Clinical Management of Cystic Echinococcosis: State of the Art, Problems, and Perspectives

INTRODUCTION

Cystic echinococcosis (CE) is among the most neglected parasitic diseases. Development of new drugs and other treatment modalities receives very little attention, if any, and is slow.1,2 Clinical management procedures have evolved over decades without adequate evaluation of important features such as efficacy, effectiveness, rate of adverse reactions, relapse rate, and cost. CE occurs in health care environments as different as Europe/North America and resource-poor countries of the South and the East. This creates setting-specific problems in the management of patients. Furthermore, studies carried out in either of the two fundamentally different environments lack external validity, i.e., results obtained in one setting may be different from those in the other and practices that can work in one may not be applicable to the other. In this paper, we review the current management procedures of CE with particular emphasis on the evidence base and setting-specific problems.

1) In most developed countries, CE is an imported disease of very low incidence and prevalence and is found almost exclusively in migrants from endemic regions. It thus meets the criteria of an orphan disease. As with all rare diseases two distinct subgroups are seen:

a) Mismanaged patients because of lack of experience in the health institutions where they present.

b) Patients treated in centers with a special interest in CE.

2) In endemic regions, predominantly settings with limited resources, patient numbers are high and medical doctors are very familiar with the disease. Whole communities do not have access to appropriate treatment, however. The choice of treatment modalities is limited because of poor infrastructure and shortage of equipment and drugs. In this context, CE meets the criteria for a neglected disease.

Furthermore, studies carried out in either of the two fundamentally different environments lack external validity (i.e., results obtained in one setting may be different from those in the other and practices that can work in one may not be applicable to the other).

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Abstrac. Clinical management of cystic echinococcosis (CE) has evolved over decades without adequate evaluation of important features such as efficacy, effectiveness, rate of adverse reactions, relapse rate, and cost. CE occurs in health care environments as different as Europe/North America and resource-poor countries of the South and the East. This creates setting-specific problems in the management of patients. Furthermore, studies carried out in either of the two fundamentally different environments lack external validity, i.e., results obtained in one setting may be different from those in the other and practices that can work in one may not be applicable to the other. In this paper, we review the current management procedures of CE with particular emphasis on the evidence base and setting-specific problems.

MATERIALS AND METHODS

Papers covering the subject were obtained by a Medline search of the literature published in English on this subject. Key words were “Echinococcal cysts,” “hydatid cysts,” “cystic echinococcosis,” “hydatidosis,” “hydatid,” “surgery,” “thiabendazole,” “flubendazole,” “mebendazole,” “albendazole,” “praziquantel,” “chemotherapy,” “PAIR,” “percutaneous treatment,” “percutaneous drainage,” and “ultrasound.” Papers published from 1970 to 2007 were included. The authors’ files were used as well. For each treatment modality, grade published from 1970 to 2007 were included. The authors’ files were used as well. For each treatment modality, grade

IMAGING-BASED APPROACH

The advent of modern imaging techniques, in particular ultrasound, represented a breakthrough in the diagnosis, treatment, and follow-up of patients with CE. With this new tool at hand, clinicians have been striving for an imaging-based classification of CE cysts for the past 25 years4–6 and to correlate individual cyst stages with the natural history and treatment-induced involution processes of the cysts.

Two classifications are most frequently used: the Gharbi and the WHO Informal Working Group on Echinococcosis (IWGE) classification (Table 1). As shown in Table 1, the WHO classification is almost the same as Gharbi’s, with Gharbi type II corresponding to CE3a and vice versa. However, there are two important additions in the WHO classification: the predominantly solid cyst with daughter cysts, which was not explicitly included in Gharbi’s classification, has been found a place in the CE3 slot, and the types are now grouped according to their biological activity (Table 1; far right column). This has important consequences for treatment decisions, as we will detail in the paper. Last but not least, the WHO classification was the first to be proposed as the result of the combined efforts of a group of experts, including Gharbi himself. Controversies still exist about the natural history of the cyst and whether WHO numbering of cysts types appropriately reflects this.7,8 An internationally accepted, standardized classification system is of paramount importance for uniform guidelines and comparison of data.

