroglu S, Celik M, Uysal A, Senol C, Keles M, Arman B. Giant hydatid cysts of the lung. J Thorac Cardiovasc Surg. April 1997;113(4):712-7.

161. Dincer SI, Demir A, Sayar A, Gunluoglu MZ, Kara HV, Gurses A. Surgical treatment of pulmonary hydatid disease: a comparison of children and adults. J Pediatr Surg. July 2006;41(7):1230-6.

162. Bilgin M, Oguzkaya F, Akçali Y. Is capitonnage unnecessary in the surgery of intact pulmonary hydatic cyst? ANZ J Surg. January 2004;74(1-2):40-2.

163. Dakak M, Caylak H, Kavakli K, Gozubuyuk A, Yucel O, Gurkok S, et al. Parenchyma-saving surgical treatment of giant pulmonary hydatid cysts. Thorac Cardiovasc Surg. © Georg Thieme Verlag KG Stuttgart · New York; April 2009;57(3):165-8.

164. Alpay L, Lacin T, Ocakcioglu I, Evman S, Dogruyol T, Vayvada M, et al. Is Video-Assisted Thoracoscopic Surgery Adequate in Treatment of Pulmonary Hydatidosis? Ann Thorac Surg. July 2015;100(1):258-62.

165. Ma J, Wang X, Mamatimin X, Ahan N, Chen K, Peng C, et al. Therapeutic evaluation of video-assisted thoracoscopic surgery versus open thoracotomy for pediatric pulmonary hydatid disease. J Cardiothorac Surg. BioMed Central; 5 August 2016;11(1):129.

166. Mehta KD, Gundappa R, Contractor R, Sangani V, Pathak A, Chawda P. Comparative evaluation of thoracoscopy versus thoracotomy in the management of lung hydatid disease. World Journal of Surgery. Springer-Verlag; August 2010;34(8):1828-31.

167. Findikcioglu A, Karadayi S, Kilic D, Hatiopoglu A. Video-assisted thoracoscopic surgery to treat hydatid disease of the thorax in adults: is it feasible? J Laparoendosc Adv Surg Tech A. Mary Ann Liebert, Inc. 140 Huguenot Street, 3rd Floor New Rochelle, NY 10801 USA; November 2012;22(9):882-5.

168. Rai SP, Panda BN, Ganguly D, Bharadwaj R. Pulmonary Hydatid : Diagnosis and Response to

Hypertonic Saline Irrigation and Albendazole. Med J Armed Forces India. January 2005;61(1):9–12.

169. Abbas N, Zaher Addeen S, Abbas F, Saadi Al T, Hanafi I, Alkhatib M, et al. Video-assisted Thoracoscopic Surgery (VATS) with mini-thoracotomy for the management of pulmonary hydatid cysts. J Cardiothorac Surg. BioMed Central; 2 May 2018;13(1):35.

170. Bakhytzhan S, Mukhtar S, Ruslan K, Denis V, Gulziya I. Single-center experience in the surgical treatment of combined lung Echinococcosis. Saudi Med J. January 2018;39(1):31-7.

171. Ahmad M, Khan SA, Shah SZ, Nazar HS, Bilal A, Khan MA, et al. Effect of size on the surgical management of pulmonary hydatid cyst. J Ayub Med Coll Abbottabad. January 2014;26(1):42-5.

172. Türk F, Yuncu G, Karabulut N, Türk T, Ozban M, Zümrütbas EA, et al. A single-center large-volume experience in the surgical management of hydatid disease of the lung with and without extrapulmonary involvement. World Journal of Surgery. Springer US; October 2013;37(10):2306-12.

173. Kabiri EH, Traibi A, Hammoumi El M, Oueriachi El F, Arsalane A. Parenchyma sparing procedures is possible for most pulmonary hydatid disease without recurrence and low complications. Med Arch. 2012;66(5):332-5.

174. Hasdıraz L, Onal O, Oguzkaya F. Bilateral staged thoracotomy for multiple lung hydatidosis. J Cardiothorac Surg. BioMed Central; 3 May 2013;8(1):121.

175. Bagheri R, Haghi SZ, Amini M, Fattahi AS, Noorshafiee S. Pulmonary hydatid cyst: analysis of 1024 cases. Gen Thorac Cardiovasc Surg. 6 ed. Springer Japan; February 2011;59(2):105-9.

176. Aldahmashi M, Alassal M, Kasb I, Elrakhawy H. Conservative Surgical Management for Pulmonary Hydatid Cyst: Analysis and Outcome of 148 Cases. Can Respir J. Hindawi; 2016;2016(3):8473070-6.

177. Yaldiz S, Gursoy S, Ucvet A, Yaldiz D, Kaya S. Capitonnage results in low postoperative morbidity in the surgical treatment of pulmonary echinococcosis. Ann Thorac Surg. March 2012;93(3):962-6.

178. Kavukcu S, Kilic D, Tokat AO, Kutlay H, Cangir AK, Enon S, et al. Parenchyma-preserving surgery in the management of pulmonary hydatid cysts. J Invest Surg. January 2006;19(1):61-8.

179. Wu M-B, Zhang L-W, Zhu H, Qian Z-X. Surgical treatment for thoracic hydatidosis: review of 1230 cases. Chin Med J. 5 October 2005;118(19):1665-7.

180. Lianos GD, Lazaros A, Vlachos K, Georgiou GK, Harissis HV, Mangano A, et al. Unusual locations of hydatid disease: a 33 year's experience analysis on 233 patients. Updates Surg. Springer Milan; September 2015;67(3):279-82.

181. Aghajanzadeh M, Safarpoor F, Amani H, Alavi A. One-stage procedure for lung and liver hydatid cysts. Asian Cardiovasc Thorac Ann. 6 ed. October 2008;16(5):392-5.

182. Sharma BC, Agarwal N, Garg S, Kumar R, Sarin SK. Endoscopic management of liver abscesses and cysts that communicate with intrahepatic bile ducts. Endoscopy. © Georg Thieme Verlag KG Stuttgart · New York; March 2006;38(3):249-53.

183. D'Altorio RA, McAllister JD, Sestric GB, Cichon PJ. Hepatopulmonary fistula: treatment with biliary metallic endoprosthesis. The American journal of gastroenterology. June 1992;87(6):784-6.

184. Chua HK, Allen MS, Deschamps C, Miller DL, Pairolero PC. Bronchobiliary fistula: principles of management. Ann Thorac Surg. October 2000;70(4):1392-4.

185. Seth HS, Mishra P, Khandekar JV, Raut C, Mohapatra CKR, Ammannaya GKK. A Concomitant Intramyocardial and Pulmonary Hydatid Cyst: A Rare Case Report. Braz J Cardiovasc Surg. March 2017;32(2):138-40.

186. Grozavu C, Ilias M, Pantile D. Multivisceral echinococcosis: concept, diagnosis, management.

Chirurgia (Bucur). November 2014;109(6):758-68.

187. Prati G, Gatti G, Belgrano M, Pinamonti B, Rauber E, Gripshi F, et al. Disseminated echinococcosis: follow your heart. J Cardiovasc Med (Hagerstown). December 2016;17 Suppl 2:e146-8.

188. Batçık OE, Öğrenci A, Koban O, Ekşi MŞ, Bilge T. Cerebral Alveolar Echinococcosis Concomitant with Liver and Lung Lesions in a Young Adult Patient: Case Report and Literature Review. Turkiye Parazitol Derg. September 2016;40(3):169-71.

189. Rosales-Castañeda E, Martínez-Ordaz JL, Estrada-Castellanos A, Goméz-Jiménez LM. [Disseminated peritoneal hydatidosis manifested as intestinal ischaemia]. Cir Cir. June 2017;85(3):269-72.

190. Tekin R, Onat S, Tekin RC. Hydatid cysts in a patient with multiple organ involvement. Revista da Sociedade Brasileira de Medicina Tropical. SBMT; July 2016;49(4):534-4.

191. Zheng X, Zou Y, Yin C. Rare presentation of multi-organ abdominal echinococcosis: report of a case and review of literature. Int J Clin Exp Pathol. e-Century Publishing Corporation; 2015;8(9):11814-8.

192. Charfeddine S, Mallek S, Gueldiche M, Triki F, Jmâa HB, Frikha I, et al. A huge cardiac hydatid cyst: An unusual cause of chest pain revealing multivisceral hydatidosis in a young woman. J Saudi Heart Assoc.October 2015;27(4):286-91.

193. Hammami A, Hellara O, Mnari W, Loussaief C, Bedioui F, Safer L, et al. Unusual presentation of severely disseminated and rapidly progressive hydatic cyst: Malignant hydatidosis. World J Hepatol. 27 March 2015;7(3):633-7.

194. Anandpara KM, Aswani Y, Hira P. Disseminated hydatidosis. BMJ Case Rep. BMJ Publishing Group Ltd; 27 February 2015;2015(feb27 1):bcr2014208839-9.

195. Popa GL, Tanase I, Popa CA, Mastalier B, Popa MI, Cretu CM. Medical and surgical management of a rare and complicated case of multivisceral hydatidosis; 18 years of evolution. New Microbiol. July 2014;37(3):387-91.

196. Kaya Z, Gursel T. A pediatric case of disseminated cystic echinococcosis successfully treated with mebendazole. Jpn J Infect Dis. February 2004;57(1):7–9.

197. Almalik A, Alsharidi A, Al-Sheef M, Enani M. Disseminated abdominal hydatidosis: a rare presentation of common infectious disease. Case Rep Infect Dis. Hindawi; 2014;2014(2):164787–3.

198. Paredes S, Torres J, Muena P, Schnettler D. [Hepatopulmonary hydatidosis: pediatric case report and literature review]. Medwave. 15 December 2014;14(11):e6053-3.

199. Goswami RP, Pal D, Das S, Ray Y, Rahman M. Multiple intramuscular and hepatic echinococcosis. The Journal of the Association of Physicians of India. December 2013;61(12):907-8.

200. Comrnejo-Juárez P, Espinosa-Altamirano A, Ibarra-del-Río M, Pacheco-Bravo I, Volkow-Fernández P. Cystic echinococcosis: a disease mimicking cancer in a non-endemic country report of two cases. West Indian Med J. March 2013;62(3):266-9.

201. Crouzet J, Grenouillet F, Delabrousse E, Blagosklonov O, Thevenot T, Di Martino V, et al. Personalized management of patients with inoperable alveolar echinococcosis undergoing treatment with albendazole: usefulness of positron-emission-tomography combined with serological and computed tomography follow-up. Clin Microbiol Infect. June 2010;16(6):788-91.

202. Caoduro C, Porot C, Vuitton DA, Bresson-Hadni S, Grenouillet F, Richou C, et al. The role of delayed 18F-FDG PET imaging in the follow-up of patients with alveolar echinococcosis. J Nucl Med. Society of Nuclear Medicine; March 2013;54(3):358-63.

203. Padhy BP. Disseminated intra-abdominal hydatid disease: surgical management. J Indian Med

Assoc. February 2014;112(2):119-20.

204. Sabouni F, Ferdosian F, Mamishi S, Nejat F, Monnajemzadeh M, Rezaei N. Multiple organ involvement with hydatid cysts. Iran J Parasitol. Tehran University of Medical Sciences; June 2010;5(2):65–70.

205. Ben Brahim M, Nouri A, Ksia A, Ezzi El O, Krichene I, Mekki M, et al. Management of multiple echinococcosis in childhood with albendazole and surgery. J Pediatr Surg. November 2008;43(11):2024-30.

206. Sfaihi L, Kamoun F, Hentati Y, Tiss O, Kamoun T, Mnif Z, et al. [Prolonged fever in a 2-year-old child. Disseminated hydatidosis treated with albendazole]. Arch Pediatr.June 2013;20(6):665–6–685–7.

207. Koubâa M, Lahiani D, Abid L, Mâaloul I, Kahla SB, Bradii M, et al. Can albendazole be the only treatment for cardiac echinococcosis with multiple organ involvement? International journal of cardiology. 29 November 2012;161(3):e58–60.

208. Tomuş C, Zaharie F, Mocan L, Bartoş D, Zaharie R, Iancu C, et al. Minimal invasive treatment of abdominal multiorgan echinococcosis. International surgery. International College of Surgeons 1516 N. Lake Shore Drive, Chicago, IL 60610 USA; January 2013;98(1):61-4.

209. Mishra PK, Agrawal A, Joshi M, Sanghvi B, Gupta R, Parelkar SV. Minimal access surgery for multiorgan hydatid cysts. Afr J Paediatr Surg. January 2010;7(1):40-2.

210. Kapoor SK, Kataria H, Patra SR, Bharadwaj M, Vijay V, Kapoor S. Multi-organ hydatidosis with extensive involvement of the hemi-pelvis and ipsilateral femur. Parasitology International. February 2013;62(1):82-5.

211. Bozbuga N, Erentug V, Akinci E, Yakut C. Is surgical therapy the only treatment of choice for cardiac echinococcosis with multiple organ involvement? Interact Cardiovasc Thorac Surg. September 2003;2(3):367-8.

212. Adel F, Ramia JM, Gijón L, la Plaza-Llamas de R, Arteaga-Peralta V, Ramiro-Perez C. [Extrahepatic and extrapulmonary hydatidosis]. Cir Cir. April 2017;85(2):121-6.

213. Durgun V, Kapan S, Kapan M, Karabiçak I, Aydogan F, Goksoy E. Primary splenic hydatidosis. Dig Surg. Karger Publishers; 2003;20(1):38–41.

214. Çakır M, Balasar M, Küçükkartallar T, Tekin A, Kartal A, Karahan Ö, et al. Management of Extra-Hepatopulmonary Hydatid Cysts (157 cases). Turkiye Parazitol Derg.June 2016;40(2):72-6.

215. Ran B, Shao Y, Yimiti Y, Aji T, Shayiding P, Jiang T, et al. Spleen-preserving surgery is effective for the treatment of spleen cystic echinococcosis. Int J Infect Dis. December 2014;29:181-3.

216. Akbulut S, Sogutcu N, Eris C. Hydatid disease of the spleen: single-center experience and a brief literature review. J Gastrointest Surg. Springer US; October 2013;17(10):1784-95.

217. Akhan O, Akkaya S, Dağoğlu MG, Akpınar B, Erbahceci A, Ciftci T, et al. Percutaneous Treatment of Splenic Cystic Echinococcosis: Results of 12 Cases. CardioVascular and Interventional Radiology. Springer US; March 2016;39(3):441-6.

218. Huang M, Zheng H. Clinical and demographic characteristics of patients with urinary tract hydatid disease. Mulvenna J, editor. PloS one. Public Library of Science; 2012;7(11):e47667.

219. Rexiati M, Mutalifu A, Azhati B, Wang W, Yang H, Sheyhedin I, et al. Diagnosis and surgical treatment of renal hydatid disease: a retrospective analysis of 30 cases. Rastaldi MP, editor. PloS one. Public Library of Science; 2014;9(5):e96602.

220. Horchani A, Nouira Y, Kbaier I, Attyaoui F, Zribi AS. Hydatid cyst of the kidney. A report of 147 controlled cases. European urology. Karger Publishers; October 2000;38(4):461-7.

