Current Management of Cystic Echinococcosis: A Survey of Specialist Practice

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Background. Cystic echinococcosis (CE) is a significant public health problem worldwide. However, there remains a dearth of evidence guiding treatment in various stages of CE. The 2010 World Health Organization (WHO) Informal Working Group on Echinococcosis (WHO IWGE) guidance is thus based on expert consensus rather than a good evidence base. This study aims to describe the way clinicians worldwide manage CE and to establish whether clinicians follow WHO IWGE guidance.

Methods. Using the online surveying tool SurveyMonkey, a questionnaire was produced detailing 5 clinical cases. Clinicians treating CE were identified and asked how to manage each case through tick-box and short-answer questions.

Results. The results showed great variation in practice worldwide. There are practices in common use that are known to be ineffectual, including puncture, aspiration, injection, reaspiration procedures on WHO type 2 cysts, or outdated, including interrupted, rather than continuous, courses of albendazole. A number of unsafe practices were identified such as using scolicidal agents in cysts communicating with the biliary tree and short-course medical therapy for disseminated disease. Most clinicians do not follow the WHO IWGE guidance, but the reasons for this are unclear.

Conclusions. Management of CE varies greatly worldwide. There are key areas of CE for which there is no evidence on which to base guidelines, and randomized controlled trials are needed together with a well-designed international registry to collect data. Further work is required to establish why clinicians do not follow the IWGE guidance, together with better dissemination of future guidance.

Keywords. cystic echinococcosis; hydatid; current management; WHO.

Cystic echinococcosis (CE) is a zoonotic infection caused by the metacestode stage of *Echinococcus granulosus*. It is a significant public health problem worldwide, particularly in pastoral communities. The World Health Organization (WHO) estimates that >1 million people are infected with the loss of at least 285 000 disability-adjusted life-years [1]. Prevalence may be underestimated due to the rural nature of the disease and lack of systematic population surveys in some endemic regions.

In 2003, the WHO Informal Working Group on Echinococcosis (WHO-IWGE) published an ultrasound classification that follows a cyst's natural history from simple and undifferentiated through a transitional stage to inactive and calcified [2]. The application of a uniform classification system aimed to standardize diagnosis and allow studies evaluating the efficacy and safety of therapeutic regimens. Despite this, there remains a dearth of evidence guiding treatment and few clinical trials.

In 2010, the same group updated previous guidance on CE [3] and produced the "Expert Consensus for the Diagnosis and Treatment of Cystic and Alveolar Echinococcosis in Humans" [4]. This offers stage- and organ-specific guidance for treatment (Table 1). Due to lack of evidence in many areas, it is based on the opinions of respected authorities; interventions achieve a recommendation and evidence grade B3, indicating moderate evidence to support recommendations based on opinions

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Table 1. Summary of World Health Organization Ultrasound Classification of Cysts and Recommended Management of Hepatic Cystic Echinococcosis

Cyst Type	Stage	Imaging Features	Expert Consensus Recommendation
CE1	Active	Unilocular simple cyst	<5 cm ABZ >5 cm PAIR and ABZ
CE2	Active	Multivesicular, multiseptate cyst Daughter cysts partly or totally fill mother cyst. "Wheel" or "honeycomb" appearance	Surgery and ABZ or OPC and ABZ
CE3a	Transitional	Detached laminated membrane floats in cyst (water lily sign) Anechoic content	<5 cm ABZ >5 cm PAIR and ABZ
CE3b	Transitional	Complex mass. Mother cyst contains both anechoic daughter cysts and echoic areas of disrupted membranes or degenerating daughter cysts	Surgery and ABZ or OPC and ABZ
CE4	Inactive	Heterogeneous hypoechoic cyst without daughter cysts Degenerating membranes may appear like "ball of wool"	Watch and wait
CE5	Inactive	Thick calcified wall	Watch and wait

Adapted from the 2010 World Health Organization Informal Working Group on Echinococcosis (WHO-IWGE) International classification of ultrasound images in CE [2] and the WHO-IWGE Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans [4].