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<table>
<thead>
<tr>
<th>Type</th>
<th>Image Description</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Unilocular unechoic cystic lesion with double line sign</td>
<td>Active</td>
</tr>
<tr>
<td>Type III</td>
<td>Multiseptated, “rosette-like” “honeycomb” cyst</td>
<td></td>
</tr>
<tr>
<td>Type II</td>
<td>Cyst with detached membranes (water-lily-sign)</td>
<td>Transitional</td>
</tr>
<tr>
<td>Type III</td>
<td>Cyst with daughter cysts in solid matrix</td>
<td></td>
</tr>
<tr>
<td>Type IV</td>
<td>Cyst with heterogenous hypoechoic/hyperechoic contents. No daughter cysts</td>
<td>Inactive</td>
</tr>
<tr>
<td>Type V</td>
<td>Solid plus calcified wall</td>
<td></td>
</tr>
</tbody>
</table>

Comparison of the Gharbi and WHO ultrasound classifications of echinococcal cysts.

A distinction between CE3a and CE3b is expressly made by the authors of this review on grounds of clinical response to PAIR and albendazole. Recent papers and our unpublished experience report that CE3b has a higher rate of relapses. With recent observations of high relapse rates in PAIR-treated CE3b cysts (see section on PT), other PTs should be explored for this cyst type. CE 3b also seems to respond poorly to albendazole (we thank Dr. W. Hosch, Department of Radiology, University Hospital Heidelberg, for contributing images in the table).

WHO CE3b has not been explicitly described by Gharbi. CE3b might be classified as type III, although in the original Gharbi paper, there was no distinction between multivesiculated (honeycomb-like) cysts and cysts with daughter cysts in solid matrix.
TREATMENT MODALITIES CURRENTLY IN USE

Surgery. For many years, surgery has been the only treatment available for CE. Surgical procedures range from simple puncture and aspiration of cyst content to partial resection of the affected organ. We discuss here surgery of the liver and lungs, the two most frequently affected organs: 70% and 20%, respectively. The most common technique is total or partial cystectomy. Although surgical techniques have improved, there is considerable controversy as to what is the most effective technique, the role of cyst aspiration and external drainage, hepatic and lung resection, management of the residual cavity in CE of the liver, cyst recurrence after surgery, and high rates of complications and mortality related to reoperation in recurrent disease.10–14 An immediate cure is claimed for surgical treatment of liver cysts, but even with radical procedures, this is far from being achieved, with morbidity, mortality, and relapse rates of 32%, 8%, and 20%, respectively.9,10,15 For surgery of lung cysts, reported morbidity ranges between 0% and 13% and mortality rates between 0% and 5%.12,14,16–18

With alternative treatment modalities advancing, it is pertinent to clarify the current position of surgery among other options.11,13,14,19 In patients with complicated cysts (rupture, cysto-biliary and most cases of cysto-bronchial fistulas, compression of vital organs and vessels, hemorrhage, secondary bacterial infection), surgery maintains its place as the treatment of choice. In uncomplicated liver cysts, surgery is increasingly being replaced with other treatment options (percutaneous treatment in liver cysts, chemotherapy, watch and wait) depending on the stage of the cyst. This is, however, not based on appropriate comparative prospective clinical trials with long-term follow-up. The uncertainties of making the right treatment choice on the basis of current evidence are further highlighted by recently reported complications after medical treatment of lung cysts with rupture into the bronchial tree, expulsion of its content, or, especially with large cysts, rupture into the thoracic cavity and subsequent secondary CE. These complications require surgical intervention, which is burdened with its own set of serious complications, such as empyema and lung abscess.20 Similar observations have been made in patients with liver cysts treated with albendazole and rupture of the endocyst into the biliary tree during treatment (Junghanss, personal observations).

Surgical procedures. The most commonly used procedures can be divided in conservative and radical.

Conservative procedures aim at sterilization and evacuation of cyst content, including the hydatid membrane (hydatidectomy), and partial removal of the cyst. The evacuation and the hydatidectomy consists of puncture of the cyst and aspiration of part of the content, to permit introduction of the scolicidal agent, and total aspiration thereafter. The risks are anaphylactic shock,21,22 chemical cholangitis or alveolar/bronchial damage, if the cyst communicates with the biliary or bronchial tree,23,24 and spillage of the cyst contents and secondary hydatidosis, with relapse rates of up to 20% being reported after surgery of liver cysts25 and up to 11.3% for lung cysts.13 After partial removal of the cyst, a residual cavity remains, bearing the risk of secondary bacterial infection and abscess formation.25 [strength of recommendation: B, quality of evidence: II] (see Tables 5 and 6).