221. Shukla S, Singh SK, Pujani M. Multiple disseminated abdominal hydatidosis presenting with gross hydatiduria: a rare case report. Indian J Pathol Microbiol. April 2009;52(2):213-4.

222. Brunetti E, Garcia HH, Junghanss T, International CE Workshop in Lima, Peru, 2009. Cystic echinococcosis: chronic, complex, and still neglected. Lustigman S, editor. PLoS Neglected Tropical Diseases. Public Library of Science; July 2011;5(7):e1146.

223. Kaya K, Gokce G, Kaya S, Kilicarslan H, Ayan S, Gultekin EY. Isolated renal and retroperitoneal hydatid cysts: a report of 23 cases. Trop Doct. SAGE PublicationsSage UK: London, England; October 2006;36(4):243-6.

224. Turgut AT, Odev K, Kabaalioglu A, Bhatt S, Dogra VS. Multitechnique evaluation of renal hydatid disease. AJR American journal of roentgenology. American Roentgen Ray Society; February 2009;192(2):462-7.

225. Stojkovic M, Rosenberger K, Kauczor H-U, Junghanss T, Hosch W. Diagnosing and staging of cystic echinococcosis: how do CT and MRI perform in comparison to ultrasound? Garcia HH, editor. PLoS Neglected Tropical Diseases. Public Library of Science; 2012;6(10):e1880.

226. Buckley RJ, Smith S, Herschorn S, Comisarow RH, Barkin M. Echinococcal disease of the kidney presenting as a renal filling defect. J Urol. April 1985;133(4):660-1.

227. Sheikh El A, Malki Al A, Shiekh El MA, Robayan Al A. Non-surgical management in 336 patients of hydatid disease: 23 years experience at Riyadh Military Hospital. Hepatogastroenterology. March 2011;58(106):336-46.

228. Ozbey I, Aksoy Y, Biçgi O, Polat O. Hydatid disease of the urinary tract: review of the management of 9 cases. Int Urol Nephrol. 2001;33(2):329-34.

229. Ozbey I, Aksoy Y, Polat O, Atmaca AF, Demirel A. Clinical management of hydatid disease of the urinary tract. J Int Med Res. SAGE PublicationsSage UK: London, England; May 2002;30(3):346-52.

230. Ozden E, Bostanci Y, Mercimek MN, Yakupoglu YK, Yilmaz AF, Sarıkaya S. Renal hydatid cyst treatment: retroperitoneoscopic «closed cyst» pericystectomy. Int J Urol. Wiley/Blackwell (10.1111); March 2011;18(3):237-9.

231. Shah KJ, Ganpule AP, Desai MR. Isolated renal hydatid cyst managed by laparoscopic transperitoneal nephrectomy. Indian J Urol. Medknow Publications; October 2009;25(4):531-3.

232. Basiri A, Nadjafi-Semnani M, Nooralizadeh A. Case report: laparoscopic partial nephrectomy for isolated renal hydatid disease. J Endourol. Mary Ann Liebert, Inc. 2 Madison Avenue Larchmont, NY 10538 USA; January 2006;20(1):24-6.

233. Kumar S, Pandya S, Acharya N, Agarwal M, Mandal AK, Singh SK. Laparoscopic management of atypical ureteropelvic junction obstruction: alternative and simple techniques for complex situations. Urol Int. Karger Publishers; 2008;81(1):87–93.

234. Bilen CY, Ozkaya O, Sarikaya S, Aşci R, Büyükalpelli R. Laparoscopic excision of renal hydatid cyst in a preadolescent. J Pediatr Urol. June 2006;2(3):210-3.

235. Divarci E, Ulman I, Avanoğlu A. Retroperitoneoscopic laparoscopic treatment of renal hydatid cyst in a child. J Pediatr Surg. January 2010;45(1):262-4.

236. Khan M, Sajjad Nazir S, Ahangar S, Farooq Qadri SJ, Ahmad Salroo N. Retroperitoneal laparoscopy for the management of renal hydatid cyst. Int J Surg. 2010;8(4):266-8.

237. Rabii R, Mezzour MH, Essaki H, Fekak H, Joual A, Meziane F. Laparoscopic treatment for renal hydatid cyst. J Endourol. Mary Ann Liebert, Inc. 2 Madison Avenue Larchmont, NY 10538 USA; March 2006;20(3):199–201.

238. Kahlfuß S, Flieger RR, Roepke TK, Yilmaz K. Diagnosis and treatment of cardiac echinococcosis. Heart. 1 September 2016;102(17):1348-53.

239. Fiengo L, Bucci F, Giannotti D, Patrizi G, Redler A, Kucukaksu DS. Giant cardiac hydatid cyst in children: case report and review of the literature. Clin Med Insights Case Rep. SAGE PublicationsSage UK: London, England; 2014;7:111-6.

240. Lahdhili H, Hachicha S, Ziadi M, Thameur H. Acute pulmonary embolism due to the rupture of a right ventricle hydatic cyst. Eur J Cardiothorac Surg. September 2002;22(3):462-4.

241. Kopp CW, Binder T, Grimm M, Merl O, Thalhammer F, Ullrich R, et al. Images in cardiovascular medicine. Left ventricular echinococcosis with peripheral embolization. Circulation. 24 September 2002;106(13):1741-2.

242. Giorgadze, Nadareishivili A, Goziridze M, Zodelava E, Nachkepia M, Grigolia G, et al. Unusual recurrence of hydatid cysts of the heart: report of two cases and review of the clinical and surgical aspects of the disease. J Card Surg. May 2000;15(3):223-8.

243. Yasim A, Ustunsoy H, Gokaslan G, Hafız E, Arslanoglu Y. Cardiac Echinococcosis: A Single-Centre Study with 25 Patients. Heart Lung Circ. February 2017;26(2):157-63.

244. Kaplan M, Demirtas M, Cimen S, Ozler A. Cardiac hydatid cysts with intracavitary expansion. Ann Thorac Surg. May 2001;71(5):1587-90.

245. Tuncer E, Tas SG, Mataraci I, Tuncer A, Donmez AA, Aksut M, et al. Surgical treatment of cardiac hydatid disease in 13 patients. Tex Heart Inst J. Texas Heart Institute; 2010;37(2):189-93.

246. Malouf J, Saksouk FA, Alam S, Rizk GK, Dagher I. Hydatid cyst of the heart: diagnosis by two-dimensional echocardiography and computed tomography. Am Heart J. March 1985;109(3 Pt 1):605-7.

247. Oliver JM, Benito LP, Ferrufino O, Sotillo JF, Nuñez L. Cardiac hydatid cyst diagnosed by two-dimensional echocardiography. Am Heart J. July 1982;104(1):164-5.

248. Ben-Hamda K, Maatouk F, Ben-Farhat M, Betbout F, Gamra H, Addad F, et al. Eighteen-year experience with echinococcosus of the heart: clinical and echocardiographic features in 14 patients. International journal of cardiology. October 2003;91(2-3):145-51.

249. Makaryus AN, Hametz C, Mieres J, Kort S, Carneglia J, Mangion J. Diagnosis of suspected cardiac echinococcosis with negative serologies: role of transthoracic, transesophageal, and contrast echocardiography. Eur J Echocardiogr. June 2004;5(3):223-7.

250. Yucesoy C, Ozturk E, Hekimoglu B. Radiologic findings and percutaneous treatment of a rare giant soft tissue hydatid cyst. JBR-BTR. September 2013;96(5):286-9.

251. Dursun M, Terzibasioglu E, Yilmaz R, Cekrezi B, Olgar S, Nisli K, et al. Cardiac hydatid disease: CT and MRI findings. AJR American journal of roentgenology. American Roentgen Ray Society; January 2008;190(1):226-32.

252. Braggion-Santos MF, Abdel-Aty H, Hofmann N, Katus HA, Steen H. Cardiac cystic echinococcosis: a long-term follow-up case report. Clin Res Cardiol. January 2013;102(1):85-8.

253. Xing Y, Bawudong D, Zhang W-B, Liu W-Y, Pan C-X, Wen H, et al. Multidetector CT and MR imaging cardiac hydatidosis: case report and review of the literature. Int J Cardiovasc Imaging. December 2011;27 Suppl 1(S1):97–102.

254. Petik B, Hazirolan T, Uysal G, Erturk SM. Cardiac Hydatid Cysts: Computed Tomography and Magnetic Resonance Imaging Findings of the 5 Cases. Journal of computer assisted tomography. September 2015;39(5):816-9.

255. Bakkali A, Jaabari I, Bouhdadi H, Razine R, Bennani Mechita N, Harrag El J, et al. [Cardiac hydatid cyst about 17 operated cases]. Ann Cardiol Angeiol (Paris). April 2018;67(2):67–73.

256. Palmerini E, Federici D, Ballo P, Mondillo S, Chiavarelli M. Surgical management of cardiac hydatidosis. J Card Surg. Wiley/Blackwell (10.1111); May 2011;26(3):292-3.

257. Jain PK, Malik V, Divya A, Narula J, Hote M. Interventricular septal hydatid cyst: Transesophageal echocardiography as a therapeutic tool during bypass. Ann Card Anaesth. Medknow Publications; July 2015;18(3):421-4.

258. Agnino A, Lanzone AM, Spira G, Anselmi A. Surgical treatment of left ventricular echinococcosis

through the HeartPort technique. Interact Cardiovasc Thorac Surg. 1 February 2018;26(2):357-9.

259. Limaiem F, Bellil S, Bellil K, Chelly I, Mekni A, Khaldi M, et al. Primary hydatidosis of the central nervous system: a retrospective study of 39 Tunisian cases. Clin Neurol Neurosurg. January 2010;112(1):23-8.

260. Luo K, Luo D-H, Zhang T-R, Wen H. Primary intracranial and spinal hydatidosis: a retrospective study of 21 cases. Pathog Glob Health. March 2013;107(2):47–51.

261. Tapia E O, Vidal T A, Antonio P L. [Brain hydatidosis: report of four cases]. Revista médica de Chile. Sociedad Médica de Santiago; March 2012;140(3):358-63.

262. Duishanbai S, Geng D, Liu C, Guo H-R, Hao Y-J, Liu B, et al. Treatment of intracranial hydatid cysts. Chin Med J. September 2011;124(18):2954-8.

263. Turgut M. Hydatidosis of central nervous system and its coverings in the pediatric and adolescent age groups in Turkey during the last century: a critical review of 137 cases. Childs Nerv Syst. Springer-Verlag; December 2002;18(12):670-83.

264. Altinörs N, Bavbek M, Caner HH, Erdogan B. Central nervous system hydatidosis in Turkey: a cooperative study and literature survey analysis of 458 cases. J Neurosurg. July 2000;93(1):1–8.

265. Turgut M. Intracranial extradural hydatid cysts: review of the literature. Acta Neurochir (Wien). Springer Vienna; October 2010;152(10):1805-6.

266. Basraoui D, Idrissi El I, Jalal H, Hiroual M, Essadki O, Ousehal A, et al. [Intracranial hydatid cysts in children: a report of 9 cases]. J Radiol. March 2010;91(3 Pt 1):293-6.

267. Bükte Y, Kemaloglu S, Nazaroglu H, Ozkan U, Ceviz A, Simsek M. Cerebral hydatid disease: CT and MR imaging findings. Swiss Med Wkly. 7 August 2004;134(31-32):459-67.

268. Hajhouji F, Aniba K, Laghmari M, Lmejjati M, Ghannane H, Benali SA. Epilepsy: unusual presentation of cerebral hydatid disease in Children. Pan Afr Med J. 2016;25:58.

269. Asri F, Tazi I, Maaroufi K, Moudden El A, Ghannane H, Ait Benali S. [Cerebral hydatic cyst and psychiatric disorders. Two cases]. Encephale. March 2007;33(2):216-9.

270. Osborn AG, Preece MT. Intracranial cysts: radiologic-pathologic correlation and imaging approach. Radiology. Radiological Society of North America; June 2006;239(3):650-64.

271. Mohindra S, Savardekar A, Gupta R, Tripathi M, Rane S. Varied types of intracranial hydatid cysts: radiological features and management techniques. Acta Neurochir (Wien). Springer Vienna; January 2012;154(1):165-72.

272. Taslakian B, Darwish H. Intracranial hydatid cyst: imaging findings of a rare disease. BMJ Case Rep. BMJ Publishing Group Ltd; 12 September 2016;2016:bcr2016216570.

273. Turgut M. Intracranial hydatidosis in Turkey: its clinical presentation, diagnostic studies, surgical management, and outcome. A review of 276 cases. Neurosurg Rev. December 2001;24(4):200-8.

274. Zain Al TJ, Al-Witry SH, Khalili HM, Aboud SH, Zain Al FT. Multiple intracranial hydatidosis. Acta Neurochir (Wien). November 2002;144(11):1179-85.

275. Duishanbai S, Jiafu D, Guo H, Liu C, Liu B, Aishalong M, et al. Intracranial hydatid cyst in children: report of 30 cases. Childs Nerv Syst. Springer-Verlag; June 2010;26(6):821-7.

276. Cataltepe O, Colak A, Ozcan OE, Ozgen T, Erbengi A. Intracranial hydatid cysts: experience with surgical treatment in 120 patients. Neurochirurgia (Stuttg). July 1992;35(4):108-11.

277. Ciurea AV, Fountas KN, Coman TC, Machinis TG, Kapsalaki EZ, Fezoulidis NI, et al. Long-term surgical outcome in patients with intracranial hydatid cyst. Acta Neurochir (Wien). April 2006;148(4):421-6.

278. Altas M, Serarslan Y, Davran R, Evirgen O, Aras M, Yilmaz N. The Dowling-Orlando technique in a giant primary cerebral hydatid cyst: a case report. Neurol Neurochir Pol. May 2010;44(3):304-7.

279. Izci Y, Tüzün Y, Seçer HI, Gönül E. Cerebral hydatid cysts: technique and pitfalls of surgical management. Neurosurg Focus. American Association of Neurological Surgeons; 2008;24(6):E15.

280. Tüzün Y, Solmaz I, Sengul G, Izci Y. The complications of cerebral hydatid cyst surgery in children. Childs Nerv Syst. January 2010;26(1):47–51.

281. Tüzün Y, Kadioglu HH, Izci Y, Suma S, Keles M, Aydin IH. The clinical, radiological and surgical aspects of cerebral hydatid cysts in children. Pediatr Neurosurg. Karger Publishers; July 2004;40(4):155-60.

282. Khaldi M, Mohamed S, Kallel J, Khouja N. Brain hydatidosis: report on 117 cases. Childs Nerv Syst. Springer-Verlag; November 2000;16(10-11):765-9.

283. Altas M, Aras M, Serarslan Y, Davran R, Evirgen O, Yilmaz N. A medically treated multiple cerebral hydatid cyst disease. J Neurosurg Sci.June 2010;54(2):79–82.

284. Vutova K, Mechkov G, Vachkov P, Petkov R, Georgiev P, Handjiev S, et al. Effect of mebendazole on human cystic echinococcosis: the role of dosage and treatment duration. Annals of tropical medicine and parasitology. June 1999;93(4):357-65.