Abbreviations: ABZ, albendazole; CE, cystic echinococcosis; OPC, other percutaneous procedure; PAIR, puncture, aspiration, injection, reaspiration.

from respected authorities or descriptive studies. As a result, and due to the wide geographical distribution and rural nature of the disease, we may expect considerable variation in management of CE worldwide. This study aims to describe this and to establish whether clinicians follow Expert Consensus guidance.

METHODS

Using the online surveying tool SurveyMonkey, a questionnaire was produced detailing 5 clinical cases, including history, examination, serological results, and imaging (Figure 1). These cases were those of patients seen at the Hospital for Tropical Diseases

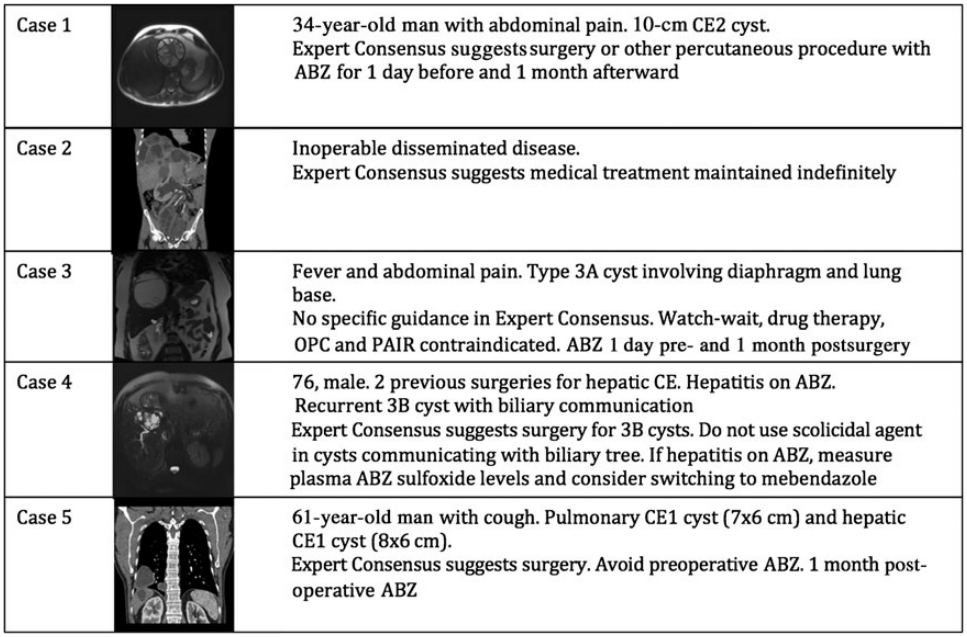

Figure 1. A summary of the clinical cases used in this survey and World Health Organization Expert Consensus guidance on their management. Abbreviations: ABZ, albendazole; CE, cystic echinococcosis; OPC, other percutaneous procedure; PAIR, puncture, aspiration, injection, reaspiration.

in London. Written consent was obtained from each patient for the use of their history and imaging, and all data were anonymized. Clinicians were asked how they would manage each case through a series of tick boxes and short answer questions.

Survey recipients were identified in 3 ways. PubMed was searched using the terms *cystic echinococcosis*, *hydatid*, and *Echinococcus granulosus* to identify people who had published on CE within the last 10 years. Infectious disease and parasitology societies worldwide were approached for contact details of members with an interest in CE, and members of both the International Association of Hydatidology (IAH) and WHO-IWGE were contacted directly. Once identified, recipients were emailed a summary detailing the aims and methods of the survey and an email link to the SurveyMonkey site.

The ethics committee at University College London Hospitals agreed that ethics committee approval was not necessary for this project.

