



# Acceptance of standardized ultrasound classification, use of albendazole, and long-term follow-up in clinical management of cystic echinococcosis: a systematic review

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## Purpose of review

Cystic echinococcosis is a chronic, complex, and neglected disease. The need for a simple classification of cyst morphology that would provide an accepted framework for scientific and clinical work on cystic echinococcosis has been addressed by two documents issued by the WHO Informal Working Group on Echinococcosis in 2003 (cyst classification) and in 2010 (Expert consensus for the diagnosis and treatment of echinococcosis).

## Recent findings

Here we evaluate the use of the WHO Informal Working Group on Echinococcosis classification of hepatic cystic echinococcosis, the acceptance by clinicians of recommendations regarding the use of albendazole, and the implementation of the long-term follow-up of patients with hepatic cystic echinococcosis in the scientific literature since the WHO Informal Working Group on Echinococcosis recommendations were issued.

## Summary

Of the publications included in our review, 71.2% did not indicate any classification, whereas 14% used the WHO Informal Working Group on Echinococcosis classification. Seventy-four percent reported the administration of peri-interventional albendazole, although less than half reported its modality, and 51% the length of patient follow-up. A joint effort is needed from the scientific community to encourage the acceptance and implementation of these three key issues in the clinical management of cystic echinococcosis.

## Keywords

albendazole, classification, cystic echinococcosis, follow-up, hydatid cyst stages, systematic review, WHO Informal Working Group on Echinococcosis

## INTRODUCTION

Cystic echinococcosis is a chronic, complex, and neglected zoonotic disease, endemic in livestock breeding areas throughout the world [1,2]. It is caused by the larval form (metacestode – hydatid cyst) of the dog tapeworm *Echinococcus granulosus*, which develops in organs and tissues of the intermediate hosts. These hosts include sheep and other livestock; however, humans can be accidental intermediate hosts. Although all organs and tissues can be affected, the cysts develop most commonly in the liver, in which they evolve over years, often in the absence of symptoms. Although the exact sequence of structural and metabolic changes during their natural history is still

unclear, longitudinal studies using ultrasound in untreated people have shown that echinococcal cysts may evolve spontaneously from unilocular

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## KEY POINTS

- Cystic echinococcosis is a chronic, complex and neglected disease with a worldwide distribution.
- Cystic echinococcosis cysts show morphological heterogeneity, which reflects different biological activities and, of great importance, correlate with different response rates to nonsurgical treatments, implying the need for a stage-specific clinical approach.
- Two documents issued by the WHO-IWGE in 2003 (cyst classification) and in 2010 (Expert Consensus for the Diagnosis and Treatment of Echinococcosis) provided a framework for scientific and clinical work on cystic echinococcosis.
- The WHO-IWGE classification of hepatic cystic echinococcosis, the indications regarding use of albendazole, and the need for a long-term follow-up of patients are three key points in clinical management of cystic echinococcosis indicated by these documents.
- This literature survey shows that these three crucial updates are still underreported, and likely ignored, indicating that a joint effort is needed, from all the scientific community, to encourage their reception and implementation.

fluid-filled cysts to forms with semi-solid content and calcified wall, passing through other morphologically different stages, including detached endocyst and presence of daughter vesicles [3]. This morphological heterogeneity reflects different states of the cysts' biological activity [4] and, of great importance, correlates with different response rates to nonsurgical treatments [5–7]. Furthermore, the rate of positive serology differs between patients with hepatic cystic echinococcosis in different stages [8]. As a consequence, there has been a need for a simple classification of cysts morphology that reflects biological changes, to provide an internationally accepted framework for clinical and scientific work on cystic echinococcosis, and for stage-specific clinical management guidelines. This has been addressed by the WHO Informal Working Group on Echinococcosis (WHO-IWGE) in 2003 when it issued the 'International classification of ultrasound images in cystic echinococcosis for application in clinical and field epidemiological settings' [9] and in 2010 with the publication of the 'Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans' [10<sup>11</sup>]. However, substantial heterogeneity in reporting cystic echinococcosis morphology and patients clinical management still exists. Recently, Chiodini and Nabarro (Symposium 'Innovation for the management of

Echinococcosis', 27–29 March 2014, Besançon, France) conducted an online survey on the treatment options that clinicians around the world would choose in five clinical cases of cystic echinococcosis. They found not only extremely heterogeneous managements of the same cases but also a worrying number of unsafe or not recommended practices.