285. Balak N, Cavumirza C, Yildirim H, Ozdemir S, Kinay D. Microsurgery in the removal of a large cerebral hydatid cyst: technical case report. Neurosurgery. October 2006;59(4 Suppl 2):ONSE486–discussionONSE486.

286. Monge-Maillo B, Chamorro Tojeiro S, López-Vélez R. Management of osseous cystic echinococcosis. Expert Review of Anti-infective Therapy. December 2017;15(12):1075-82.

287. Meinel TR, Gottstein B, Geib V, Keel MJ, Biral R, Mohaupt M, et al. Vertebral alveolar echinococcosis-a case report, systematic analysis, and review of the literature. The Lancet infectious diseases. March 2018;18(3):e87–e98.

288. Bracanovic D, Djuric M, Sopta J, Djonic D, Lujic N. Skeletal manifestations of hydatid disease in Serbia: demographic distribution, site involvement, radiological findings, and complications. The Korean journal of parasitology. The Korean Society for Parasitology and Tropical Medicine; August 2013;51(4):453-9.

289. Neumayr A, Tamarozzi F, Goblirsch S, Blum J, Brunetti E. Spinal cystic echinococcosis--a systematic analysis and review of the literature: part 1. Epidemiology and anatomy. Flisser A, editor. PLoS Neglected Tropical Diseases. Public Library of Science; 2013;7(9):e2450.

290. Loudiye H, Aktaou S, Hassikou H, El-Bardouni A, El-Manouar M, Fizazi M, et al. Hydatid disease of bone. Review of 11 cases. Joint, bone, spine : revue du rhumatisme. September 2003;70(5):352-5.

291. Steinmetz S, Racloz G, Stern R, Dominguez D, Al-Mayahi M, Schibler M, et al. Treatment challenges associated with bone echinococcosis. J Antimicrob Chemother. March 2014;69(3):821-6.

292. Liang Q, Wen H, Yunus A, Tian Z, Jiang F, Song X. Treatment experiences of pelvic bone hydatidosis. Int J Infect Dis. January 2014;18:57–61.

293. Prabhakar MM, Acharya AJ, Modi DR, Jadav B. Spinal hydatid disease: a case series. J Spinal Cord Med. Taylor & Francis; 2005;28(5):426-31.

294. Neumayr A, Tamarozzi F, Goblirsch S, Blum J, Brunetti E. Spinal cystic echinococcosis--a systematic analysis and review of the literature: part 2. Treatment, follow-up and outcome. Flisser A, editor. PLoS Neglected Tropical Diseases. 2013;7(9):e2458.

295. Zlitni M, Ezzaouia K, Lebib H, Karray M, Kooli M, Mestiri M. Hydatid cyst of bone: diagnosis and treatment. World Journal of Surgery. January 2001;25(1):75–82.

296. Oğüt AG, Kanberoğlu K, Altuğ A, Cokyüksel O. CT and MRI in hydatid disease of cervical vertebrae. Neuroradiology. 1992;34(5):430-2.

297. Mehta P, Prakash M, Khandelwal N. Radiological manifestations of hydatid disease and its complications. Trop Parasitol. July 2016;6(2):103-12.

298. Erol B, Onay T, Çalışkan E, Okay E. Oncological approach with antihelminthic chemotherapy and wide resection in the treatment of musculoskeletal hydatidosis. A review of 10 cases with mean follow-up of 64 months. Acta Orthop Belg. September 2015;81(3):530-7.

299. Gennari A, Almairac F, Litrico S, Albert C, Marty P, Paquis P. Spinal cord compression due to a primary vertebral hydatid disease: A rare case report in metropolitan France and a literature review. Neurochirurgie. August 2016;62(4):226-8.

300. Kalinova K, Proichev V, Stefanova P, Tokmakova K, Poriazova E. Hydatid bone disease: a case report and review of the literature. J Orthop Surg (Hong Kong). 1st ed. SAGE PublicationsSage UK: London, England; December 2005;13(3):323-5.

301. Martínez AA, Herrera A, Cuenca J, Herrero L. Hydatidosis of the pelvis and hip. Int Orthop. Springer; 2001;25(5):302-4.

302. Güneçs M, Akdemir H, Tuğcu B, Günaldi O, Gümüçs E, Akpinar A. Multiple intradural spinal hydatid disease: a case report and review of literature. Spine. 20 April 2009;34(9):E346-50.

303. Muscolo DL, Zaidenberg EE, Farfalli GL, Aponte-Tinao LA, Ayerza MA. Use of Massive Allografts to Manage Hydatid Bone Disease of the Femur. Orthopedics. SLACK Incorporated; October 2015;38(10):e943-6.

304. Herrera A, Martínez AA, Rodríguez J. Spinal hydatidosis. Spine. 1 November 2005;30(21):2439-44.

305. Yildiz Y, Bayrakci K, Altay M, Saglik Y. The use of polymethylmethacrylate in the management of hydatid disease of bone. J Bone Joint Surg Br. September 2001;83(7):1005-8.

306. Xie Z, Chen L, Xie Q, Bao Y, Luo X, Yi C, et al. Surgery or radiotherapy for the treatment of bone hydatid disease: a retrospective case series. Int J Infect Dis. April 2015;33:114-9.

307. Akhan O, Salik AE, Ciftci T, Akinci D, Islim F, Akpinar B. Comparison of Long-Term Results of Percutaneous Treatment Techniques for Hepatic Cystic Echinococcosis Types 2 and 3b. AJR American journal of roentgenology. American Roentgen Ray Society; April 2017;208(4):878-84.

308. Örmeci N. PAIR vs Örmeci technique for the treatment of hydatid cyst. Turk J Gastroenterol. August 2014;25(4):358-64.

309. Losanoff JE, Gruber SA, Basson MD. Percutaneous treatment of giant abdominal hydatid cysts. Surg Endosc. Springer-Verlag; 7 February 2007;21(4):688-9.

310. Shera TA, Choh NA, Gojwari TA, Shera FA, Shaheen FA, Wani GM, et al. A comparison of imaging guided double percutaneous aspiration injection and surgery in the treatment of cystic echinococcosis of liver. Br J Radiol. 4 ed. April 2017;90(1072):20160640.

311. Schipper HG, Laméris JS, van Delden OM, Rauws EA, Kager PA. Percutaneous evacuation (PEVAC) of multivesicular echinococcal cysts with or without cystobiliary fistulas which contain non-drainable material: first results of a modified PAIR method. Gut. BMJ Group; May 2002;50(5):718-23.

312. Kahriman G, Ozcan N, Dogan S, Karaborklu O. Percutaneous treatment of liver hydatid cysts in 190 patients: a retrospective study. Acta Radiol. SAGE PublicationsSage UK: London, England; June 2017;58(6):676-84.

313. Akhan O, Islim F, Balci S, Erbahceci A, Akpınar B, Ciftci T, et al. Percutaneous Treatment of Simple Hepatic Cysts: The Long-Term Results of PAIR and Catheterization Techniques as Single-Session Procedures. CardioVascular and Interventional Radiology. Springer US; June 2016;39(6):902-8.

314. Nayman A, Guler I, Keskin S, Erdem TB, Borazan H, Kucukapan A, et al. A novel modified PAIR technique using a trocar catheter for percutaneous treatment of liver hydatid cysts: a six-year experience. Diagn Interv Radiol. January 2016;22(1):47–51.

315. Bakdik S, Arslan S, Oncu F, Tolu I, Eryilmaz MA. Percutaneous treatment of hepatic cystic echinococcosis: the success of alcohol as a single endocavitary agent in PAIR, catheterization, and modified catheterization techniques. Radiol Med. Springer Milan; February 2018;123(2):153-60.

316. Sharafi SM, Sefiddashti RR, Sanei B, Yousefi M, Darani HY. Scolicidal agents for protoscolices of Echinococcus granulosus hydatid cyst: Review of literature. J Res Med Sci. Medknow Publications; 2017;22(1):92.

317. Adas G, Arikan S, Kemik O, Oner A, Sahip N, Karatepe O. Use of albendazole sulfoxide, albendazole sulfone, and combined solutions as scolicidal agents on hydatid cysts (in vitro study). World J Gastroenterol. Baishideng Publishing Group Inc; 7 January 2009;15(1):112-6.

318. Giorgio A, Calisti G, de Stefano G, Farella N, Scognamiglio U, Giorgio V. Percutaneous treatment of hydatid liver cysts: an update. Recent Pat Antiinfect Drug Discov. 1 December 2012;7(3):231-6.

319. Golemanov B, Grigorov N, Mitova R, Genov J, Vuchev D, Tamarozzi F, et al. Efficacy and safety of PAIR for cystic echinococcosis: experience on a large series of patients from Bulgaria. The American journal of tropical medicine and hygiene. The American Society of Tropical Medicine and Hygiene; January 2011;84(1):48–51.

320. Hosseini SV, Ghanbarzadeh K, Barzin J, Sadjjadi SM, Tanideh N, Mehrabani D. In vitro protoscolicidal effects of hypertonic glucose on protoscolices of hydatid cyst. The Korean journal of parasitology. Korean Society for Parasitology; September 2006;44(3):239-42.

321. Oral A, Yigiter M, Yildiz A, Yalcin O, Dikmen T, Eren S, et al. Diagnosis and management of hydatid liver disease in children: a report of 156 patients with hydatid disease. J Pediatr Surg. March 2012;47(3):528-34.

322. Ustunsoz B, Ugurel MS, Uzar AI, Duru NK. Percutaneous treatment of hepatic hydatid cyst in pregnancy: long-term results. Arch Gynecol Obstet. Springer-Verlag; June 2008;277(6):547-50.

323. Tamarozzi F, Vuitton L, Brunetti E, Vuitton DA, Koch S. Non-surgical and non-chemical attempts to treat echinococcosis: do they work? Parasite (Paris, France). EDP Sciences; 2014;21:75.

324. Rippmann K, Dietrich M, Kern P. [Long-term therapy of cystic liver echinococcosis with mebendazole]. Med Klin (Munich). 15 July 1992;87(7):350-4.

325. De Rosa F, Teggi A. Treatment of Echinococcus granulosus hydatid disease with albendazole. Annals of tropical medicine and parasitology. October 1990;84(5):467-72.

326. Rudwan MA, Mousa AM, Muhtaseb SA. Abdominal hydatid disease: follow-up of mebendazole therapy by CT and ultrasonography. International surgery. July 1986;71(1):22-6.

327. Gil-Grande LA, Boixeda D, García-Hoz F, Bárcena R, Lledo A, Suarez E, et al. Treatment of liver hydatid disease with mebendazole: a prospective study of thirteen cases. The American journal of gastroenterology. September 1983;78(9):584-8.

328. Kayser HJ. Treatment of hydatid disease with mebendazole at Frere Hospital, East London. A preliminary report. S Afr Med J. 4 October 1980;58(14):560-3.

329. Ammari FF, Omari AK. Surgery and postoperative mebendazole in the treatment of hydatid disease. Saudi Med J. May 2002;23(5):568-71.

330. Bartoloni C, Tricerri A, Guidi L, Gambassi G. The efficacy of chemotherapy with mebendazole in human cystic echinococcosis: long-term follow-up of 52 patients. Annals of tropical medicine and parasitology. June 1992;86(3):249-56.

331. Davis A, Pawlowski ZS, Dixon H. Multicentre clinical trials of benzimidazolecarbamates in human

echinococcosis. Bulletin of the World Health Organization. World Health Organization; 1986;64(3):383-8.

332. Gil-Grande LA, Sánchez-Ruano JJ, López San Román A, García-Hoz F, Bárcena R, Salinas F. [Treatment of hepatic and intra-abdominal hydatidosis with mebendazole: prospective comparison of the cyclic and the continuous regimen]. Revista española de enfermedades digestivas : organo oficial de la Sociedad Española de Patología Digestiva. December 1993;84(6):386-9.

333. Pappalardo G, Reggio D, Frattaroli FM, Teggi A, Correnti FS, Castrini G. Combined medical and surgical therapy: a new approach to abdominal hydatidosis. Ital J Surg Sci. 1987;17(4):335-9.

334. Gil-Grande LA, Rodriguez-Caabeiro F, Prieto JG, Sánchez-Ruano JJ, Brasa C, Aguilar L, et al. Randomised controlled trial of efficacy of albendazole in intra-abdominal hydatid disease. The Lancet. 20 November 1993;342(8882):1269-72.

335. Keshmiri M, Baharvahdat H, Fattahi SH, Davachi B, Dabiri RH, Baradaran H, et al. A placebo controlled study of albendazole in the treatment of pulmonary echinococcosis. Eur Respir J. September 1999;14(3):503-7.

336. Keshmiri M, Baharvahdat H, Fattahi SH, Davachi B, Dabiri RH, Baradaran H, et al. Albendazole versus placebo in treatment of echinococcosis. Transactions of the Royal Society of Tropical Medicine and Hygiene. March 2001;95(2):190-4.

337. Khuroo MS, Dar MY, Yattoo GN, Zargar SA, Javaid G, Khan BA, et al. Percutaneous drainage versus albendazole therapy in hepatic hydatidosis: a prospective, randomized study. Gastroenterology. May 1993;104(5):1452-9.

338. Davis A, Dixon H, Pawlowski ZS. Multicentre clinical trials of benzimidazole-carbamates in human cystic echinococcosis (phase 2). Bulletin of the World Health Organization. World Health Organization; 1989;67(5):503-8.

339. Franchi C, Di Vico B, Teggi A. Long-term evaluation of patients with hydatidosis treated with benzimidazole carbamates. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. August 1999;29(2):304-9.

340. Teggi A, Lastilla MG, De Rosa F. Therapy of human hydatid disease with mebendazole and albendazole. Antimicrob Agents Chemother. American Society for Microbiology (ASM); August 1993;37(8):1679-84.

341. Smego RA Jr, Sebanego P. Treatment options for hepatic cystic echinococcosis. International Journal of Infectious Diseases. 2005;9(2):69–76.

342. Shams-Ul-Bari, Arif SH, Malik AA, Khaja AR, Dass TA, Naikoo ZA. Role of albendazole in the management of hydatid cyst liver. Saudi J Gastroenterol. September 2011;17(5):343-7.

343. Vuitton DA. Benzimidazoles for the treatment of cystic and alveolar echinococcosis: what is the consensus? Expert Review of Anti-infective Therapy. 2009;7(2):145-9.

344. Falagas ME, Bliziotis IA. Albendazole for the treatment of human echinococcosis: a review of comparative clinical trials. Am J Med Sci. September 2007;334(3):171-9.

345. Horton RJ. Albendazole in treatment of human cystic echinococcosis: 12 years of experience. Acta Tropica. 1 April 1997;64(1-2):79–93.

346. Kern P. Echinococcus granulosus infection: clinical presentation, medical treatment and outcome. Langenbecks Arch Surg. Springer-Verlag; December 2003;388(6):413-20.

347. Bygott JM, Chiodini PL. Praziquantel: neglected drug? Ineffective treatment? Or therapeutic choice in cystic hydatid disease? Acta Tropica. August 2009;111(2):95–101.