RESULTS

Four hundred twenty-seven recipients were contacted. Sixty-three replies were received, but 22 were discounted as the recipient did not clinically manage CE patients or had seen <3 CE cases within the last year. Forty-one replies were received from clinicians in 23 countries on 5 continents; 26 came from highly endemic countries, 9 from endemic countries, and 2 from countries with sporadic transmission (Figures 2 and 3). Nineteen were physicians, 18 surgeons. The respondents included 2 of the 3 lead writers of the IWGE Expert Consensus and 6 members of the IAH.

Respondents managed between 3 and 250 cases of CE each year. Clinicians in highly endemic countries managed more patients than those in endemic countries (20.8 vs 6.1; $P = .04$), surgeons and nonsurgeons managed similar numbers of patients ($P = .48$).

The first patient (case 1) was a young man with a 9-cm WHO CE2 hepatic cyst. The Expert Consensus recommendation for a type 2 cyst is surgery or other percutaneous procedure (OPC), both with albendazole cover [4]. OPC is an umbrella term for a diverse group of interventions that remove the endocyst and daughter cysts using large-bore catheters or cutting devices and aspiration equipment. Among respondents, 62.5% (n = 25) recommended surgery, 12.5% (n = 5) recommended PAIR (puncture, aspiration, injection, reaspiration), and 10% (n = 4) recommended OPC (Table 2). Most clinicians used albendazole monotherapy (Table 3). The Expert Consensus suggests that

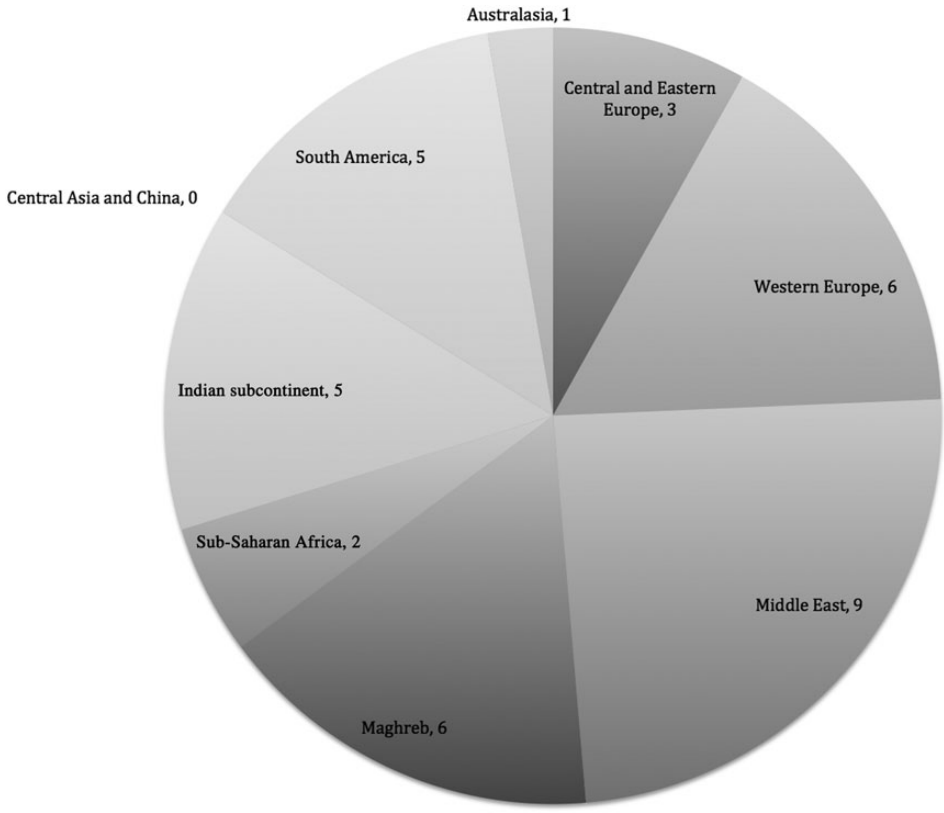

Figure 2. Region of origin of clinicians completing the survey. 4 respondents did not disclose their region of origin.