Radical procedures aim at complete removal of the cyst with or without hepatic or lung resection. Peripherally located lung cysts of any size and small- to medium-sized centrally located cysts can be excised without sacrificing lung parenchyma. Standard radical procedures are wedge resection of lung parenchyma of less than one segment, and for liver and lung cysts, segmentectomy and lobectomy. Total cystectomy is the ideal procedure25 to reduce complication and relapse rates. It can be performed by an open or a closed method (Napalkoff) and under videosurgery.22 With the small series of laparoscopically treated patients available in the literature, it is impossible to draw conclusions regarding comparison with open surgery.26–28 Hepatic resection and lung segmentectomy/lobectomy are rarely performed.14,29 Radical procedures bear greater intraoperative risks, with less postoperative complications and relapses.9,10,15,25,30 Conservative procedures are preferred for lung cysts, with radical procedures such as segmentectomy and lobectomy necessary for extended parenchymal involvement severe pulmonary suppuration and complications such as pulmonary fibrosis, bronchectasis, or severe hemorrhage.13,14 [strength of recommendation: B, quality of evidence: II].

Adjunctive treatment. There is some evidence for the following adjunctive measures to play a useful role.

1) Prevention of secondary CE and relapses
   a) Albendazole—starting 1 week before surgery and continuing to up to 3 month after surgery.13,31–33 There is no uniform recommendation, however, and the efficacy is not known [strength of recommendation: B, quality of evidence III] (Tables 5 and 6).
   b) Surgical field protection with pads soaked with scolicidal agents9,14,30,34 [strength of recommendation B, quality of evidence III] (Tables 5 and 6).
2) Prevention of cholangitis
   a) In liver cysts, if deroofing is performed, search for cystobiliary fistulae, bile-stained fluid content, determination of bilirubin in the aspirated fluid, and anterograde cholangiography if necessary [strength of recommendation B, quality of evidence III] (Tables 5 and 6).
   b) Strictly avoiding injection of scolicidal solution into cysts that communicate with the biliary or bronchial tree (cysto-biliary and cysto-bronchial fistulas).13,35–37
3) Management of the residual cavity
   a) Ideally, cysts are completely removed to avoid residual cavities. This prevents suppuration, reduces the risk of biliary or bronchial fistulas, and achieves faster healing and shorter hospital stay38–40 [strength of recommendation B, quality of evidence III] (Tables 5 and 6).
   b) When hydatidectomy or partial or subtotal cystectomy is performed, the residual cavities need attention. In liver cysts, simple drainage with suction and filling with epiploon (omentoplasty) are options to reduce the risk of complications.39 In lung cysts, the residual cavity can be obliterated by capitonnage using multiple purse-string sutures from the deepest level to surface level13,14 [strength of recommendation B, quality of evidence III] (Tables 5 and 6).

Risk, benefit, and safety profile. The principal advantage of cyst resection is the immediate cure of the disease. For hepatic cysts, the more radical the intervention, the higher the intraoperative risk and the lower the frequency of relapse, and vice versa in the more conservative approach.41 From
current evidence, conservative surgery seems preferable for most lung cysts. Only in extensive lung disease is radical surgery given preference.

**Percutaneous treatment.** Percutaneous treatment of abdominal CE was introduced in the mid-1980s. Initially received with skepticism by some, it developed into an attractive alternative to surgery and benzimidazole derivatives for certain cyst stages.

These treatment modalities aim to destroy the germinal layer with scolicidal agents or to evacuate the entire endocyst.