348. Safety of the combined use of praziquantel and albendazole in the treatment of human hydatid disease. American Society of Tropical Medicine and Hygiene; May 2014;90(5):819-22.

349. Silva MA, Mirza DF, Bramhall SR, Mayer AD, McMaster P, Buckels JAC. Treatment of hydatid

disease of the liver. Evaluation of a UK experience. Dig Surg. Karger Publishers; 2004;21(3):227–33–discussion233–4.

350. Ayles HM, Corbett EL, Taylor I, Cowie AGA, Bligh J, Walmsley K, et al. A combined medical and surgical approach to hydatid disease: 12 years' experience at the Hospital for Tropical Diseases, London. Ann R Coll Surg Engl. Royal College of Surgeons of England; March 2002;84(2):100-5.

351. Bonifacino R, Carter SD, Craig PS, Almeida I, Da Rosa D. Assessment of the immunological surveillance value of humoral and lymphocyte assays in severe human cystic echinococcosis. Transactions of the Royal Society of Tropical Medicine and Hygiene. January 2000;94(1):97–102.

352. Fahim F, Salamah Al SM. Cystic echinococcosis in Central Saudi Arabia: a 5-year experience. Turk J Gastroenterol. March 2007;18(1):22-7.

353. Haralabidis S, Diakou A, Frydas S, Papadopoulos E, Mylonas A, Patsias A, et al. Long-term evaluation of patients with hydatidosis treated with albendazole and praziquantel. Int J Immunopathol Pharmacol. April 2008;21(2):429-35.

354. Yasawy MI, Karawi al MA, Mohamed AR. Combination of praziquantel and albendazole in the treatment of hydatid disease. Trop Med Parasitol. September 1993;44(3):192-4.

355. Salto E, Juárez E, Roiz MP, Abad J. [Combined chemotherapy (mebendazole plus praziquantel) in patients with hydatidosis]. Enfermedades infecciosas y microbiologia clinica. November 1991;9(9):527-9.

356. Mohamed AE, Yasawy MI, Karawi al MA. Combined albendazole and praziquantel versus albendazole alone in the treatment of hydatid disease. Hepatogastroenterology. September 1998;45(23):1690-4.

357. Cobo F, Yarnoz C, Sesma B, Fraile P, Aizcorbe M, Trujillo R, et al. Albendazole plus praziquantel versus albendazole alone as a pre-operative treatment in intra-abdominal hydatisosis caused by Echinococcus granulosus. Tropical medicine & international health : TM & IH. June 1998;3(6):462-6.

358. Optimal timing of post-operative albendazole prophylaxis in E. granulosus. February 1988;82(1):65-6. Accessed via: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=3401071&retmode=ref&cmd=prlinks

359. Jamshidi M, Mohraz M, Zangeneh M, Jamshidi A. The effect of combination therapy with albendazole and praziquantel on hydatid cyst treatment. Parasitology Research. Springer-Verlag; June 2008;103(1):195-9.

360. Siles-Lucas M, Casulli A, Cirilli R, Carmena D. Progress in the pharmacological treatment of human cystic and alveolar echinococcosis: Compounds and therapeutic targets. Raso G, editor. PLoS Neglected Tropical Diseases. April 2018;12(4):e0006422.

361. Chai JJ, Menghebat, Jiao W, Sun DY, Liang B, Shi JC, et al. [Efficacy of ablendazole emulsion in treatment of 212 patients with cystic echinococcosis]. Zhongguo ji sheng chong xue yu ji sheng chong bing za zhi = Chinese journal of parasitology & parasitic diseases. 2001;19(3):129-34.

362. Li H-T, Shan J-Y, Shao Y-M, Tuergan A, Ayifuhan A, Ran B, et al. [Clinical effect and safety of liposomal-albendazole and tablet-albendazole for the treatment of human cystic echinococcosis]. Zhonghua Gan Zang Bing Za Zhi. July 2011;19(7):532-6.

363. Corodner JO, Lanari A. [Treatment of hydatidosis. Clinical trial with thiabendazole]. Medicina. 1976;36(5):509-10.

364. Pérez Molina JA, Díaz-Menéndez M, Gallego JI, Norman F, Monge-Maillo B, Ayala AP, et al. Evaluation of nitazoxanide for the treatment of disseminated cystic echinococcosis: report of five cases and literature review. The American journal of tropical medicine and hygiene. American Society of Tropical Medicine and Hygiene; February 2011;84(2):351-6.

365. Romig T, Zeyhle E, Macpherson CN, Rees PH, Were JB. Cyst growth and spontaneous cure in hydatid disease. The Lancet. 1986;1(8485):861.

366. Larrieu E, Del Carpio M, Salvitti JC, Mercapide C, Sustersic J, Panomarenko H, et al. Ultrasonographic diagnosis and medical treatment of human cystic echinococcosis in asymptomatic school age carriers: 5 years of follow-up. Acta Tropica. June 2004;91(1):5–13.

367. Larrieu E, Del Carpio M, Mercapide CH, Salvitti JC, Sustercic J, Moguilensky J, et al. Programme for ultrasound diagnoses and treatment with albendazole of cystic echinococcosis in asymptomatic carriers: 10 years of follow-up of cases. Acta Tropica [Internet]. January 2011;117(1):1–5. Accessed via: http://linkinghub.elsevier.com/retrieve/pii/S0001706X10002081

368. Li T, Ito A, Pengcuo R, Sako Y, Chen X, Qiu D, et al. Post-treatment follow-up study of abdominal cystic echinococcosis in tibetan communities of northwest Sichuan Province, China. Garcia HH, editor. PLoS Neglected Tropical Diseases. Public Library of Science; October 2011;5(10):e1364.

369. Frider B, Larrieu E, Odriozola M. Long-term outcome of asymptomatic liver hydatidosis. Journal of Hepatology. February 1999;30(2):228-31.

370. Del Carpio M, Mercapide CH, Salvitti JC, Uchiumi L, Sustercic J, Panomarenko H, et al. Early diagnosis, treatment and follow-up of cystic echinococcosis in remote rural areas in Patagonia: impact of ultrasound training of non-specialists. Flisser A, editor. PLoS Neglected Tropical Diseases. January 2012;6(1):e1444.

371. Caremani M, Benci A, Maestrini R, Accorsi A, Caremani D, Lapini L. Ultrasound imaging in cystic echinococcosis. Proposal of a new sonographic classification. Acta Tropica. 15 September 1997;67(1-2):91–105.

372. Piccoli L, Tamarozzi F, Cattaneo F, Mariconti M, Filice C, Bruno A, et al. Long-term sonographic and serological follow-up of inactive echinococcal cysts of the liver: hints for a «watch-and-wait» approach. Lustigman S, editor. PLoS Neglected Tropical Diseases. Public Library of Science; August 2014;8(8):e3057.

373. Moro PL, Gilman RH, Verastegui M, Bern C, Silva B, Bonilla JJ. Human hydatidosis in the central Andes of Peru: evolution of the disease over 3 years. Clinical Infectious Diseases. 1999;29(4):807-12.

374. Wang Y, He T, Wen X, Li T, Waili A, Zhang W, et al. Post-survey follow-up for human cystic echinococcosis in northwest China. Acta Tropica. April 2006;98(1):43–51.

375. Wang Y, Zhang X, Bartholomot B, Liu B, Luo J, Li T, et al. Classification, follow-up and recurrence of hepatic cystic echinococcosis using ultrasound images. Transactions of the Royal Society of Tropical Medicine and Hygiene. March 2003;97(2):203-11.

376. Zhang W-B, Xing Y, Xu X-C, Abudukadeer X-K, Wang Y-H, Wen H. Community survey, treatment and long-term follow-up for human cystic echinococcosis in northwest China. Chin Med J. October 2011;124(19):3176-9.

377. Solomon N, Kachani M, Zeyhle E, Macpherson CNL. The natural history of cystic echinococcosis in untreated and albendazole-treated patients. Acta Tropica. July 2017;171:52-7.

378. Menezes da Silva A. Hydatid cyst of the liver-criteria for the selection of appropriate treatment. Acta Tropica. February 2003;85(2):237-42.

379. Frider B, Larrieu E. Treatment of liver hydatidosis: how to treat an asymptomatic carrier? World J Gastroenterol. Baishideng Publishing Group Inc; 7 September 2010;16(33):4123-9.

380. Vuitton DA. The WHO informal working group on echinococcosis. The Coordinating Board of the WHO-IWGE. Acta Tropica. 15 September 1997;67(1-2):147-8.

381. Junghanss T, da Silva AM, Horton J, Chiodini PL, Brunetti E. Clinical management of cystic echinococcosis: state of the art, problems, and perspectives. The American journal of tropical medicine and hygiene. September 2008;79(3):301-11.

382. Stojkovic M, Rosenberger KD, Steudle F, Junghanss T. Watch and Wait Management of Inactive Cystic Echinococcosis - Does the Path to Inactivity Matter - Analysis of a Prospective Patient Cohort. Casulli A, editor. PLoS Neglected Tropical Diseases. December 2016;10(12):e0005243.

383. Solomon N, Zeyhle E, Subramanian K, Fields PJ, Romig T, Kern P, et al. Cystic echinococcosis in Turkana, Kenya: 30 years of imaging in an endemic region. Acta Tropica. February 2018;178:182-9.

384. Kern P, Menezes da Silva A, Akhan O, Müllhaupt B, Vizcaychipi KA, Budke C, et al. The Echinococcoses: Diagnosis, Clinical Management and Burden of Disease. Advances in parasitology. Elsevier; 2017;96:259–369.

385. Vuitton DA. The ambiguous role of immunity in echinococcosis: protection of the host or of the parasite? Acta Tropica. February 2003;85(2):119-32.

386. Chauchet A, Grenouillet F, Knapp J, Richou C, Delabrousse E, Dentan C, et al. Increased incidence and characteristics of alveolar echinococcosis in patients with immunosuppression-associated conditions. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 15 October 2014;59(8):1095-104.

387. Noormahomed EV, Nhacupe N, Mascaró-Lazcano C, Mauaie MN, Buene T, Funzamo CA, et al. A cross-sectional serological study of cysticercosis, schistosomiasis, toxocariasis and echinococcosis in HIV-1 infected people in Beira, Mozambique. Flisser A, editor. PLoS Neglected Tropical Diseases. Public Library of Science; September 2014;8(9):e3121.

388. Ran B, Shao Y, Guo Y, Yimiti Y, Aji T, Jia J, et al. Surgical treatment of hepatic cystic echinococcosis in patients co-infected with HIV/AIDS. Journal of helminthology. Cambridge University Press; January 2016;90(1):125-8.

389. Coupland U, Dobosz S, Zawadka K, Marczyńska M. Cystic echinococcosis in a child infected with HIV. Ann Parasitol. 2012;58(2):101-3.

390. Javed A, Kalayarasan R, Agarwal AK. Liver hydatid with HIV infection: an association? J Gastrointest Surg. Springer-Verlag; June 2012;16(6):1275-7.

391. Erayman I, Kalkan E, Erdi F, Kerimoglu Ü, Esen H. Primary spinal hydatid cyst in a patient with acquired immunodeficiency syndrome. Eur Spine J. Springer-Verlag; July 2011;20 Suppl 2(S2):S235-8.

392. Ramos JM, Masiá M, Padilla S, Bernal E, Martin-Hidalgo A, Gutiérrez F. Fatal infection due to larval cysts of cestodes (neurocysticercosis and hydatid disease) in human immunodeficiency virus (HIV) infected patients in Spain: report of two cases. Scandinavian journal of infectious diseases. 2007;39(8):719-23.

393. Shenoy VV, Joshi SR, Aklujkar AP, Kotwal VS, Nadkarni NA, Ramraje NN. Pulmonary hydatid cyst in HIV-1 disease. The Journal of the Association of Physicians of India. December 2005;53:1070-2.

394. Zingg W, Renner-Schneiter EC, Pauli-Magnus C, Renner EL, van Overbeck J, Schläpfer E, et al. Alveolar echinococcosis of the liver in an adult with human immunodeficiency virus type-1 infection. Infection. October 2004;32(5):299–302.

395. Kakrani AL, Chowdhary VR, Bapat VM. Disseminated pulmonary hydatid disease presenting as multiple cannon ball shadows in human immunodeficiency virus infection. The Journal of the Association of Physicians of India. December 2000;48(12):1208-9.

396. Palmiero G, Ciampi R, Gallo R, Federico S, Sabbatini M. Liver echinococcosis in a renal transplant patient: a particularly intriguing case report. J Nephrol. May 2008;21(3):442-5.

397. Sqalli TH, Buchler M, Najjar Al A, Paris A, Halimi J-M, Nivet H, et al. Hydatid cyst disease in a renal allograft recipient. Saudi J Kidney Dis Transpl. November 2009;20(6):1057-60.

398. Cavdar C, Celik A, Saglam F, Toprak O, Gungor O, Tuna B, et al. Isolated hydatid disease of the native kidney in a renal transplant recipient. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. February 2007;22(2):656-7.

399. Kim J, Delioukina ML, Lee W, Soriano P, Prendergast C, D'Apuzzo M, et al. Successful allogeneic hematopoietic stem cell transplantation for acute myelogenous leukemia in a patient with hepatic

echinococcal cyst managed by delayed hepatectomy. Transplant infectious disease : an official journal of the Transplantation Society. Wiley/Blackwell (10.1111); June 2011;13(3):273-7.

400. Bhat RA, Wani I, Khan I, Wani M. Renal allograft transplant recipient with ruptured hydatid native kidney. Urol Ann. Medknow Publications; July 2014;6(3):267-9.

401. Sobrino JM, Pulpón LA, Crespo MG, Silva L, Segovia J, Serrano-Fiz S, et al. Heart transplantation in a patient with liver hydatidosis. J Heart Lung Transplant. May 1993;12(3):531-3.

402. Escolà-Vergé L, Salvador F, Sánchez-Montalvá A, Escudero-Fernández JM, Sulleiro E, Rando A, et al. Retrospective Study of Cystic Echinococcosis in a Recent Cohort of a Referral Center for Liver Surgery. J Gastrointest Surg. Springer US; 21 September 2018;115(8):4261-9.

403. Pawluk SA, Roels CA, Wilby KJ, Ensom MHH. A review of pharmacokinetic drug-drug interactions with the anthelmintic medications albendazole and mebendazole. Clin Pharmacokinet. Springer International Publishing; April 2015;54(4):371-83.

404. Corti N, Heck A, Rentsch K, Zingg W, Jetter A, Stieger B, et al. Effect of ritonavir on the pharmacokinetics of the benzimidazoles albendazole and mebendazole: an interaction study in healthy volunteers. Eur J Clin Pharmacol. Springer-Verlag; October 2009;65(10):999–1006.

405. Yeh WW, Saint S, Weinberger SE. Clinical problem-solving. A growing problem--a 36-year-old pregnant woman at 21 weeks of gestation presented with a 4-week history of a dry, nonproductive cough. The New England journal of medicine. 2 August 2007;357(5):489-94.