Here we evaluate the use of the WHO-IWGE classification of hepatic cystic echinococcosis, the reception of indications regarding use of albendazole, which is still the only drug available for cystic echinococcosis, and the need for a long-term follow-up of patients with hepatic cystic echinococcosis, three key points in clinical management of cystic echinococcosis indicated by these documents, in the scientific literature on hepatic cystic echinococcosis since their publication.

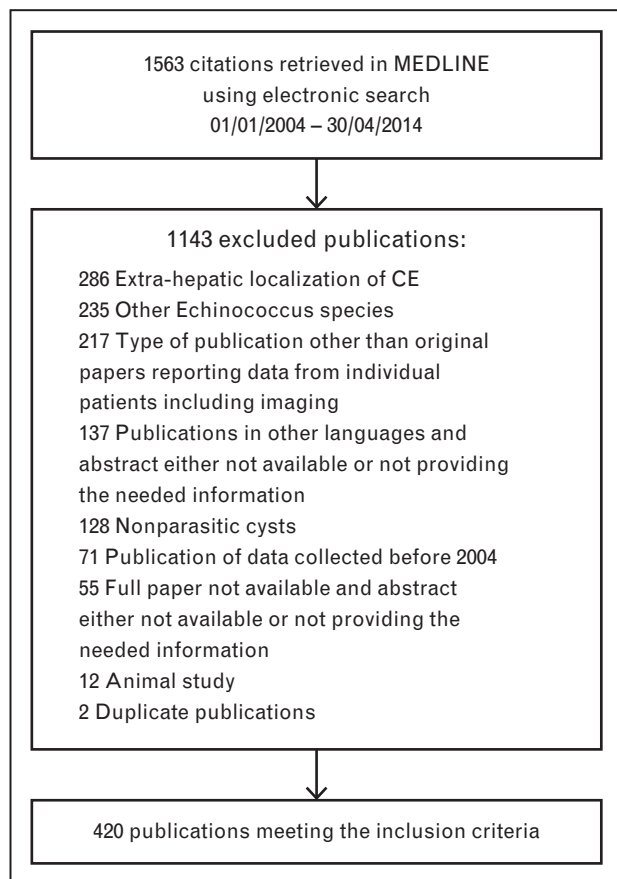
## LITERATURE SEARCH

We performed a *PubMed* (*MEDLINE*) literature search using the keywords '*Echinococcus*', '*Echinococcus granulosus*', 'cystic echinococcosis', 'cystic hydatidosis', 'hydatid disease', 'liver', 'hepatic'. We restricted the search to human studies and to the period 1 December 2010–30 April 2014 for the investigation on the use of albendazole and follow-up reporting, and to the period 1 January 2004–30 April 2014 for the investigation on the use of cystic echinococcosis classification. These dates were chosen accounting for about 1 year between the issue of the two reference WHO-IWGE documents and the implementation of their content in field and clinical practice, and therefore in publications. Original papers (case reports, case series, cohort studies, case-control studies, cross-sectional studies, clinical trials, diagnostic studies) reporting data from individual patients with hepatic cystic echinococcosis and including imaging were considered eligible. Publications on postinterventional complications not providing data on the preinterventional hepatic cystic echinococcosis lesion were excluded. Studies investigating the performances of diagnostic tools (serology or imaging) or diagnostic case reports were included only in the investigation on the use of cystic echinococcosis classification. Similarly, when data reported in papers published after December 2010 referred explicitly to patients visited before this date, only data regarding the use of the cystic echinococcosis classification were extracted. Data on albendazole use and follow-up were extracted from eligible papers published after December 2010. Publications in English, French, Spanish, Italian, or German, and publications in other languages in which the abstract in English did report the required

information, were considered eligible. The complete list of publications included in the analysis is available as supplementary material. These were 33 case-control or cohort studies, 93 case series (including  $\geq$  four patients), 239 case reports, two clinical trials, nine cross-sectional studies, and 44 diagnostic studies. The flow diagram of electronic search and selection of publications is shown in Fig. 1.