* Destruction of the germinal layer: PAIR. Historically, the first percutaneous treatment used was to puncture the cyst, aspirate cyst fluid, inject a scolicidal agent, and re-aspirate the cyst content (PAIR). 43,44

The classic PAIR technique is widely known. 43,44 Several series with minor variations of the essential steps have been published. 45–47 The technique is increasingly being used as documented in the literature. 48 However, as with all other treatment modalities of CE, systematic appraisal is far from satisfactory. 49

Only two randomized clinical trials are available. 50,51 Most studies lack sufficiently long follow-up periods to assess the long-term relapse rate. Three studies cover ~3 years 46,52,53 and two other studies cover 4 years of follow-up. 57

Khuroo and others 51 found PAIR combined with per interventional benzimidazole derivatives to be as effective as open surgical drainage with fewer complications and less cost. A recent paper from Turkey reported a single-center experience comparing surgery, laparoscopic surgery, and percutaneous treatments in 355 patients over a period of 10 years and concluded that PAIR is an effective and safe option. 27

Giorgio and others 54 showed that PAIR of multivesiculated cysts does not allow complete healing (solidification, i.e., progression to stages CE4 or CE5), and in 30% of cases resulted in an intracystic recurrence that required up to four repeat procedures.

Smego and others 55 conducted a meta-analysis across 21 studies made up of 769 patients with 1,072 hepatic cysts undergoing PAIR and compared the findings with 952 unmatched surgically treated historical controls. They claimed that the rate of clinical and parasitologic cure was greater in patients receiving PAIR plus chemotherapy than in those receiving surgery. Disease recurrence, major complications (anaphylaxis, biliary fistulas, cyst infection, liver/intra-abdominal abscesses, and sepsis), minor complications, and death occurred more frequently among patients treated with surgery than among patients treated with PAIR. The mean durations of hospital stay were 2.4 days for patients treated with PAIR and 15.0 days for the surgical control group.

Such results are interesting but suffer from the same flaws plaguing the studies that have been subjected to meta-analysis (small series, retrospective, overlapping of patients in subsequent publications, short follow-up, etc.). 49

Giorgio and others 54 and Kabaaiglu and others 56 reported repeated failures of PAIR in multivesiculated cysts (CE2 and CE3B). These findings prompted most clinicians to use PAIR exclusively for unilocular cysts, with or without detached endocysts. For this reason, CE2 and CE3b cysts are now preferably treated with cutting devices and large bore catheters, which are more effective (see below) [strength of recommendation: A/B, quality of evidence: I/II] (Tables 5 and 6).

**Risk, benefit, and safety profile.** The major risks of percutaneous techniques are anaphylactic shock, secondary echinococcosis caused by spillage of cystic fluid, and chemical cholangitis caused by contact of the scolicidal agent with the biliary tree. It is imperative to have resuscitation measures in place, to choose a safe approach to the cyst, and to give peri-interventional prophylaxis with benzimidazoles and to exclude communications with the biliary tree before injection of any scolicidal agent.

No systematic evaluation of side effects of the various percutaneous techniques has been undertaken thus far, with the exception of two preliminary reviews. 48,57 Ninety-six publications reporting on percutaneous drainage of 4,209 cysts in 3,005 patients were screened. 48 One hundred sixty-six cysts were punctured for diagnosis and 4,043 for treatment. Major and minor complications are listed in Table 2. The references used are cited in ref. 48.

The statistics of the pooled data from published studies in Table 2 must be interpreted carefully. No information was available on 213 cysts in 19 studies, and heterogeneity of studies limits the usefulness of such statistics. Publication bias is of particular concern, because adverse outcomes tend to remain unpublished. With major life-threatening complications (e.g., anaphylactic shock), details of the circumstances of fatal outcome need to be known to avoid discrediting a promising technique 58 for reasons that are setting specific. The setting in which PAIR can be performed safely needs to be defined. Secondary echinococcosis as a result of spillage of fluid was not mentioned in any of the 96 studies reviewed. It is unclear whether this is because of spillage-free puncture, albendazole prophylaxis, or underreporting because of incomplete follow-up regarding length and imaging techniques used.

Safety and efficacy of percutaneous treatments is also related to the anatomical site of the cyst. Percutaneous treatment is mostly used in liver and extrahepatic abdominal cysts, including peritoneal. Cysts in other locations have also been approached (Table 3), particularly when other methods have failed. Some sites are intrinsically difficult to treat. For example, percutaneous puncture of spinal and paraspinal cysts have failed at long-term follow-up. It is well known that cysts in these sites are difficult to cure when radical surgery is not feasible. 59

A much less well-evaluated percutaneous technique to destroy the germinal layer by means of high temperature is radiofrequency (RF) thermal ablation. This procedure uses the same needle electrodes that are used for local treatments.