406. Robertson M, Geerts L, Gebhardt GS. A case of hydatid cyst associated with postpartum maternal death. Ultrasound Obstet Gynecol. Wiley-Blackwell; June 2006;27(6):693-6.

407. Rodrigues G, Seetharam P. Management of hydatid disease (echinococcosis) in pregnancy. Obstet Gynecol Surv. February 2008;63(2):116-23.

408. Berberian G, Rosanova T, Inda L, Sarkis C, Questa H, Paulin P, et al. Echinococcosis in children: Experience in a tertiary care hospital outside the endemic area. Arch Argent Pediatr. 1 June 2017;115(3):282-6.

409. Reto Valiente LV, Pichilingue Reto C, Pichilingue Reto P, Angulo G, Agusto C, Pichilingue Prieto OA. [Clinical and therapeutic issues in children and adolescents with liver hidatidosis at the Hipolito Unanue National Hospital]. Rev Gastroenterol Peru. July 2012;32(3):290-6.

410. Manterola C, Otzen T, Urrutia S, MINCIR Group (Methodology and Research in Surgery). Risk factors of postoperative morbidity in patients with uncomplicated liver hydatid cyst. Int J Surg. 2014;12(7):695-9.

411. Jerraya H, Khalfallah M, Osman SB, Nouira R, Dziri C. Predictive factors of recurrence after surgical treatment for liver hydatid cyst. Surg Endosc. Springer US; January 2015;29(1):86–93.

412. Bedioui H, Ayari H, Bouslama K, Maghrebi H, Hsairi H, Jouini M, et al. [Recurrence of hydatid cyst of liver: predictive factors: Tunisian experience]. Bulletin de la Société de pathologie exotique (1990). October 2012;105(4):265-9.

413. Malki El HO, Mejdoubi El Y, Souadka A, Zakri B, Mohsine R, Ifrine L, et al. Does primary surgical management of liver hydatid cyst influence recurrence? J Gastrointest Surg. Springer-Verlag; July de 2010;14(7):1121-7.

414. Mottaghian H, Saidi F. Postoperative recurrence of hydatid disease. Br J Surg. April 1978;65(4):237-42.

415. Prousalidis J, Kosmidis C, Anthimidis G, Kapoutzis K, Karamanlis E, Fachantidis E. Postoperative recurrence of cystic hydatidosis. Can J Surg. February 2012;55(1):15–20.

416. Akhan O, Yildiz AE, Akinci D, Yildiz BD, Ciftci T. Is the adjuvant albendazole treatment really needed with PAIR in the management of liver hydatid cysts? A prospective, randomized trial with short-term follow-up results. CardioVascular and Interventional Radiology. Springer US; December de 2014;37(6):1568-74.

417. Akyildiz HY, Akcan A, Karahan I, Kucuk C, Sözüer E, Esin H. Recurrent liver hydatid disease: when does it become symptomatic and how does one diagnose it? Clin Imaging. January 2009;33(1):55-8.

418. Malki El HO, Souadka A. Postoperative recurrence of cystic hydatidosis: what are the predictive factors? Can J Surg. June 2013;56(3):E44-4.

419. Bozkurt B, Soran A, Karabeyoğlu M, Unal B, Coşkun F, Cengiz O. Follow-up problems and changes in obliteration of the residual cystic cavity after treatment for hepatic hydatidosis. J Hepatobiliary Pancreat Surg. Springer-Verlag; 2003;10(6):441-5.

420. Stojkovic M, Adt H-M, Rosenberger K, Boubaker G, Hernandez-Gonzalez A, Junghanss T, et al. Follow-up of surgically treated patients with cystic echinococcosis: can novel recombinant antigens compete with imaging? Analysis of a patient cohort. Tropical medicine & international health : TM & IH. 23rd ed. May 2017;22(5):614-21.

421. Pagnozzi D, Addis MF, Biosa G, Roggio AM, Tedde V, Mariconti M, et al. Diagnostic Accuracy of Antigen 5-Based ELISAs for Human Cystic Echinococcosis. Torgerson PR, editor. PLoS Neglected Tropical Diseases. Public Library of Science; March 2016;10(3):e0004585.

422. Tenguria RK, Naik MI. Evaluation of human cystic echinococcosis before and after surgery and chemotherapy by demonstration of antibodies in serum. Ann Parasitol. 2014;60(4):297–303.

423. Reiterová K, Auer H, Altintaś N, Yolasigmaz A. Evaluation of purified antigen fraction in the immunodiagnosis of cystic echinococcosis. Parasitology Research. August 2014;113(8):2861-7.

424. Delunardo F, Ortona E, Margutti P, Perdicchio M, Vacirca D, Teggi A, et al. Identification of a novel 19 kDa Echinococcus granulosus antigen. Acta Tropica. January 2010;113(1):42-7.

425. Hernandez-Gonzalez A, Sánchez-Ovejero C, Manzano-Román R, González Sánchez M, Delgado JM, Pardo-García T, et al. Evaluation of the recombinant antigens B2t and 2B2t, compared with hydatid fluid, in IgG-ELISA and immunostrips for the diagnosis and follow up of CE patients. Periago MV, editor. PLoS Neglected Tropical Diseases. Public Library of Science; September 2018;12(9):e0006741.

426. Ben Nouir N, Gianinazzi C, Gorcii M, Müller N, Nouri A, Babba H, et al. Isolation and molecular characterization of recombinant Echinococcus granulosus P29 protein (recP29) and its assessment for the post-surgical serological follow-up of human cystic echinococcosis in young patients. Transactions of the Royal Society of Tropical Medicine and Hygiene. April 2009;103(4):355-64.

427. Hernandez-Gonzalez A, Muro A, Barrera I, Ramos G, Orduña A, Siles-Lucas M. Usefulness of four different Echinococcus granulosus recombinant antigens for serodiagnosis of unilocular hydatid disease (UHD) and postsurgical follow-up of patients treated for UHD. Clin Vaccine Immunol. American Society for Microbiology; January 2008;15(1):147-53.

428. Ben Nouir N, Nuñez S, Gianinazzi C, Gorcii M, Müller N, Nouri A, et al. Assessment of Echinococcus granulosus somatic protoscolex antigens for serological follow-up of young patients surgically treated for cystic echinococcosis. Journal of clinical microbiology. American Society for Microbiology Journals; May 2008;46(5):1631-40.

429. Nouir NB, Nuñez S, Frei E, Gorcii M, Müller N, Gianinazzi C, et al. Post-surgical follow-up (by ELISA and immunoblotting) of cured versus non-cured cystic echinococcosis in young patients. Parasitology. Cambridge University Press; January 2008;135(Pt 1):105-14.

430. Yin YJ, Zhang Q, Yang YX, Yang SK, Wang HF, Shi JX, et al. [Study of the genes correlated with cyst calcification in patients with cystic echinococcosis]. Zhonghua Yu Fang Yi Xue Za Zhi. May de 2016;50(5):434-8.

431. Reuter S, Grüner B, Buck AK, Blumstein N, Kern P, Reske SN. Long-term follow-up of metabolic activity in human alveolar echinococcosis using FDG-PET. Nuklearmedizin. 2008;47(4):147-52.

432. Chow C, Gauci CG, Cowman AF, Lightowlers MW. Echinococcus granulosus: oncosphere-specific transcription of genes encoding a host-protective antigen. Experimental Parasitology. March 2004;106(3-4):183-6.

433. Lightowlers MW, Jensen O, Fernandez E, Iriarte JA, Woollard DJ, Gauci CG, et al. Vaccination trials in Australia and Argentina confirm the effectiveness of the EG95 hydatid vaccine in sheep. International Journal for Parasitology. April 1999;29(4):531-4.

434. Alvarez Rojas CA, Gauci CG, Lightowlers MW. Antigenic differences between the EG95-related proteins from Echinococcus granulosus G1 and G6 genotypes: implications for vaccination. Parasite Immunology. John Wiley & Sons, Ltd (10.1111); February 2013;35(2):99–102.

435. Heath DD, Jensen O, Lightowlers MW. Progress in control of hydatidosis using vaccination--a review of formulation and delivery of the vaccine and recommendations for practical use in control programmes. Vol. 85, Acta Tropica. 2003. pp. 133-43.

436. Pourseif MM, Moghaddam G, Saeedi N, Barzegari A, Dehghani J, Omidi Y. Current status and future prospective of vaccine development against Echinococcus granulosus. Biologicals. January 2018;51:1–11.

437. Barnes TS, Deplazes P, Gottstein B, Jenkins DJ, Mathis A, Siles-Lucas M, et al. Challenges for diagnosis and control of cystic hydatid disease. Acta Tropica. July 2012;123(1):1–7.

438. Rojo-Vazquez FA, Pardo-Lledias J, Francos-Von Hunefeld M, Cordero-Sánchez M, Alamo-Sanz R, Hernandez-Gonzalez A, et al. Cystic echinococcosis in Spain: current situation and relevance for other endemic areas in Europe. Brooker S, editor. PLoS Neglected Tropical Diseases. Public Library of Science; 2011;5(1):e893.

Table 1. EIMC levels of evidence

Strength of recommendation and quality of evidence.

Category/grading strength of recommendations	Definition
A	Strongly supports a recommendation for use
B	Moderately supports a recommendation for use
C	Marginally supports a recommendation for use
D	Supports a recommendation against use
Quality of evidence	
I	Evidence from at least one properly designed randomized, controlled trial
II	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from 1 center); from multiple time series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies

Table 2. CE locations and the main associated clinical features

Location	Frequency (%)	Location details	Clinical features
Liver	46-70	Most frequent location, most often in right lobe (60-85%).	Asymptomatic (11-14%), epigastric or right hypochondrial abdominal pain (42-57%), hepatomegaly (38%), nausea and vomiting (15%), fever (14%), jaundice (9%), weight loss (8%), abdominal distension (3%). In advanced phases, portal hypertension and ascites.
Lung	25-27	Most frequent location in children (70%).	Asymptomatic (12%), dry cough, chest pain, fever, expectoration, anorexia, dyspnoea, respiratory distress, expectoration of cysts (sudden copious expectoration of pus).
Spleen	0.6-4	Along with hepatic involvement.	Asymptomatic (50%), depending on the size, left hypochondrial abdominal pain (50%), dyspepsia (25%).
Kidney and genitourinary	1-3	Most often in kidney, less so in prostate, bladder, or testicle.	Mostly asymptomatic, haematuria, renal fossa-hypogastrium pain, palpable mass, glomerulonephritis, nephrotic syndrome, amyloidosis or hydatiduria.
Abdominal cavity	1.8-4	Multiple, secondary to recurrence.	Asymptomatic (14%), abdominal pain (97%), distention, vomiting, weight loss, acute abdomen, irregular vaginal bleeding or infertility.
Heart	1-2	Interventricular septum, sometimes right ventricle and atrium, occasionally pericardium.	Chest pain, dyspnoea, haemoptysis, peripheral emboli (45%), heart failure, angina due to compression, arrhythmias, heart block. Rarely asymptomatic. High mortality.
Brain	1-2	Space occupying lesion, generally a single lesion, in the territory of the middle cerebral artery, particularly the parietal lobe. Mostly in children.	Headache, vomiting, bilateral papilloedema, seizures, visual deficits, focal neurology, ataxia, reduced conscious level, and brain herniation.
Bone	1.6-3	Axial skeleton (40-50%), long bones (25-30%) and pelvis (15-20%). Uncommon in the skull, sternum, scapula and phalanges.	Asymptomatic, neurological deficit (spinal cord compression), pathological fractures (long bones), soft tissue fistulisation, secondary infection.
Subcutaneous tissue	1.6	Mostly in lower limbs (particularly thighs), cervical, lumbar regions, thorax, upper limbs.	Progressive tumour growth (92%), non-painful (65%).
Muscle	0.7-0.9	Mostly in lower limbs (quadriceps), paravertebral muscles, uncommon in upper limbs.	Slow, non-painful tumour growth, under intact skin, pain (compression of adjacent nerves).
Pancreas	0.1-2	Single cysts (90%), head of pancreas (50-58%), body (24-34%), tail (16-19%).	Jaundice (bile duct compression). In the body and tail of pancreas, usually asymptomatic until cysts produce pain (compression of adjacent structures). In the tail they can cause splenomegaly and portal hypertension. Cholangitis, recurrent pancreatitis, pancreatic abscess, pancreatic fistula or duodenal obstruction.

Table 3. WHO stages. WHO Informal Working Group on Echinococcosis

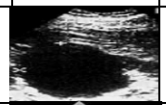
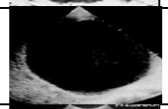
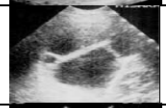
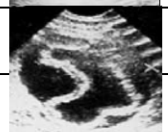
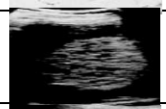
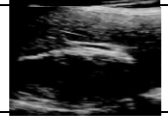
Stage	Ultrasound findings	Ultrasound image	Viability
CL	Unilocular cyst with cyst wall not visible		
CE1	Unilocular cysts with double-membrane sign (cyst wall)		+++
CE2	Multilocular or multiseptated cyst with "cart-wheel" or "honeycomb" pattern		+++
CE3a	Unilocular cyst with germinal layer detached or folded		+
CE3b	Multiple cysts associated with heterogeneous solid tissue		+
CE4	Heterogeneous contents in a ball shape inside the cyst		+/-
CE5	Cysts with thickened, calcified wall		-

Table 4. WHO diagnostic criteria

Criteria		Definitions
A	**Clinical**	Must have at least one of the following three: i) Anaphylactic reaction due to cyst rupture. ii) Cystic mass diagnosed on imaging in a symptomatic patient. iii) Cystic mass diagnosed incidentally on imaging in an asymptomatic patient.
B	**Epidemiological**	Likely epidemiological setting.
C	**Radiological**	Characteristic images on ultrasound, computed tomography, or magnetic resonance imaging.
D	**Serological**	Positive result from an anti-*E. granulosus* antibody detection technique (performed using a highly-sensitive serological technique and confirmed using a highly-specific technique).
E	**Direct**	i) Microscopic examination of cyst contents or suitable histological sample (visualisation of protoscoleces or hooks); ii) Pathognomonic findings on gross examination of the cyst from surgical samples.
Case type		
Possible		A or B, plus C or D.
Probable		A or B, plus C and D (on 2 occasions).
Confirmed		Probable case plus one of the following: i) Demonstration of protoscoleces or their components on direct microscopy or molecular biology of cystic content aspirated via percutaneous puncture or surgical sample; ii) Presence of progressive changes on ultrasound, either spontaneous changes or after scolicidal treatment.

Table 5. Correlation between CE stages and serological results.