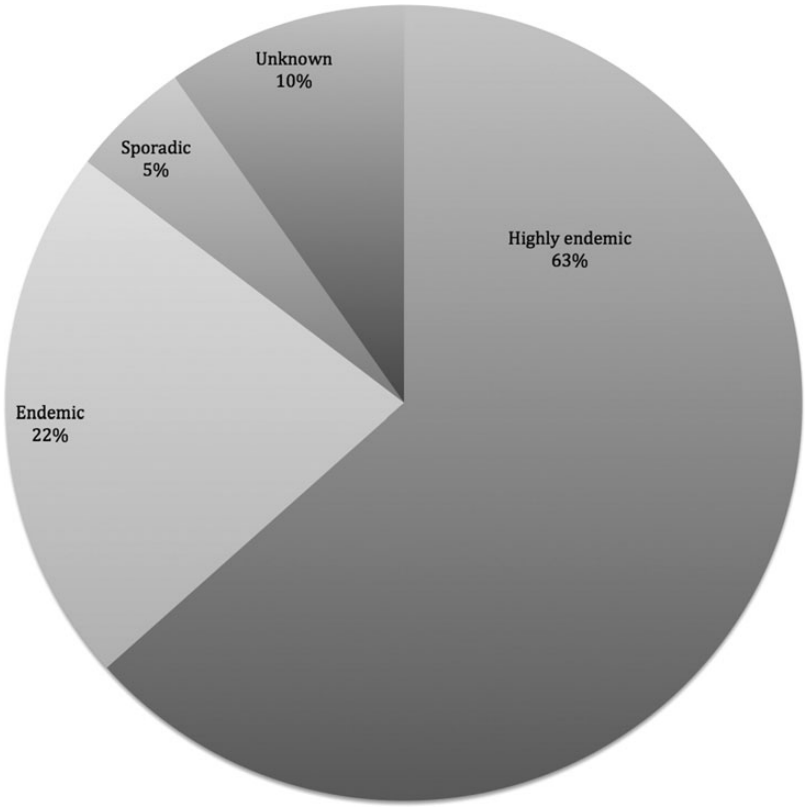

Figure 3. Origins of clinicians completing the survey classified by regions of endemicity. Replies were received from World Health Organization–classified highly endemic countries including Argentina, Iran, Iraq, Italy, Lebanon, Libya, Peru, Portugal, Russia, Sudan, Tunisia, and Turkey. Some replies were received from endemic countries including Australia, Bhutan, France, India, Pakistan, Poland, and Saudi Arabia. A few replies were received from countries with sporadic transmission, including Germany and the Netherlands.

albendazole be given for 1 day before and 1 month after the procedure [4]. The median length of treatment before the procedure was 10 days (range, 0–6 months). The median length of treatment after the procedure was 8 weeks (range, 0.5–12 months).

The second patient (case 2) was a 33-year-old man with inoperable disseminated abdominopelvic and pulmonary CE. There is no evidence base for treatment of disseminated disease, but the Expert Consensus suggests that medical treatment should be " 'maintained for an indefinite length of time" and "discontinuation is often associated with recurrence" [4]. An increased proportion of clinicians used albendazole-praziquantel combination therapy compared with case 1 (Table 3). The length of drug treatment ranged from 6 weeks to lifelong, with a mean of 55 weeks (Table 4). All respondents who treated for <3 months came from low- or middle-income countries. Mean treatment duration ranged from 66 weeks for clinicians in endemic areas to 45 weeks for those in highly endemic areas ($P = .230$). Surgeons and nonsurgeons treated for a similar time (mean duration, 51 vs 58 weeks; $P = .65$; Table 4). Follow-up ranged from 2 years to lifelong, with 45% (n = 15) requesting indefinite follow-up (median, 12.5 years). All clinicians followed patients with imaging and clinical review, and 36% performed CE serology.