## CLASSIFICATION OF HEPATIC CYSTIC ECHINOCOCCOSIS CYSTS

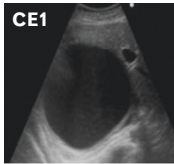
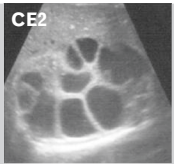




The diagnosis and clinical management of cystic echinococcosis have evolved over decades in the absence of a systematic approach [11,12]. The first widely used ultrasound classification of hepatic cystic echinococcosis cysts has been proposed by Gharbi *et al.* [13] in 1981 and has been used in the following years as the basis for a number of other classifications [14–18]. The heterogeneity of these classifications resulted in the impossibility to compare the observations and treatment protocols made by investigators in various clinical and



**FIGURE 1.** Flow diagram of electronic search and selection of publications for the evaluation of the use of WHO Informal Working Group on Echinococcosis classification.

epidemiological settings, which were not reported in a uniform manner. To overcome this problem, in 2003, the WHO-IWGE issued a standardized classification of hepatic cystic echinococcosis cysts ‘to facilitate both the uniform reporting of results from field epidemiological studies as well as in clinical studies conducted in different parts of the world’, which could be easy to use in different settings and could reflect physiopathological mechanisms of cystic echinococcosis [9] (Fig. 2). The main differences between WHO-IWGE and Gharbi classifications are the introduction of the category ‘cystic lesion’ to accommodate uniloculated cysts without pathognomonic signs of cystic echinococcosis for which further diagnostic procedures are necessary and the reversing of the order between Gharbi type II and type III cysts into cystic echinococcosis type 3 and cystic echinococcosis type 2 stages, respectively. The WHO-IWGE classification also introduced the differentiation of multiloculated cysts into two distinct categories to accommodate univocally those cysts with daughter vesicles immersed in a semi-solid matrix. This overcame the ambiguity in the classification of these cysts, which could be assigned either to type III or type IV when using the Gharbi classification. Moreover, the WHO-IWGE classification introduced the grouping of cystic echinococcosis cysts into three clinical categories: active, transitional, and inactive, reflecting the current knowledge of the natural history of cystic echinococcosis (CE). Accordingly, unilocular cysts (CE1) and multiloculated cysts with daughter vesicles without solid matrix (CE2) were classified as active cysts; cysts with detached endocysts and multiloculated cysts with daughter vesicles in a solid matrix were classified in the transitional group (CE3); and cysts with solid content with (CE5) or without (CE4) calcifications were classified as inactive cysts. CE3 cysts have been further differentiated into CE3a (with detached endocyst) and CE3b (predominantly solid with daughter vesicles) [11]. This important distinction not only reflects the difference in cyst morphology but also mirrors substantial differences in their biological activity (CE3a cysts are inactive in about half of the cases, whereas CE3b are metabolically active), and in their response to nonsurgical treatment (CE3a cysts respond well to nonsurgical treatments, whereas CE3b cysts most frequently relapse after these interventions) [4,7,11].

Our literature search of scientific papers published after January 2004 retrieved 1563 results. Of these, 420 were eligible according to inclusion criteria (Fig. 1). Overall, 299 eligible publications (71.2%) did not include any classification of the hepatic cystic echinococcosis cysts described. Of

WHO-IWGE [2003]		Gharbi [1981]	Perdomo [1995]	Caremani [1997]
		GI	P 1a, P 1b, P 1c	C Ia C Ib
Active		GIII		CIIa, CIIb
		GII	P 3	CIIIa, C IIIb
Transitional		GIV		CIV
		GV	P 4, P 4a	CVa, CVb
Inactive			P 5, P 6	CVI CVIIa, CVIIb