### Table 2

Complications and recurrences of percutaneous treatments 1983–2004

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. punctured cysts</th>
<th>No. of events</th>
<th>Percent complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths caused by anaphylactic shock</td>
<td>4209</td>
<td>2</td>
<td>0.047</td>
</tr>
<tr>
<td>Major complications*</td>
<td>4209</td>
<td>16</td>
<td>0.38</td>
</tr>
<tr>
<td>Minor complications†</td>
<td>4043</td>
<td>268</td>
<td>6.62</td>
</tr>
<tr>
<td>Recurrence‡</td>
<td>3830</td>
<td>49</td>
<td>1.27</td>
</tr>
</tbody>
</table>

* Major complications were death, anaphylactic shock, chemical cholangitis, and secondary echinococcosis caused by spillage.
† Minor complications (detailed in text) were calculated only on cysts punctured for therapeutic reasons.
‡ Rate of recurrence is calculated only on cysts punctured for therapeutic purpose. Data on recurrence unavailable for 213 cysts.
of hepatocellular carcinomas. The experience with RF is still very limited, however, and preliminary reports are rather disappointing because nearly all the cysts treated relapsed after a few months.

Other percutaneous techniques. These are generally reserved for cysts that are difficult to drain or tend to relapse after PAIR (multivesiculated cysts or cysts with predominantly solid content and daughter cysts). They are based on the aspiration of the “solid” content of the cyst, the germinal and the laminated layer, through a large-bore catheter or device. Two types of approaches are currently in use: the catheterization technique and the laminated layer, through a large-bore catheter or device. Two types of approaches are currently in use: the percutaneous evacuation (PEVAC) technique, in particular PEVAC (percutaneous evacuation) MoCaT (modified catheterization technique), and DMFT (dilatable multi-function trocar) (see below) [strength of recommendation: C, quality of evidence III] (Tables 5 and 6).

A large-bore cutting-aspiration device was used by Saremi and McNamara in 32 patients to fragment and evacuate daughter cysts and the laminated membrane. A 2-year follow-up showed a high rate of success (90%) and a low incidence of major complications (3%).

Another group treated 699 multivesiculated abdominal cysts with a device called DMFT. This is linked to an aspiration apparatus to extract the endocyst, daughter cysts, and other cystic contents. Thereafter, the cavity is irrigated with 10–20% saline, and, if necessary, curettage is done. The catheter remains in the cavity for 2–3 days. No deaths but four anaphylactic reactions were observed. The recurrence rate in a 3-year follow-up was 2.3% in situ and 1% in other locations.

Large-bore 14-Fr van Sonnenberg sump drainage catheters under sonographic guidance were used by Haddad and others to treat nine solid cysts with daughter cysts. They evacuated the cyst contents and irrigated the cyst cavity with hypertonic saline. At 15 months, there were no major complications, deaths, or recurrences.

Schipper and others treated 12 patients with unilocal and multivesiculated cysts, including complicated ones, with PEVAC. Aspiration and evacuation of cyst content were performed with a 14-Fr catheter. Cysto-biliary fistulas were treated with an endoprosthesis, introduced endoscopically into the common bile duct. In a mean period of 17.9 months (range, 4–30 months), seven cysts disappeared and five decreased in size. The main complications of this procedure were caused by cysto-biliary fistulas and secondary infections.

These complications prolonged hospitalization from 11.5 (range, 8–14 days) to 72.3 days (range, 28–128 days).

Recently, Akhan and others used a MoCaT to treat six echinococcal cysts of the muscle. The mean catheterization time was 13.7 days (range, 1–54 days). An average of 96.1% volume reduction was obtained. No sign of re-activation was observed during the mean follow-up period of 34.8 months (range, 6–57 months) [strength of recommendation: C, quality of evidence: III] (Tables 5 and 6).