The third patient (case 3) was a 58-year-old woman with a WHO CE3A cyst involving the diaphragm and lung bases. There is no guidance in the Expert Consensus with regard to complex abdominopulmonary cysts. However, medical therapy is unlikely to work in large cysts, and PAIR procedures are contraindicated in pulmonary cysts due to the risk of rupture into the lung or thoracic cavity [4]. Seventy-four percent (n = 25) advised surgery, 21% (n = 7) PAIR, and 6% (n = 2) OPC (Table 2). Most clinicians advised albendazole monotherapy; preprocedure treatment ranged from no treatment to 6 months, whereas postprocedure treatment ranged from 1 month to 1 year.

The fourth patient (case 4) was a 76-year-old man with multiple comorbidities, 2 previous operations for CE, and a previous albendazole-induced hepatitis. On this occasion, he presented with abdominal pain and eosinophilia. Magnetic resonance cholangiopancreatography showed a WHO CE3B hepatic cyst; endoscopic retrograde cholangiopancreatography confirmed a communication between the cyst and biliary tree. The Expert Consensus recommends surgery or OPC for

Table 2. Modes of Treatment for Each Case

Treatment Mode	All Clinicians, % Used (No.)	Highly Endemic vs Endemic		Surgeons vs Nonsurgeons	
		Highly Endemic, % Used (No.)	Endemic, % Used (No.)	Surgeons, % Used (No.)	Nonsurgeons, % Used (No.)
Case 1					
Watch-wait	2.5 (1)	3.8 (1)	0	0	5 (1)
Drug	0	0	0	0	0
PAIR	12.5 (5)	11.5 (3)	22.2 (2)	5 (1)	25 (4)
OPC	10 (4)	15.3 (4)	0	5 (1)	15 (3)
Surgery	62.5 (25)	53.8 (14)	77.7 (7)	75 (15)	50 (10)
Case 3					
Watch-wait	0	0	0	0	0
Drug	0	0	0	0	0
PAIR	20.6 (7)	18.2 (4)	25 (2)	11.1 (2)	31.3 (5)
OPC	5.9 (2)	9.1 (2)	0	0	12.5 (2)
Surgery	73.5 (25)	72.7 (16)	75 (6)	88.9 (16)	56.3 (9)
Case 4					
Watch-wait	3.6 (1)	5.88 (1)	0	6.7 (1)	0
Drug	10.7 (3)	0	28.6 (2)	13.3 (2)	8.3 (1)
PAIR	0	0	0	0	0
OPC	14.3 (4)	17.6 (3)	14.3 (1)	13.3 (2)	16.6 (2)
Surgery	67.9 (19)	76.5 (13)	57.1 (4)	66.7 (10)	75 (9)
Case 5					
Watch-wait	0	0	0	0	0
Drug therapy	10.7 (3)	5.6 (1)	14.3 (1)	6.7 (1)	14.3 (2)
PAIR	7.1 (2)	5.6 (1)	14.3 (1)	13.3 (2)	0
OPC	0	0	0	0	0
Surgery	82 (23)	88.9 (16)	71.4 (5)	80 (12)	84.6 (11)

Clinicians are divided into surgeons and nonsurgeons. Clinicians are also divided into those from highly endemic areas and endemic areas. Note that clinicians from areas of sporadic transmission or whose area of origin was not disclosed are not represented in this table. Case 2 is not included in this table, as clinicians were advised that the case was inoperable and so all undertook medical therapy.

Abbreviations: OPC, other percutaneous procedure; PAIR, puncture, aspiration, injection, reaspiration.

CE3B cysts. Scolicidal use is contraindicated in cysts communicating with the biliary tree due to the risk of chemical sclerosing cholangitis. In cases where albendazole is not tolerated, the Expert Consensus suggests monitoring plasma albendazole sulfoxide levels and then reducing the dose of albendazole or switching to mebendazole [4]. Sixty-eight percent (n = 19) of respondents advised surgery, 14% (n = 4) OPC, and 11% (n = 3) drug therapy alone (Table 2). Most clinicians still recommended albendazole monotherapy (48%), but 14% started at a lower dose than 400 mg twice daily. Increasing numbers used mebendazole (8%), praziquantel (12%), or no drug at all (24%), given the previous hepatitis (Table 3). Of concern, 55% (n = 15) recommended using a scolicide despite the documented communication between the cyst and the biliary tree.