Table 6. Usage of the different radiological techniques in CE

	Main uses	Locations	Advantages	Disadvantages
X-ray	CE of bone or lung Hepatic calcification	Skeleton Liver Thorax	Availability Cheap Accessible	Low specificity
Ultrasound	Hepatic and abdominal CE Pulmonary CE adjacent to pleura Accessible soft tissues	Abdomen and soft tissues Lung adjacent to pleura	Allows classification of CE No radiation Useful for diagnosis and follow-up	Not useful in locations that are not accessible with ultrasound
CT	Diagnosis and follow-up in locations not accessible with ultrasound Sensitive in detection of calcification	Any location	High sensitivity	High dose of radiation if frequent follow-up scans
MR	Diagnosis and follow-up in locations not accessible with ultrasound Skull and axial skeleton	Any location Skull and CNS	High sensitivity Diagnosis of complications (bile duct communication)	Low availability
PET-CT	Not established. Need for higher level of evidence	Mainly liver and lung	Ring of uptake in complicated CE	Low availability

Table 7. Most commonly used surgical techniques

Technique	Reference/ Number of patients	Main uses	Main locations	Advantages	Disadvantages
HEPATIC SURGERY					
RADICAL SURGERY	Ramia JM et al. 2018, n=145 Pang Q et al. 2018, n=2274 He YB et al. 2015, n=1267	Active cysts CL-CE3	Favourable hepatic segments not associated with major biliovascular structures	Radical Immediate cure Lower postoperative morbidity	Higher intraoperative morbidity More technically complex Not accessible to all hospitals
CONSERVATIVE SURGERY	Ramia JM et al. 2018, n=145 Pang Q et al. 2018, n=1853 He YB et al. 2015, n=1267	Active cysts CL-CE3 Inactive symptomatic cysts CE4-CE5	Large cysts Complex locations Close to main biliovascular structures	Less technically complex Lower intraoperative morbidity Accessible to many hospitals, does not require highly-specialised units	Higher postoperative morbidity, mainly biliary fistulas and infectious complications relating to the management of the residual cavity Need for postoperative anthelminthic treatment Higher relapse rate
PAIR	Bakdik S et al. 2018, n=347 Akhan O et al. 2017, n=73	CL–CE3, infected cysts, multiple cysts, pregnant patients, children older than 3 years, patients who refuse surgery or have contraindications	Accessible to puncture	Minimally invasive technique Can be performed by non-surgeons Minimal complications	Not radical Does not treat the residual cavity Requires treatment with benzimidazoles Contraindicated in cystobiliary fistulas
PULMONARY SURGERY					
CYSTECTOMY	Aldahmashi M et al. 2016, n=148 Burgos R et al.1999, n=240	Medium-sized cysts with little destruction of parenchyma	Avoid if in the base of the right lower lobe due to possible communication with hepatic cyst	Preservation of functional parenchyma	More air leak (requires closure of bronchiolar openings)
ASSOCIATED RESECTION OF PARENCHYMA	Dakak M et al. 2009, n=78 Bagheri B et al. 2011, n=1024	Cysts in which local resection is not possible due to size or location	Any	Less postoperative air leak than cystectomy	Loss of functioning lung parenchyma

Table 8. Usage of the main interventional techniques in CE

Technique	References	Main indications	Details	Locations	Advantages	Disadvantages
PAIR	Brunetti E et al. 2010	Cysts > 5 cm and < 10 cm CL, CE1 and CE3a Hepatic or accessible to puncture	Puncture with an 18G Chiba needle, aspiration of the cyst (1/3-1/2 of the contents), injection of scolicidal solution and reaspiration after 15 minutes (10-30 minutes depending on the series). Requires prophylaxis with benzimidazoles.	Liver, soft tissues, and structures accessible to puncture with CT or US guidance	Cheap Minimally invasive Can be repeated if required	Not effective in complex or complicated cysts Not indicated in CNS cysts, cardiac cysts, or locations that are difficult to puncture Requires hospital admission and the technique is performed under sedation Complications due to anaphylaxis or sclerosing cholangitis
PAIRD	Tamarozzi F et al. 2014	Cysts > 10 cm Technique similar to PAIR in cysts of greater volume	Puncture and insertion of drainage catheter (6-12Fr) that is kept in until output is less than 10 mL/day. Subsequent scolicidal injection and evacuation. Withdrawal of catheter 24 hours after the intervention.	Liver, soft tissues, and adjacent structures suitable for puncture with CT or US guidance	Accessible and cheap for centres with experience in CT- or US-guided puncture	Longer hospital stay Not indicated in CNS cysts, cardiac cysts or locations that are difficult to puncture Not effective in complex or complicated cysts
D-PAI	Giorgio A et al. 2012	Same as PAIR Double puncture, aspiration and injection	Puncture of cyst with 22G Chiba needle. Aspiration of all cyst contents, injection with scolicidal agent, NOT reaspirated. Procedure repeated 3-7 days after first procedure.	Liver, soft tissues, and adjacent structures suitable for puncture with CT or US guidance	Can be used in “solid” cysts	Slightly higher morbidity and mortality (1.3% mortality) than PAIR, although it is considered a safe and effective technique Not indicated in CNS cysts, cardiac cysts or locations that are difficult to puncture
ÖRMECI	Örmeci N. 2014	Same as PAIR	Puncture of cyst with 22G needle. A volume of 3 times the diameter of the cyst is removed. This corresponds to approximately 2% of the contents of the cyst. The quantity removed is replaced with 2/3 alcohol 95% and 1/3 Aethoxysklerol. Patient observed for 2 hours for possible anaphylactic complications then discharged.	Liver, soft tissues, and adjacent structures suitable for puncture with CT or US guidance	Does not require hospital admission Does not require administration of benzimidazoles Safe and effective Low morbidity and mortality Lower risk of developing biliary fistulas	Not indicated in CNS cysts, cardiac cysts or locations that are difficult to puncture Fewer cases than PAIR (less evidence)
MOCAT	Kahriman G et al. 2017	CE2 and CE3b. Can be used in other types of active cysts.	Insertion of a 14Fr catheter with expulsion of all cyst contents including the germinal layer, solid components, daughter vesicles and infectious components. Once all has been evacuated, an 8-10Fr catheter is placed and the procedure is similar to PAIRD.	Cysts accessible to puncture with CT or US guidance	Broadens treatment options for cysts according to WHO-IWGE	Morbidity and mortality similar to surgical procedures Series with small numbers and short follow-up

Table 9. Key studies on the medical treatment of CE

Reference	Study design	Study population	Sample size (N)	Location	Objectives	Anthelminthics	Results/Conclusions
Aktan AO et al. 1996	Nonrandomized control study	Adults	70	Liver	Evaluate preoperative ABZ (3 weeks) in 2 groups: 1st group (experimental group) had ABZ for 3 weeks preoperatively, 2nd group (control) had surgery with no ABZ	ABZ	More nonviable cysts in the 1st group ($p<0.05$). ABZ demonstrated to reduce hepatic cyst viability when given for 3 weeks pre-surgery.
Di Matteo G et al. 1996	Prospective, descriptive, noncomparative study (1985-1992)	Adults (mean age 42)	95	Liver	Demonstrate that radical surgery is more effective when accompanied by benzimidazoles (MBZ) pre- and post-surgery	MBZ	Better surgical outcomes when combined with benzimidazoles (MBZ) pre- and post-surgery.
Doğru D et al. 2005	Retrospective study	Children	82	Lung	Analyse the safety and efficacy of medical treatment	MBZ *vs* ABZ	The results did not permit recommendation of a standard treatment, as the duration of treatment should be individualised for each patient.
el-Mufti M et al. 1993	Prospective, descriptive, noncomparative study	Adults	40	Multi-organ	Evaluate the efficacy of preoperative ABZ	ABZ	It is suggested that patients with uncomplicated CE should receive a preoperative course of ABZ.
Ghoshal AG et al. 2012	Retrospective study (5 years)	Adults	106	Lung	Determine the presentation, treatment (ABZ and surgery) and the outcomes of pulmonary CE	ABZ	Surgery is a safe and effective treatment for thoracic CE along with perioperative ABZ. ABZ may be considered in inoperable cases.
Larrieu E et al. 2004	Prospective cohort study (5-6 years)	Children	5745	Abdominal	Evaluate the outcomes of a screening programme (1997-2002)	ABZ	Confirmed the action of ABZ to modify the prognosis of CE. Positive effects in 76% of patients. None of the treated patients required surgery. The combination of ultrasound examination and ABZ gave promising results.
Li T et al. 2011	Prospective, descriptive, noncomparative study	Adults	49	Abdominal	Evaluate the efficacy of cyclical ABZ	ABZ	Treatment with cyclical ABZ was demonstrated to be effective in most patients with CE. ABZ for more than 18 months increased the probability of CE cure.
Mikić D et al. 1998	Retrospective study	Adults and children	119	Liver	Evaluate the efficacy of postoperative ABZ	ABZ	Surgery is essential in the management of hepatic CE. In selected cases with high surgical risk, anthelminthic treatment is important.
Nahmias J et al. 1994	Prospective, descriptive, noncomparative study (3-7 years)	Adults	68	Multi-organ	Evaluate the efficacy of long-term ABZ	ABZ	Follow-up for 3-7 years. In many patients with ABZ, CE was eradicated. In the rest progression was halted. Two patients had recurrence.
Perez Molina JA et al. 2011	Case series	Adults	7	Multi-organ	Describe the efficacy and tolerability of nitazoxanide, combined with ABZ, with or without PZQ, in patients with chronic disseminated CE	ABZ *vs* ABZ+PZQ	Combined therapy with nitazoxanide appears to be effective for disseminated CE in soft tissues, muscles and viscera, and does not appear to have a role in bone lesions.
Redzić B et al. 1995	Prospective, descriptive, noncomparative study (1989-1993)	Adults	73	Liver	Assess the efficacy of PZQ	PZQ	Anthelminthic treatment should be given pre- and post-surgery.
Salinas JL et al. 2011	Retrospective study (January 1997 - December 2007)	Adults (mean age 51±14)	27	Liver	Determine the factors associated with ABZ success in the treatment of uncomplicated hepatic CE	ABZ	In hepatic CE the success rate of prolonged ABZ is limited, it appears that 3 cycles are too few and it may be necessary to extend treatment to 6 to 12 months.
Tarnovetchi C et al. 2010	Retrospective study (2004-2009 and 2000-2009)	Children	111	Abdominal	Assess the efficacy of ABZ and surgery (partial pericystectomy)	ABZ	Relatively high rate of postoperative complications (some of them minor).

Todorov T et al. 1992	Prospective, descriptive, study	Adults and children	51 (28 MBZ, 23 ABZ)	Multi-organ	Assess the efficacy of MBZ and ABZ	MBZ or ABZ	Treatment with MBZ was successful in 28.6%, partially successful in 28.6% and unsuccessful in 42.8%. Treatment with ABZ was successful in 43.5%, partially successful in 43.5% and unsuccessful in 13.0%.
Yasawy MI et al. 1993	Case series	Adults	4	Pelvic, abdominal and thoracic	Evaluate combined treatment with ABZ + PZQ	ABZ+PZQ *vs* ABZ	The clinical response to combined treatment (ABZ + PZQ) was better and faster than with ABZ alone.
Yilmaz Y et al. 2006	Retrospective study (10 years)	Adults and children	372 (8 with urinary disease)	Liver, spleen, brain and kidney	Analysis of different nonprotocolled treatment options	ABZ	Surgical treatment (271 cases). Percutaneous drainage (99 cases). Total nephrectomy in 4 cases. ABZ given to 192 patients.

*ABZ, Albendazole; MBZ, Mebendazole; PZQ, Praziquantel.

Table 10. Key studies assessing the outcomes with a W&W approach

Reference	Country	Study design (years conducted; follow-up period)	Sample size (N)	WHO stage* and location of cyst	Results/Conclusions
Caremani M et al. 1997	Italy	Observational (1987-1996; 1-9 years on W&W)	113 with 159 cysts (W&W in 39 with 42 cysts)	W&W, according to Caremani classification: 1 type Ia, 1 IIb, 1 Va, 39 VIa-b or VII a-b. Hepatic: 107 cysts, 39 peritoneal, 2 splenic, 1 renal, 8 multiple.	Type IIb (multiple vesicles, septated), VI (heterogeneous) and VII (calcified) cysts remained in the same stage. Ia (simple) and Va (heterogeneous with ball of wool appearance) regressed to Vb and VIa, respectively.
Frider B et al. 1999	Argentina	Observational prospective epidemiological (1st survey between 1984-86 and 2nd in 1996; 10-12 years)	33 (of 59 patients diagnosed in the first epidemiological survey)	All. Only 2 patients in initial inactive stages (current CE4 and CE5). Hepatic.	21 of 28 not operated on (75%) remained asymptomatic. 7 were operated on due to symptoms. 5 (15%) underwent surgery but did not have symptoms. Only 14 of them had true ultrasound follow-up: 8 (57%) were the same size, 6 grew (1 of them (7%) >4 cm). Substantial loss to follow-up (26/59 no follow-up). Possibility of re-exposure. Does not specify the specific stage of cyst that progressed to other stages.
Larrieu E et al. 2011.	Argentina	Observational prospective epidemiological (1997-2009; follow-up 4-10 years)	157 children between 6 and 14 years. 2 cohorts: 44 patients in cohort 1 with 10-year follow-up (of them, n=16 on W&W). 29 on W&W in cohort 2.	All. In the group with 10-year follow-up on W&W: 13 cysts CE1 <3 cm, 1 CE2, 1 CE4, 1 CE5. Hepatic (except 1 splenic and 3 renal).	W&W cohort 1: complete regression in 4 (25%). 1 (6.3%) required surgery. In cysts <3 cm: 81% had positive changes (reduced size, degeneration of cyst, transforming to CE3a or calcification; 28.2% had negative changes (growth of cyst or onset of symptoms) at 44 months, 6% in those with 10-year follow-up data. Substantial loss to long-term follow-up. No detailed data on W&W in one of the cohorts.
Lissandrin R et al. 2018	Italy	Observational retrospective (1991-2017; follow-up of at least 2 years, median 52 months)	53 with 66 cysts	CE4 (n=41 cysts) and CE5 (n=25), never treated. Hepatic.	98.5% of cysts remained inactive. 1 cyst in 1 patient reactivated (1.9% of patients; 1.5% of cysts). No other complications. Very high (n=102) loss to follow-up in CE4 and CE5 before 2 years of follow-up (excluded), with data available – by telephone – from: 22 with good clinical condition, 2 died from other causes, 1 with unspecified complications. Included 37 patients from the series by Piccoli et al, with a longer follow-up time.
Moro PL et al. 1999	Peru	Observational prospective epidemiological (3 years)	28 of 37 from a previous epidemiological study. Only 8 on W&W without any type of treatment.	3 of these 8 patients had type 5 cysts according to Gharbi classification (calcified). Hepatic (except 1 pulmonary).	50% did not progress. 1 of 3 calcified progressed. 9/37 lost to follow-up. Prospective study (community/epidemiology-based) on the natural history. Very small sample size. The natural history of some cysts can lead to the degeneration and calcification of the cyst. Some calcified cysts can have viable protoscoleces.
Piccoli L et al. 2014	Italy	Observational retrospective (prospective cohort); (1994-2013; minimum follow-up 2 years)	38 with 47 cysts	CE4 (n=26 cysts) and CE5 (n=21), never treated. Hepatic.	97% (37/38) remained inactive after a median follow-up of 59 months. At 2 years, 1 CE4 reactivated to CE3b. High loss to follow-up (21/38), although information obtained after telephone contact in 11 of these 21, all asymptomatic.
Rinaldi F et al. 2014	Italy	Observational retrospective (1985-2012; median follow-up 43 months)	60 with 62 cysts (W&W without ABZ n=8; the rest with albendazole: on treatment with ABZ n=17; stopped ABZ >24 months before observation: n= 35)	CE3b. Hepatic.	In those observed >24 months after stopping ABZ, 19/35 recurred after inactivity, 13 remained in CE3b. 40% loss to follow-up if >2 years. Of these, 40% could not be contacted by telephone. Watch & wait approach may be an option to consider when there is no strict indication for surgery and follow-up is possible.
Romig T et al. 1986	Kenya	Observational prospective epidemiological (up to 18 months or until having treatment)	36 patients with 44 cysts	Not specified.	Surgery for asymptomatic cysts should be performed after an observation period to observe if there is growth of the cysts. Although 66% of the cysts grew, 34% remained stable, collapsed, or disappeared. The evolution of the cysts according to the different stages is not given.
Solomon N et al. 2017	Kenya, Morocco	Observational retrospective (untreated patients: median 208	Never treated: n=257 with 360 cysts. Treated with ABZ: n=157 with 288 cysts.	All. Not treated: 10 CL cysts, 140 CE1, 7 CE2a, 14 CE2b, 5 CE3a, 144 CE3b, 38 CE4, 2 CE5. Hepatic.	Not treated: same stage in 87% of 852 before/after observations. Progression to a more advanced stage in 11.9% (101/852 observations; 22/368 observations in CE3b transformed to CE4 or CE5, the rest remained in CE3b). 6% (7/116) of the observations in CE4 transformed