**FIGURE 2.** Ultrasound classification systems of cystic echinococcosis cysts.

the remaining 121 publications that included a cyst classification, 59 (48.8%) used the WHO-IWGE classification, 58 (47.9%) the Gharbi classification, and four (3.3%) other classifications (cystic echinococcosis classification of the Tunisian surgical association,  $n=1$ ; Caremani classification,  $n=1$ ; Kilani classification of hydatid disease of the liver with thoracic involvement,  $n=1$ , parasite, node, metastasis (PNM) staging,  $n=1$ ). Of note, PNM staging is used in case of alveolar echinococcosis; however, the manuscript referring to it, a case series paper from Greece, constantly referred to 'hydatid cysts of the liver', therefore assuming that *E. granulosus* was the etiological agent of the cysts.

When we investigated the use of cystic echinococcosis classifications by publication type, we found that the majority (85.4%) of case reports did not indicate any cyst classification in the case description, although absence of classification occurred in 66.7% of cross-sectional studies, 58.1% of case series, 54.5% of diagnostic studies, and 51.5% of case control/cohort studies. When publications reported a cyst classification, this was prevalently the Gharbi compared with the WHO-IWGE in case series (23.7 vs. 18.3%), case reports (7.5 vs. 6.3%), and case control/cohort studies (27.3 vs. 21.2%), whereas the reverse was found for diagnostic studies (6.8 vs. 38.6%) and cross-sectional studies (11.1 vs. 22.2%). Either WHO-IWGE or Gharbi classification were used in the two clinical trials

included in the analysis. Results are detailed in Table 1.

When we considered the results by year of publication, we found no fundamental changes over time in the proportion of publications reporting or not reporting a cystic echinococcosis classification, with less than 40% of publications actually including any cystic echinococcosis classification. Of these, the Gharbi and WHO-IWGE classifications were used in comparable proportions (Fig. 3).

### ALBENDAZOLE USE AND REPORT OF FOLLOW-UP

The clinical management of cystic echinococcosis performed by different centres is extremely heterogeneous. In the past, surgery has been the only treatment modality for cystic echinococcosis, but with the introduction of benzimidazoles from the mid-1970s [19,20] and the development of percutaneous treatment in the mid-1980s [21], new options became available and were widely used in the following decades. Furthermore, the so-called 'watch-and-wait' approach to uncomplicated inactive cysts has also been introduced on the basis of the observation that a good proportion of cysts become spontaneously inactive without any treatment and such cysts are likely to remain stable over time [11]. No 'one-size-fits-all' treatment for cystic echinococcosis exists because of the proteiform presentation and

**Table 1.** Results of the literature search

Reporting of cystic echinococcosis classification between January 2004 and April 2014 per type of publication						
	Case report	Case series	Cohort case-control	Cross-sectional	Clinical trials	Diagnostic studies
No classification	205 (85.4%)	54 (58.1%)	17 (51.5%)	6 (66.7%)	–	24 (54.5%)
WHO-IWGE	15 (6.3%)	17 (18.3%)	7 (21.2%)	2 (22.2%)	1 (50%)	17 (38.6%)
Gharbi	18 (7.5%)	22 (23.7%)	9 (27.3%)	1 (11.1%)	1 (50%)	3 (6.8%)
Other	2 (0.8%)	2 (2.2%)	–	–	–	–
Total	240	93	33	9	2	44

Reporting of albendazole usage and follow-up in publications between January 2010 and April 2014										
Treatment	N papers	N patients (hepatic cysts)	Peri-operative medical treatment			Type of albendazole administration (for publications reporting albendazole treatment)			Follow-up	
			Y	N	Not stated	Continuous	Discontinuous	Not stated	Reported (months)	Not stated
Medical treatment only	10	>29 (>29)	–	–	–	2	8	0	2 (0–16) <sup>d</sup>	8
Percutaneous treatment	13	192 (>192)	10 <sup>a</sup>	0	3	6 (1-month therapy)	0	7	10 (3–50)	3
Surgery	72	>10008 (>10008)	53	5 <sup>b</sup>	14	11	6	36	37 (0–120) <sup>d</sup>	35
Other	2 <sup>e</sup>	2 (>2)	1	1 <sup>c</sup>	0	–	–	1	1 (0)	1
Total	96 <sup>f</sup>	>10231 (>10231)	64	6	17	17	14	44	50	47

WHO-IWGE, WHO Informal Working Group on Echinococcosis.