Table 3. Difference in Drug Use Between Cases

Drug	Case 1, % Used (No.)	Case 2, % Used (No.)	Case 4, % Used (No.)
Albendazole alone	75 (27)	64.7 (22)	48 (12)
Mebendazole alone	2.8 (1)	2.9 (1)	8 (2)
Albendazole-praziquantel combination therapy	11.1 (4)	29.4 (10)	8 (2)
Praziquantel alone	0	0	12 (3)
No drug	11.1 (4)	0	24 (6)

The fifth patient (case 5) presented with a cough to his local hospital. Chest radiograph showed 2 cystic lesions in the lung. Aspiration prior to referral to The Hospital for Tropical Diseases found protoscoleces. The Expert Consensus recommends surgery for pulmonary cysts and advises avoiding preoperative albendazole due to risk of cyst rupture. PAIR procedures are contraindicated in pulmonary cysts [4]. Eighty-two percent (n = 23) advised surgery, 68% (n = 15) of whom recommended albendazole preoperatively (range, 4 hours to 6 months preoperatively; median, 1 week). Postoperative treatment ranged from 1 to 6 months (median, 3 months). Eleven percent (n = 3) of clinicians

Table 4. Length of Pre- and Postprocedure Benzimidazole

Length of BMZ	All Clinicians, Mean No.	Highly Endemic/Endemic, Mean No. (*P* Value)	Surgeons/Nonsurgeons, Mean No. (*P* Value)
Total (case 1, 3, 4, 5)			
Length of preprocedure BMZ, wk	2.56	1.4/3.7 (.03)	3.2/1.6 (.17)
Length of postprocedure BMZ, wk	11.5	12.1/10.7 (.54)	12.5/10.1 (.59)
Case 2			
Length of BMZ, wk	54.5	45/65.5 (.230)	51.1/57.9 (.65)

Cases 1, 3, 4, and 5 have been combined as the World Health Organization Expert Consensus suggests the same treatment length for each (1 day before and 1 month after the procedure). Results for case 2 are given independently, as the Expert Consensus recommendation is for "indefinite" BMZ.

Abbreviation: BMZ, benzimidazole.

advised treating this patient with drug therapy alone, all of whom advocated at least 6 months of albendazole monotherapy. Seven percent (n = 2) recommended a PAIR procedure (Table 2).

In all cases except case 4, albendazole was used at the recommended dose range of 10–15 mg/kg/day or 400 mg twice daily in agreement with the Expert Consensus. Fifteen percent (n = 6) of clinicians from 6 countries used interrupted courses of albendazole in at least 1 of the 5 cases. All came from endemic areas; 67% (n = 4) came from highly endemic areas.

Mebendazole was used by only 2 clinicians in the survey; 1 used the standard dose of 50 mg/kg/day, and the other used 15 mg/kg/day [4].

Praziquantel was used in at least 1 case by 29% of clinicians. These clinicians were spread throughout the world, including 2 each from Western Europe, South America, sub-Saharan Africa, and the Indian subcontinent and 1 each from Eastern Europe and the Middle East. The dose of praziquantel varied greatly; regimens used included 100 mg twice daily, 40 mg/kg once a week, 50 mg/kg/day, and a single dose of 2400 mg. The suggested dose in the Expert Consensus is 40 mg/kg once a week.

Length of drug treatment did not differ significantly between surgeons and nonsurgeons. In endemic areas, clinicians give more preprocedure treatment than in highly endemic areas (mean, 1.4 vs 3.7 weeks; $P = .03$). There was no difference in postprocedure treatment (Table 4).

Surgeons chose surgery 80% of the time, whereas nonsurgeons chose surgery only 62% of the time, relying more heavily on PAIR (4.4% vs 16%) and OPCs (7.3% vs 11.3%). This study was not designed to assess surgical technique, but open surgery is clearly preferred over laparoscopic techniques (93% vs 4.4% of procedures).