		days, max. 9787 days; treated: median 149 days)			to CE3b. In those treated with ABZ, regression from CE4 to CE3b occurred in 29/206 observations. In 70/724 observations, CE3b transformed to CE4, the rest remained in CE3b. Very heterogeneous follow-up periods, sometimes too short. In Berbers, data available on only 16 of the 126 initially diagnosed.
Stojkovic M et al. 2016	Germany	Observational prospective (1999-2016; minimum follow-up 5 years)	45 (W&W: n=30 with 46 inactive cysts with no previous medical treatment *versus* group with previous medical treatment: n=15 with 17 cysts).	CE4 and CE5 (stage reached with or without previous treatment) Hepatic (except 2 pulmonary, 1 splenic and 1 peritoneal).	Reactivations: 0 on W&W (though 20% loss to follow-up); *versus* 8/17 cysts that were previously treated (7 transformed from CE4 to CE3b). All of these were <18 months after treatment. A follow-up of 3-5 years W&W, and 5 years in those who previously received treatment may be sufficient.
Velasco-Tirado V et al. 2018	Spain	Observational retrospective (1998-2015; mean 3.4 years)	491 (W&W: n=131)	On W&W: 2 CE1 cysts, 18 CE2, 14 CE3, 22 CE4, 68 CE5. Hepatic (95%).	W&W: mean age 75 years, 70% with comorbidities. 99/131 (76%) asymptomatic, 42 (32%) with cysts ≥ 7 cm. 48 (37%) immunosuppressed. Complications on W&W: 19 (15%) superinfections, 10 (7.6%) mechanical, 3 (2.3%) both. There were 11 (8.4%) recurrences. 7 patients (5.3%) died due to CE versus 2.9% of the total cohort. W&W strategy was a factor associated with mortality, though the patients in this group were older and had more comorbidities.
Wang Y et al. 2003	China, Mongolia, Jordan	Observational retrospective (epidemiological: 1995-2000 *versus* clinical Hospital Xinjiang:1995-1998; follow-up 1-5 years)	N = 277 with 385 cysts (6 only W&W with follow-up)	All. Hepatic.	In total, 18 CE4 or CE5 cysts in the community survey and 35 in the clinical survey, mostly with no signs of progression. On W&W with no previous treatment: only 3 CE2 (1 with disappearance at 4 years, 1 remained in CE2 at 1 year), 1 CE3 (transformed to CE2 at 1 year), and 3 CE4 (2 remained in CE4 and 1 transformed to CE at 4 and 5 years, respectively).
Wang Y et al. 2006	China	Observational prospective epidemiological (1995-2003; 1-8 years)	51 (W&W: 14; 8 of them calcified).	On W&W: 2 CE2, 1 CE3a, 3 CE4, 8 CE5. Hepatic.	On W&W: 1 CE2 disappeared at 4 years, 1 CE2 unchanged at 1 year, 1 regression from CE3a to CE2 at 1 year, 1 CE4 unchanged at 1 year, 1 CE4 decreased size, and 1 CE4 reduced size and partially calcified (CE5) after 8 years. 7/8 calcified cysts disappeared, and 1 was unchanged.

Abreviations: ABZ, Albendazole; CE, cystic echinococcosis; W&W, watch and wait.
* Unless otherwise indicated.

Table 11. Studies on CE recurrence

Reference	Study design/ period	Country	Sample size (n)	Location	Percentage of patients with recurrence (%)	Treatment with anthelminthics (first episode)	Morbidity (%)	Mortality (%)	Mean follow-up (months)	Interval before recurrence (months)	Risk factors
Saidi F, 1978	Retrospective 1963-1973	Iran	106	159 liver 118 lung 67 other	11.3	ND	ND	8.3	6-36	21.5±14.8	Local leak of CE
Kapan M, 2006	Retrospective 1998-2003	Turkey	172	172 liver	4.65	Albendazole pre- and post-operative	5.8	0.58	60.5	23.4±5.3	Multiple cysts
Little JM, 1988	Retrospective 1980-1986	Australia	39	39 liver	22	No	7.6	0	0-60	30	CE rupture
Gollackner B et al, 2000	Retrospective 1949-1995	Austria	74	69 liver 3 spleen 2 other	15	50% patients albendazole/mebendazole pre- and post-operative	25.0	2.7	93.6 (24-564)	3-240	ND
El Malki HO et al, 2010	Retrospective 1990-2004	Morocco	672	672 liver	8.5	No	ND	ND	24 (10-48)	75 (40-119)	>3 hepatic cysts
Prousalidis J, 2012	Retrospective 1970-2003	Greece	584	436 liver 101 lung 21 peritoneum 12 spleen 13 other	8.7	Albendazole pre- and post-operative	27	ND	58 (48-204)	6-204	Local leak of CE Sub-total pericystectomy
Bedioui H et al, 2012	Retrospective 1996-2006	Tunisia	391	391 liver	12	ND	ND	ND	51.6	50	Rural origin Cyst > 7cm
Akyildiz H, 2009	Retrospective 1988-2006	Turkey	412	412 liver	9.2	ND	ND	ND	69.6 (12-180)	24-120	ND
Atmatzidis KS, 2005	Retrospective 1982-2001	Greece	109	97 liver 12 other	36	ND	22	2.7	144	84	Surgical technique
Meimarakis G, 2009	Retrospective 1982-2004	Germany	10	10 spleen	0	Albendazole/mebendazole	40	0	105.6	0	ND
Velasco-Tirado V et al, 2018	Retrospective 1998-2015	Spain	217	>90% at same location	11.5	ND	64	0	26.04 (41-42)	148.2±111.6	Not located in liver or lung Higher in patients treated with laparoscopic surgery Sub-total surgery

Chautems R et al, 2005	Retrospective 1980-1999	Switzerland	84	84 liver	0	15% Albendazole postoperative	37	0	103.2	0	ND

ND: No data

Table 12. The main candidate molecules for vaccines against cystic echinococcosis in intermediate hosts and their efficacy in in vivo animal models. Adapted from Pourseif et al. 2018

Vaccine	Route of administration	Host	Immune response generated
EG95	Subcutaneous	Mouse	↑IgG1, IgG2a, IgG2b, IgG3 ↑TNFα, INF_{γ}, IL-12 ↑IL-10, IL-4
	Subcutaneous	Sheep	IgG1, IgG2
	Subcutaneous	Sheep, llama	↑ Ab titre, ↓ viable cysts
EgA31	Oral	Mouse	↑ IgG1, IgG2a, IgA, ↑ INF_{γ}, IL-5, IL-2
	Intraperitoneal	Mouse	IgG1>IgG2b>IgG2a> ↑IgG3- ↑IgA- ↑IgM ↑IL-10, INF-$_{\gamma}$ ↔ IL-12, IL-6 ↑CD4+, ↓CD8+
EgDf1	Intravenous	Mouse	↑ IgG1, IgG2a, IgA
Eg14-3-3	Subcutaneous	Mouse	85% immunoprotection ↑IgG1, IgG2a, IgG2b ↑INF-$_{\gamma}$ and IL-2 ↔IL-4 and IL-10

Figure 1. Initial stages of development of *Echinococcus granulosis* in an intermediate host. **A**) Egg (30–40 µm); **B**) Oncosphere or hexacanth; **C**) Oncosphere anchored in intestinal brush border, beginning to penetrate the mucosa. Image reproduced with permission from M. Conchedda, Universitá degli Studi di Cagliari, Monserrato, Italy.

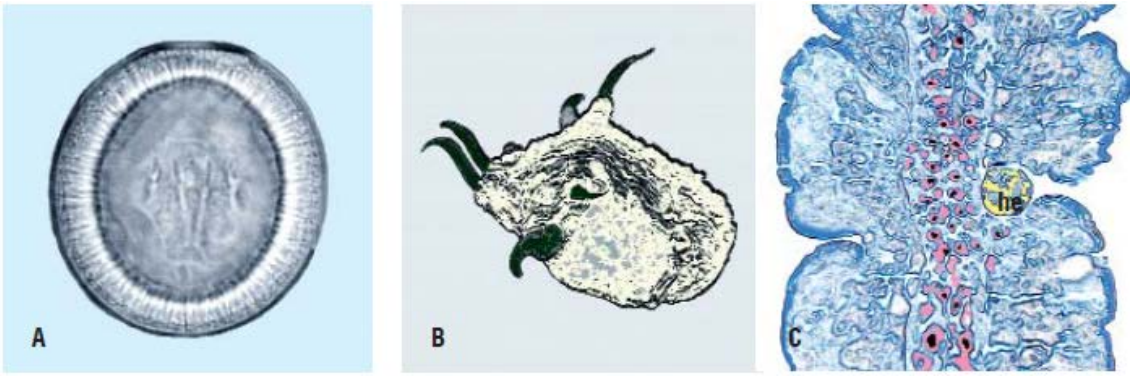


Figure 2. Hydatid cyst morphology. **A**) An intact unilocular cyst; **B**) A dissected unilocular cysts containing hydatid fluid and daughter vesicles or capsules attached to the germinal layer; **C**) Multilocular cyst with an incision showing daughter cysts inside it; **D**) Daughter cysts with cyst walls of varying thickness. Images reproduced with permission from M. Conchedda, Universitá degli Studi di Cagliari, Monserrato, Italy.

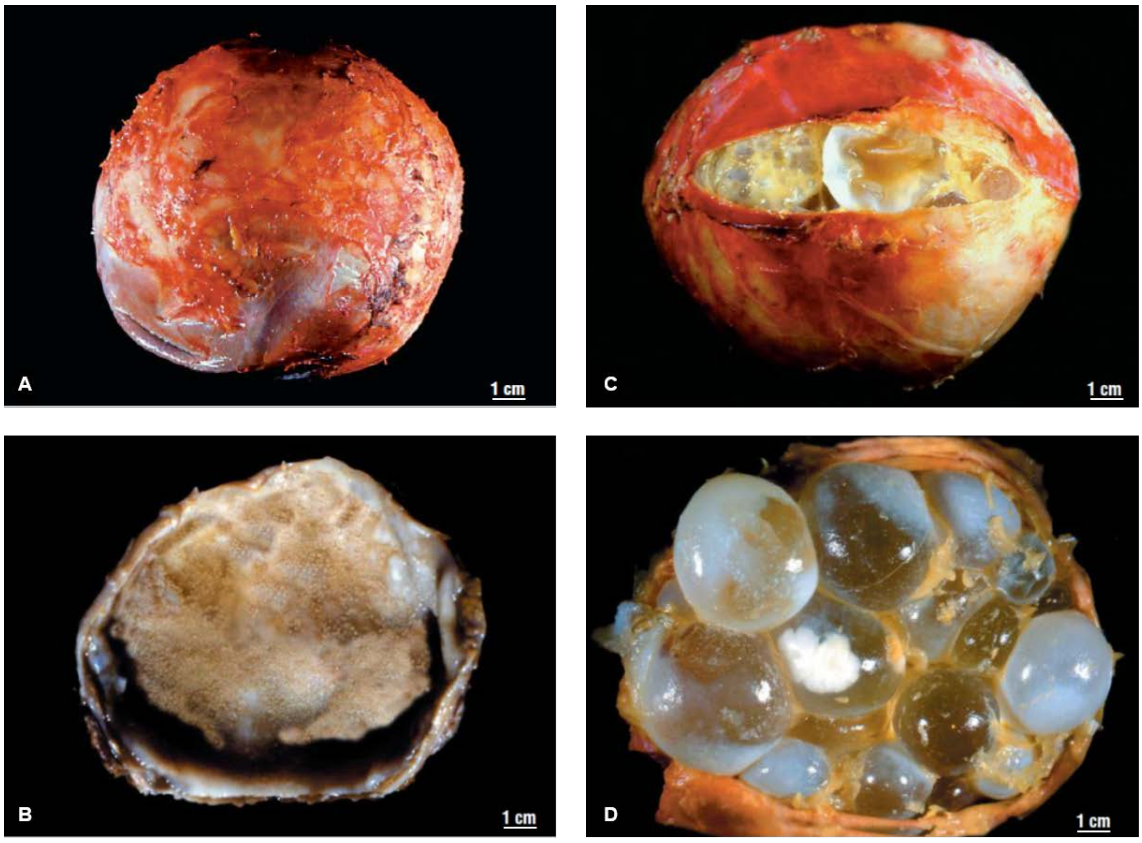


Figure 3. Human CE cases (presented as cases per 100 000 population) for the period 2000-2015 reported to the System of Mandatory Reportable Diseases of the Spanish National Network for Epidemiological Surveillance, showing the regions where the disease is considered endemic.