<sup>a</sup>One publication reported the use of mebendazole.

<sup>b</sup>In one case, albendazole was not given because the cyst was classified as a type V calcified cyst; in one case, albendazole was considered too expensive.

<sup>c</sup>The patient refused any therapy.

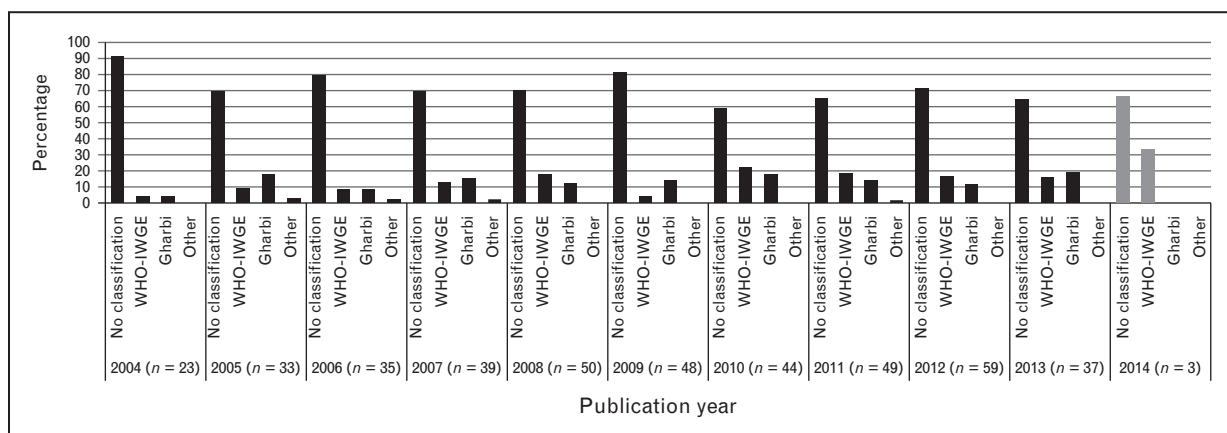
<sup>d</sup>'Zero' follow-up length refers to death or expatriation of patient immediately after treatment.

<sup>e</sup>One patient refused therapy; one patient received therapy only for an extrahepatic cyst.

<sup>f</sup>The total of publications does not match the sum of the columns because some papers contain data of patients treated in different ways.

evolution of this infection. Moreover, in the vast majority of cases, active hepatic infection is an asymptomatic disease with a spontaneous benign evolution [22–25], which poses the question whether treatment is always absolutely required. So far, no clinical trial has compared all the different management modalities, and the optimal length of

albendazole treatment is still undefined. This is mostly because of the chronicity of the disease, which requires years long follow-up to appropriately ascertain relapse rates, and to the relative low prevalence of diagnosed infection even in endemic areas, which makes very difficult the design and implementation of prospective clinical trials. However,



**FIGURE 3.** Use of cystic echinococcosis classification by year of publication. WHO-IWGE, WHO Informal Working Group on Echinococcosis.



the accumulated knowledge based on single-centre experiences and on the few clinical trials comparing at least some of these treatment modalities [22,26–28] supports a stage-specific approach to hepatic cystic echinococcosis [10<sup>11</sup>]. The WHO-IWGE expert consensus for the diagnosis and treatment of echinococcosis in humans, issued in 2010, indicated several stage-specific options for the management of hepatic cystic echinococcosis, although it also acknowledged that the choice of treatment for individual patients depends on a number of variables, including not only cyst stage but also other characteristics of the cyst, the patient, and the centre where the patient is visited [10<sup>11</sup>]. Additional important advancements introduced with this document concern the agreement on the use of benzimidazoles. These should be used as a peri-operative adjuvant to prevent iatrogenic seeding leading to local or systemic/extrahepatic secondary echinococcosis. Furthermore, when used as the only treatment, they should be administered continuously, without the 2-week interruption between monthly cycles recommended previously. Moreover, the need for a long-term follow-up of cystic echinococcosis patients was also stated, although a definite length in years could not be provided.