DISCUSSION

This survey shows great variation in management of CE worldwide. It highlights a number of concerning practices, broadly split into 3 groups.

First, there are practices known to be ineffectual, for instance, PAIR procedures on WHO CE2 cysts. The relapse rate is between 48% and 59% due to persistence of daughter cysts not punctured during the procedure [5, 6]. Surgery or OPC, as advocated by the Expert Consensus [4], offers a better chance of cure.

A number of clinicians continue to use albendazole in cyclic interrupted courses. When first introduced, the manufacturer advised cycles of 28 days of albendazole followed by 14 days drug-free, repeated 3 times, due to limited long-term safety data. The 1996 WHO guidelines suggested that albendazole was safe for continuous long-term use, and Franchi et al's study of 448 patients later confirmed this [7]. There are no trials that compare continuous albendazole with interrupted courses but, as albendazole blocks glucose uptake by the parasite, an interrupted course would allow the parasite to restock, thus reducing drug efficacy.

Six clinicians from 6 countries recommended interrupted courses; 4 were from low- and middle-income countries. These clinicians advised 3–6 cycles of treatment and so were giving a higher total dose than the Expert Consensus guidance of 1 day before and 1 month after a surgical procedure [4]. This suggests that the decision is not financially motivated. Interestingly, only 1 of 5 respondents from highly endemic Tunisia and 1 in 3 from Turkey used interrupted courses. This patchy distribution suggests this practice might be due to limited access to IWGE guidance.

Second, there are practices in common use that are known to be unsafe. Of greatest concern is the injection of scolicidal agents into cysts continuous with the biliary tree. At least 40 cases of chemical sclerosing cholangitis are described in such patients [8], including 1 patient who subsequently required a liver transplant [9]. The true incidence of this complication is difficult to estimate without a systematic data registry due to reporting bias. Most clinicians use hypertonic sodium chloride as their scolicidal agent, as it is perceived to be lower risk than other scolicides. However, there have been documented cases in humans [10] and in a rabbit model [11].

The use of short-course albendazole in disseminated abdominopelvic disease is also concerning. The Expert Consensus suggests, in inoperable cases, that "medical treatment alone with albendazole maintained for an indefinite length of time is the only option available in most cases" [4]. There is no evidence base to guide length of treatment, and most case reports are seriously flawed by short or undisclosed length of follow-up [12, 13]. All clinicians who treated for <3 months were from lower- and middle-income countries; hence, short-course therapy may be due to financial constraints.

Third, there are areas in which there is no evidence to guide clinicians in their management; for example, the length of albendazole treatment before and after procedures. The Expert Consensus states that the length of albendazole "usually ranges from 1 day before to 1 month after surgery" [4] but does not qualify the origin of this statement. Certainly this is not usual in our center and, in this survey, the median length of treatment exceeded this guidance in every case. Two members of the Expert Consensus group also exceeded 1 month of postintervention treatment in 1 case each.

The evidence guiding length of albendazole treatment is minimal. Two small trials, with between 16 and 18 patients in each arm, showed that 2–3 months of albendazole preoperatively reduced protoscolex viability to between 6% and 12% [14, 15]. The recurrence rate following 8 weeks of preoperative albendazole was 6.25%, compared with 18% without albendazole and 0% with 8 weeks of postoperative albendazole [14]. A randomized controlled trial (RCT) is needed to establish the optimal length of pre- and postprocedure albendazole. Its absence so far cements CE's status as both an orphan and neglected disease.

The role of praziquantel is unclear, and clinicians use it in varying ways at a wide range of doses. In case 1, 11% used albendazole-praziquantel combination therapy. This number increased to 29% when confronted with inoperable disseminated disease. Twelve percent advocated praziquantel monotherapy in albendazole-induced hepatitis. There is little evidence to guide the use of praziquantel in CE. It is not effective as monotherapy because it does not penetrate mature cysts or inhibit cyst growth. However, in vitro and in vivo data support its role as a protoscolicide to prevent disseminated disease following cyst leakage [16]. Praziquantel also boosts intracystic albendazole levels [17], and recent work in neurocysticercosis, the causative agent of which is closely related to *E. granulosus*, suggests in vivo synergism between the 2 drugs [18]. Unfortunately, the Expert Consensus suggests a dose of 40 mg/kg once per week in combination with albendazole [4], while referencing a trial where praziquantel was used at 25 mg/kg/day in combination with daily albendazole [17].