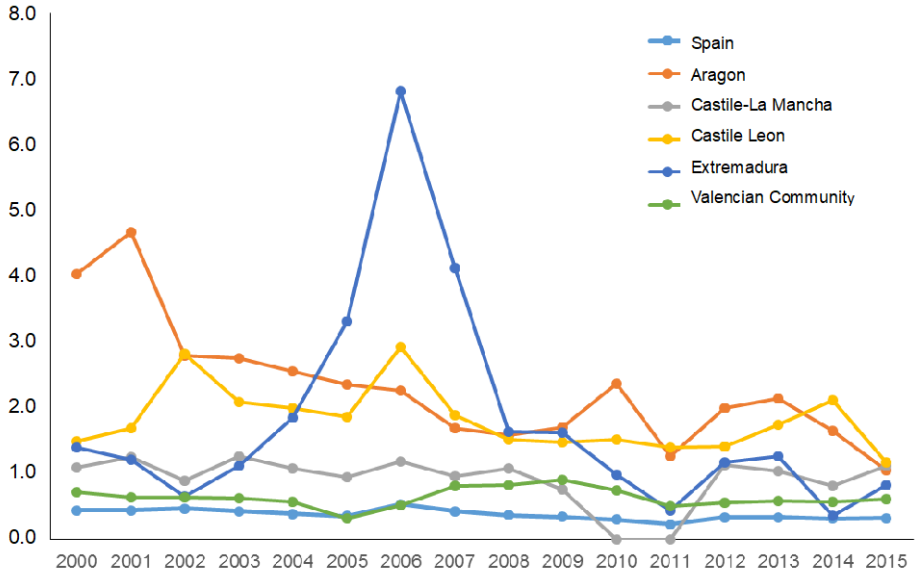


Figure 4. Prevalence of CE in livestock for the period 2005-2016. Source: European Food Safety Authority .

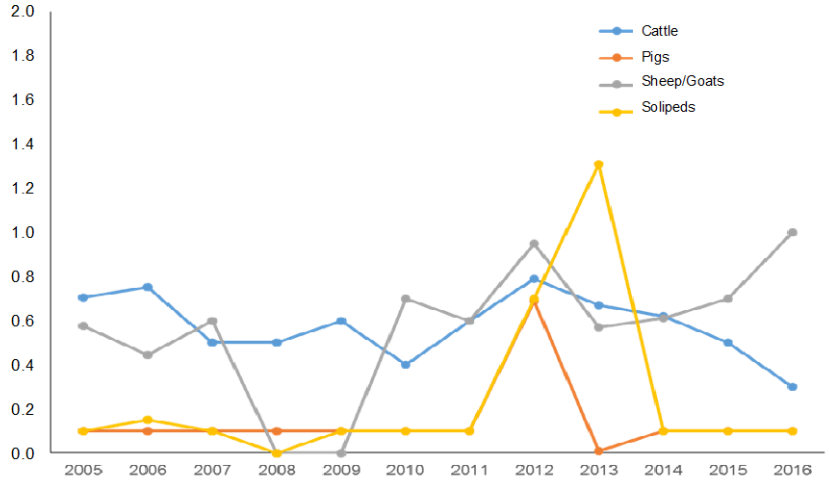


Figure 5. A comparison of the images obtained with different radiological methods. Taken from Marija Stojkovic, Kerstin Rosenberger, Hans-Ullrich Kauczor, Thomas Junghanss, Waldemar Hosch. Diagnosing and Staging of Cystic Echinococcosis: How Do CT and MRI Perform in Comparison to Ultrasound?. PLoS Negl Trop Dis. 2012;6(10):e1880.

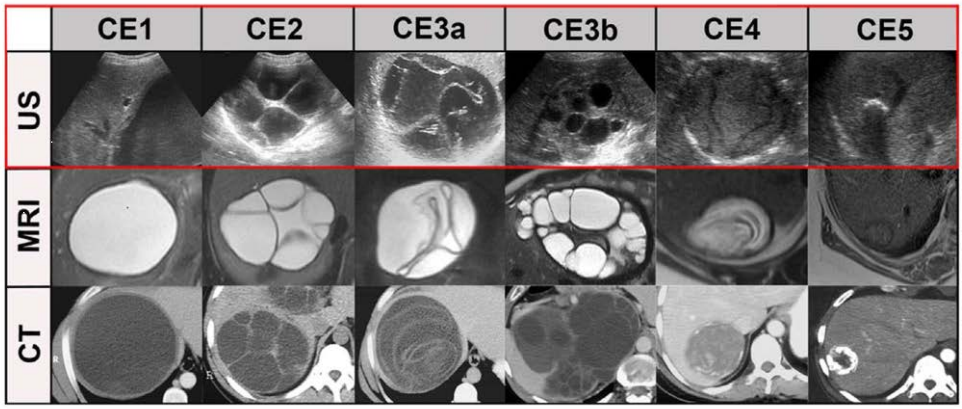


Figure 6. Overall management of CE.

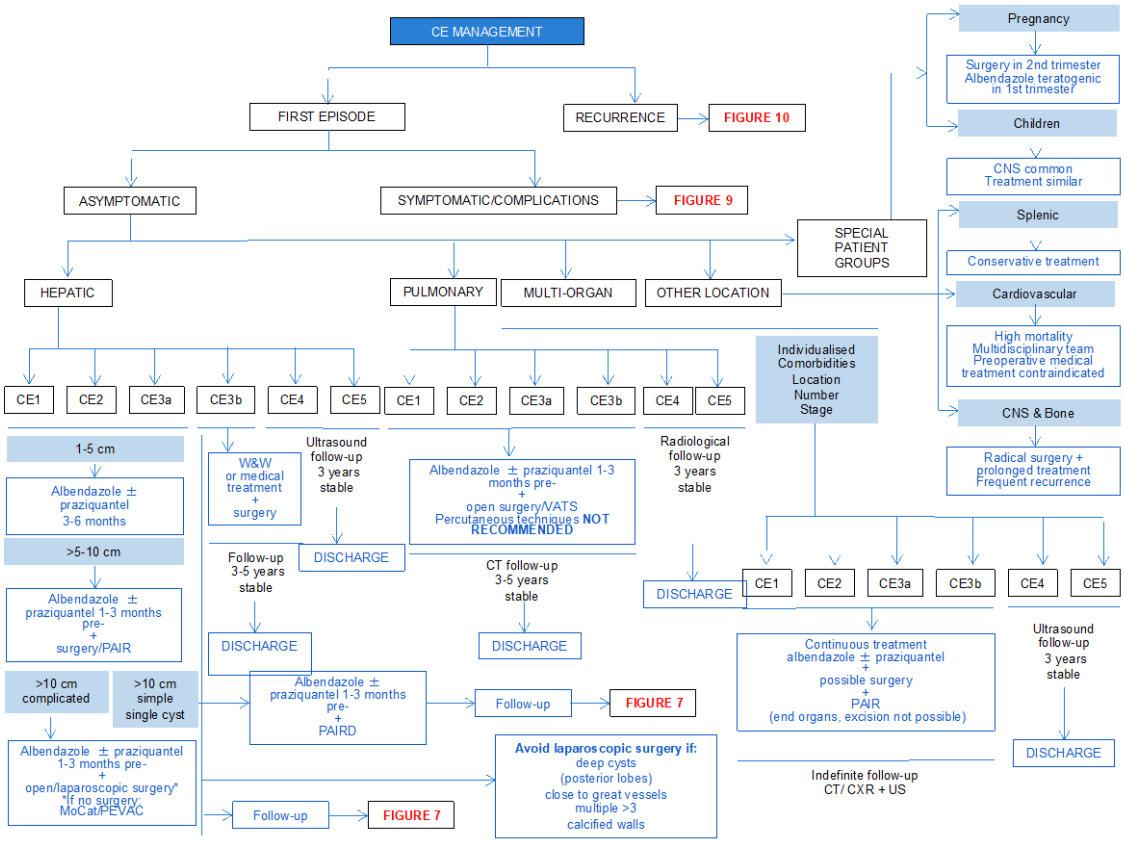


Figure 7. Follow-up schedule for patients with CE.

	1 moth				2 moth	3 moth	4 moth	5 moth	6 moth	7 moth	8 moth	9 moth	10 moth	11 moth	12 moth	1 year	2 years	3-10 years*** (annual)
Surgery																		
Percutaneous	1 Week	2 Week	3 Week	4 Week														
Pharmacological treatment only	1 Week	2 Week	3 Week	4 Week														
W&W Treatment without curative intent																		
Uncomplicated CE4 and CE5 **																		

Follow-up: clinical, radiological (ultrasound and/or CT/MR) depending on patient and cyst location, blood tests (full blood count, IgE) a and serology*.

Follow-up: radiological and blood tests.

Follow-up: clinical and radiological.

Follow-up: clinical and blood tests.

Follow-up not required.

*Only in patients with positive serology at diagnosis.
** Annual ultrasound follow-up for at least three years; if stable, discharge.
*** Very prolonged follow-up in cases of CE of the bone.

Figure 8. Thoracoabdominal CT. A) A CE3a hydatid cyst is seen in the right subhepatic space; B) Drainage using PAIR technique; C) Aspirated cyst contents; D) Follow-up CT at 48 hours. Courtesy of Dr Jose Urbano, Madrid.

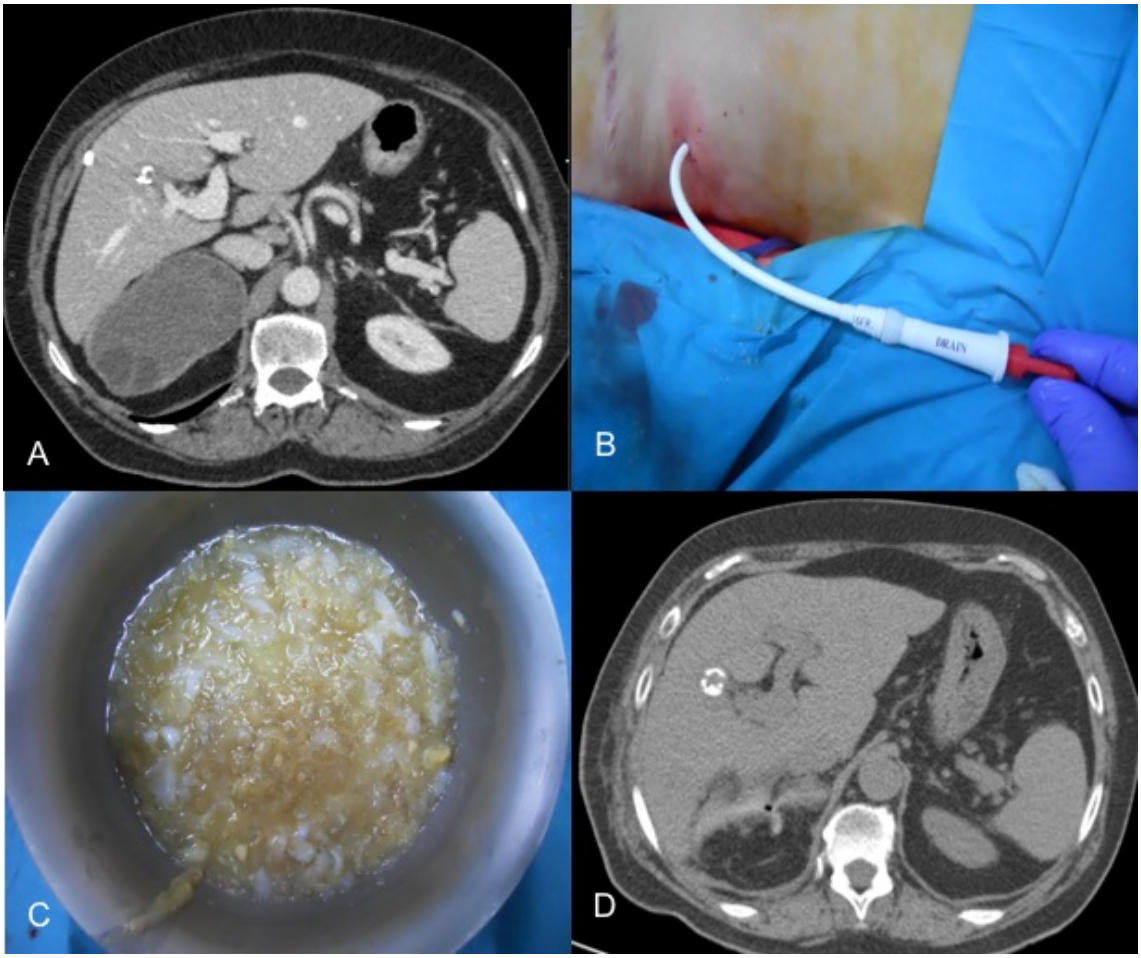


Figure 9. Management of symptomatic and/or complicated CE.

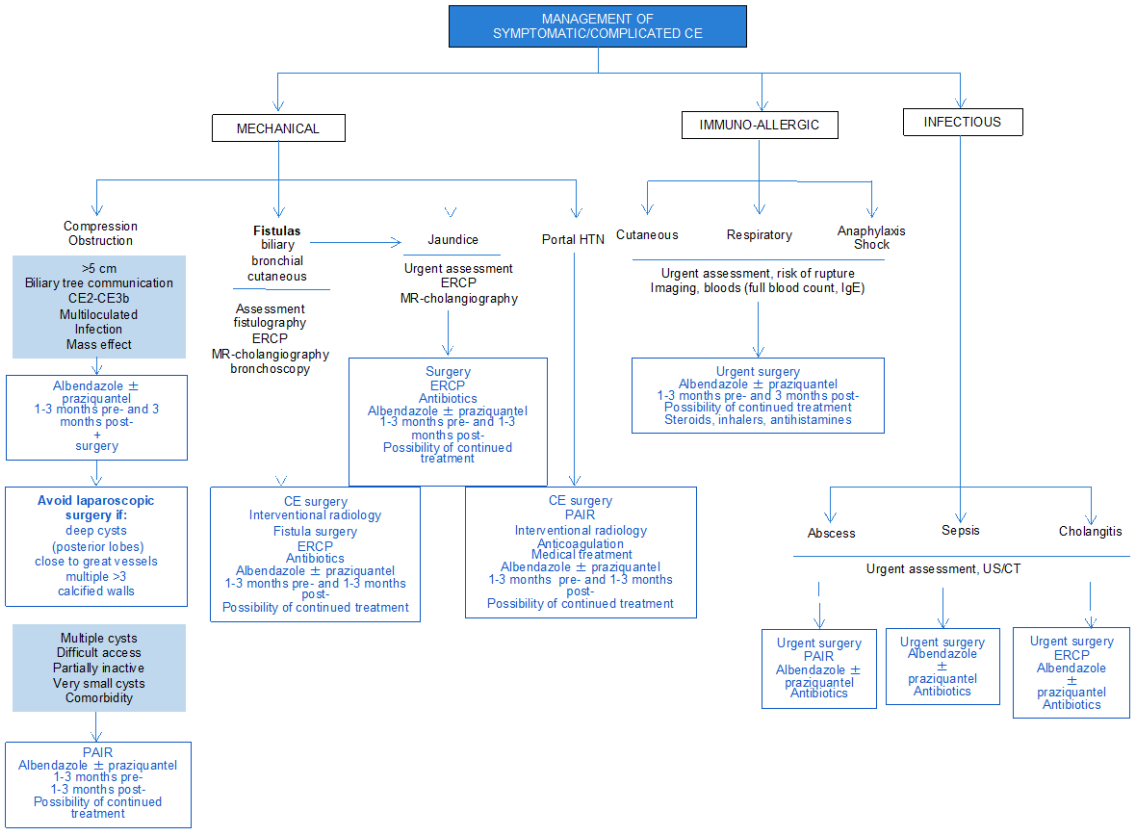


Figure 10. Management of local/distal recurrence of CE.