Medical treatment. During 1984–1986, the World Health Organization took an early initiative and established two multicenter studies in Europe to directly compare albendazole and mebendazole, using a single standard protocol. Because the available methods for following patients were limited at the time, the results were basic. The important finding was that, based on clinical outcome and in a limited number of patients, the two drugs look very similar. The differences lie in the longer duration of treatment and higher doses required using mebendazole.

The interest in investigating medical therapy of CE, facilitated by the increasing availability of ultrasound and a better understanding of imaging features reflecting involution, resulted in a series of clinical trials that made use of this new modality to evaluate the effect of medical treatment more objectively. Within 5 years, it was possible to analyze the data of a series of 253 patients with 456 cysts (Table 4). These data were used for SmithKline and French (now GlaxoSmithKline) to submit a license application for use of albendazole for CE in Europe. Although the evidence base was very limited, the registration tended to standardize treatment, using three cycles of 1 month with a break of 14 days between courses, required because of the limited long-term toxicity data available. It did not prevent some groups from continuing to use other regimens, however, and as a result, data have also accumulated on continuous treatment, especially by Teggi and others in Rome.

In recent years, the question of treatment duration has been investigated retrospectively in large series constructed by Horton that extended the data set produced 12 years earlier (Table 4). With larger numbers, it was possible to show that the number of patients showing evidence of clinical or ultrasonographic/radiologic improvement (evidence of drug effects on the cysts) increased with longer durations of treatment, whereas the proportion of patients with cure (disappeared or calcified cysts) did not significantly change. Clearly, duration of treatment of <3 months produces less than optimal response, whereas results of extension beyond 6 months have yet to be gauged because clinicians tend to adopt longer courses. Some of this effect may be because of longer periods

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients</th>
<th>Cured (%)</th>
<th>Improved (%)</th>
<th>No change/worse (%)</th>
</tr>
</thead>
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<tr>
<td>1989</td>
<td>253</td>
<td>28.5</td>
<td>51.0</td>
<td>20.5</td>
</tr>
<tr>
<td>1997</td>
<td>456</td>
<td>35.1</td>
<td>41.0</td>
<td>23.9</td>
</tr>
</tbody>
</table>

Adapted from Horton.
of follow-up, allowing more change to occur in the period of observation. This was shown in a series of patients followed long term by Nahmias and others. They showed in their series of patients followed for between 3 and > 5 years that, even in the absence of further treatment, cysts continued to change, and that this eventually led to a high proportion of cures recorded beyond 5 years. The study was small, however, and no control group was available to assess the contribution of spontaneous involution to the total change observed.

For many years, there has been a debate over whether cysts spontaneously progress to calcification and that, therefore, intervention is unnecessary. Two studies are of importance in this respect. In an attempt to resolve the question, Keshmiri and others examined the effects on cysts in patients treated with albendazole and those not treated. At least in the short term, the effect of treatment is clear, with ~80% showing evidence of changes in the treated group in contrast to only 13% in the untreated group. Similarly Gil-Grande and others conducted a surgically based study of two albendazole dose regimens compared with no treatment. Evaluation in this case was made at surgery, and the cyst contents were evaluated for viability by microscopy and supravital staining after inoculation of the cyst content into mice and compared it with the ultrasound characteristics of the cysts. They showed that treatment produced a clear effect on viability and infectivity for mice, which was greater with the longer course of treatment. Furthermore, this correlated well with the ultrasound findings [strength of recommendation B, quality of evidence II (Tables 5 and 6)].

Many and substantial questions still remain unanswered, however. What is the optimum duration of treatment? Is there a stage-specific difference in response to medical treatment? How does cyst stage relate to bioavailability of benzimidazole carbamates and active metabolites at the site of action (i.e., in the interior of cysts)? Would the reported relapse rates hold had patients been followed up long term? To which extent and at which rate do cysts undergo spontaneous involution without treatment? No single published study gives a clear picture of the efficacy of the benzimidazoles in its own right. Meta-analysis of published studies is not possible because heterogeneity between studies is too high and there is substantial overlap of published cohorts. Studies vary widely in inclusion/exclusion criteria, cyst stages enrolled, criteria used for defining treatment success, and failure and follow-up procedures and time. To get around this problem and to make as much use as possible of the data that have accumulated over decades, a study (EchinoMEDREV) was initiated in Heidelberg 2005 to re-analyze benzimidazole-treated patients from individual patient data of published studies. These data are currently being extracted and analyzed. Results are expected in 2008 (T. Junghanss, personal communication).