It is unclear why clinicians do not follow Expert Consensus guidance. Studies in general practice exploring failure to follow guidelines suggest that factors include lack of awareness of the guideline or its contents, disagreement with recommendations, difficulty in applying the guideline to a clinical environment, or unwillingness to change due to clinical experience [19, 20].

Each of these is relevant to CE and the Expert Consensus. In affluent countries, CE is usually an imported disease of low incidence. Patients are managed in specialist centers, aware of guidelines and with many resources, or in health institutions with little experience of CE who may be unaware of guidelines [21] and unable to perform PAIR or OPC due to insufficient training. In highly endemic areas, some institutions see many cases and may evolve an experience-based practice adapted to the resources of their setting. The value put on prior clinical experience is compounded, as the Expert Consensus is the product of expert opinion rather than evidence base. Furthermore, the consensus is only published in the English language, which, although it is now the lingua franca of medical literature, is only widely spoken in 1 of 33 highly endemic countries. We intend to do further work to establish how these factors contribute to failure to follow guidance.

There are a number of limitations to this study. First, clinicians managing patients with CE are widely dispersed and thus difficult to identify. We used 3 methods to identify clinicians and, in doing so, achieved a representative geographical sample with responses from endemic regions, including the most highly endemic regions, worldwide. The notable exception is that, despite much effort, there were no responses from China or Central Asia. This may have been due to language difficulties.

Forty-one responses is a small number considering the amount of CE worldwide. We suspect that management is more diverse than illustrated by this paper. Respondents probably represent those with better access to updated knowledge due to their recent publications, membership of medical societies, and reliable internet access.

A multifaceted approach is required to improve the clinical management of CE in both high- and low-income countries. First, well-planned RCTs are necessary in key areas such as the length of treatment with albendazole, the role of praziquantel, and the use of OPC over surgery in type 2 and 3B cysts. Lack of commercial interest from pharmaceutical companies together with the neglected nature of this disease makes this difficult but not impossible. Second, an international CE registry with well-defined input parameters and data collection should be created. Several countries including China and Italy [22] have local registries to collect data and follow-up cases. Expanding these cohorts to international registries would allow comparison of different practices between countries and patient groups. It could also answer questions such as the incidence of sclerosing cholangitis following use of scolicidal agents and the optimal length of treatment in disseminated disease. These scenarios occur infrequently; thus, small national registries are unlikely to identify sufficient cases to draw conclusion. Finally,

further education together with dissemination of guidance is needed. A telemedicine service developed in northwestern China remotely advises clinicians in district hospitals [23]. Mobile clinics established in Morocco aid rural clinicians in diagnosis and treatment [24]. These services should be introduced in other highly endemic areas. Guidance should also be translated into other languages (Spanish, Russian, Mandarin) to allow further local dissemination.

CONCLUSIONS

In conclusion, there is wide variation in the management of CE worldwide, and practice differs greatly from the IWGE guidelines. There are practices in common use that are both ineffectual and unsafe, putting patients at risk. Further evidence is needed to influence guidelines so that they can be more prescriptive. RCTs should be conducted in key areas such as the length of albendazole treatment and the role of praziquantel. An international CE registry should be created to gather evidence in areas where RCTs would be impossible, such as the optimal length of treatment in disseminated disease and the true incidence of caustic sclerosing cholangitis. To improve future WHO guidance, further work is planned to establish why clinicians do not follow the IWGE Expert Consensus.

Notes

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Potential conflicts of interest. P. L. C. is a member of the WHO Informal Working Group on Echinococcosis. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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