Our literature search of scientific papers published after January 2010 retrieved 455 results, and, of these, 96 (69 case reports, 19 cohort/case–control studies, eight case series) were eligible according to inclusion criteria. Of the 13 publications describing percutaneous treatment for hepatic cystic echinococcosis, nine indicated the use of peri-operative albendazole for 1 month after the procedure, one used mebendazole, but the length of therapy was not reported, and three did not report any use of adjuvant medical treatment. Of the 72 papers describing surgery, 14 did not report any use of prophylaxis, whereas in five cases, it was stated that albendazole was not given (in one case because the cyst was a type V cyst; in one case because of the cost of albendazole; and in three cases, no explanation for such a choice was provided). Ten reports used only medical therapy with benzimidazoles. When albendazole was given as peri-surgical or as only therapeutic intervention, 20.6% reported a continuous administration, 22.2% reported a discontinuous administration, and 57.1% did not mention the administration modality. Follow-up was described in half of publications, with a range of 0–120 months. Results are summarized in Table 1.

## LIMITATIONS

The limitations of this study comprise the inclusion of works: first, indexed in *MEDLINE* database only;

second, accessible in English, French, Spanish, Italian, and German; third, without a quality assessment step; and fourth, the restriction to liver echinococcosis. Concerning this last point, however, the focus on hepatic cystic echinococcosis is justified by the fact that both WHO-IWGE classification and Expert Consensus documents mainly refer to this location. It is therefore likely that the inclusion of publications on extra-hepatic cystic echinococcosis might have brought different results. It could be also argued that the inclusion of case reports may be a source of bias because case reports by definition concern ‘unusual or rare features’ as well as ‘unexpected events’. Therefore, it may be more likely that only cases from centres with little experience with hepatic cystic echinococcosis, or the description of only peculiar aspects of hepatic cystic echinococcosis, rather than the ‘routine’ experience of reference centres, would be published in this format. As a consequence of these considerations and of the exclusion of scientific literature in other languages, it is possible that our results may underestimate the use of WHO-IWGE classification and the reception of the Expert Consensus indications.

## CONCLUSION

The use of a standardized and internationally accepted classification of cystic echinococcosis cysts is not just an academic exercise, given that a correlation exists between cyst morphology and important aspects of the disease, such as cyst biological activity, response to treatment, and immunity. Therefore, diagnostic and therapeutic interventions need to be evaluated taking into account cyst stages, and a univocal cyst classification is crucial to allow comparisons between scientific works. Nonetheless, we found that the majority of papers published in the past 10 years, which included data from patients with hepatic cystic echinococcosis, did not report any cyst classification. This is particularly striking when considering serodiagnostic studies, in which the omission of accounting for cyst stage (occurring in 55.9% of publications of this type) may lead to very weak conclusions on tests performances. The majority of publications included in our review were case studies. The absence of reporting of cyst classification was somehow expected in this type of publication, especially in surgical case reports. However, we also found a rather low acceptance of indications on the use of albendazole, as advocated in the WHO-IWGE expert consensus on diagnosis and treatment of echinococcosis in 2010, and lack of reporting on follow-up.

In conclusion, this literature survey shows that three crucial updates introduced in international

documents concerning the clinical management of cystic echinococcosis are still ignored by many. A joint effort is needed from the scientific community, including not only scientists but also journal reviewers, to encourage their use and implementation. In addition, prospective trials are strongly needed to clarify the most suitable and cost-effective approach for every cyst stage, an approach so far evaluated only in the light of expert opinion and retrospective data from case series.

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### Conflicts of interest

*None declared.*

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- of special interest
- of outstanding interest

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