Setting-specific problems have not been addressed at all thus far. Is medical treatment at all feasible in resource-poor settings in the near future concerning drug delivery, compliance, long-term follow-up, and cost?

Some of the unanswered questions on medical treatment require more basic research on the clinically relevant pharmacologic features of the benzimidazole carbamates. Absorption of the two benzimidazole carbamates, albendazole and mebendazole, in humans is very variable and limited to between 5% and 20%. Absorption is mostly from the small intestine, and they are both almost completely metabolized before reaching the systemic circulation. A first pass effect occurs in the intestinal wall. The key to the differences between the two compounds lies in the metabolites that arise. Albendazole is metabolized first to albendazole sulphoxide, an active antihelminthic in its own right, and then to the relatively inactive sulphone, whereas mebendazole is converted to a number of poorly active hydroxylated products. Thus, only very high doses of mebendazole that potentially swamp metabolic conversion, allowing active parent drug into the systemic circulation or produce sufficiently high levels of metabolites, are likely to be effective. In contrast, with the production of an active metabolite systemically, albendazole is likely to be effective at much lower total doses. Thus, in this situation, albendazole is acting almost like a produg. Given the much higher lipohility of both compounds, co-administration with fatty food increases absorption and is of importance when examining possible development of improved formulations.

Looking at available data of medically treated patients, it seems that without increasing drug activity though reformulation or development of a new compound with greater efficacy, chemotherapy cannot be the sole approach to treatment.

Thus far, improvement of systemic availability of available benzimidazoles has only been explored with co-administration with a fatty meal, liposomal encapsulation, and soy bean oil emulsions, the latter two without attracting commercial interest. Addition of cimetidine and praziquantel have been tried, but the results were not unequivocal. Co-administration of other drugs for the sole reason of increasing bioavailability is not without problems, however, and needs careful consideration.

Risk, benefit, and safety profile. The benzimidazole carbamates are among the safest compounds available when used for the treatment of intestinal worms involving only short-term treatment. The situation is somewhat different when it comes to long-term treatment. Although the evidence is limited, side effects of treatment are seen, both clinically and in laboratory tests. Perhaps the most common side effect is alopecia, which, although the denominator is unclear, may occur in 1–5% of all those treated. Gastrointestinal symptoms are also not uncommon but rarely are sufficiently severe to require cessation of treatment.

The best-known effect of long-term benzimidazole treatment of CE is elevation of liver enzymes. This occurs to some extent in up to 20% of treated cases and has often led to cessation of treatment. This would suggest that there is significant hepatotoxic potential in using benzimidazoles. Although there is no doubt that some cases of drug-induced hepatocellular damage have occurred, the majority of liver enzyme elevations are limited, are not progressive, and disappear on treatment cessation. Examination of the clinical conditions associated with these elevations suggests that the effect is not a simple drug effect on the liver. The findings are uncommon in treatment of neurocysticercosis, which is much shorter, however, and in patients with echinococcal cysts remote from the liver. It has been suggested that these effects are because of the local release of antigens caused by damage to the parasite by the drug. A retrospective analysis of liver function by Teggi and others found that 85% of all raised enzyme cases had liver cysts, and furthermore, that structural changes in the cysts were present in a significantly
higher proportion (98.4% versus 67.1%; \( P = 0.0001 \)) of those patients with elevated enzymes. Others have noted that in many patients, after an initial rise, enzyme levels stabilize or even fall. Therefore, careful management with regular testing is required, and unless enzyme changes are progressive, treatment can be continued.

Similarly, it is known that benzimidazoles have the potential to suppress bone marrow function, and cases of aplastic anemia have been described with both compounds.\(^{107}\) Again, regular monitoring should eliminate the majority of these events.

Finally, long-term treatment with benzimidazole compounds carries a risk to the fetus in the first trimester of pregnancy, and treatment should be avoided during pregnancy where possible and should be screened for in all female patients of childbearing age. Although a number of accidental exposures have occurred, these have not had untoward results thus far.\(^{108}\) However, the denominator for calculating fetal risk is small.

“Watch and wait.” The idea of leaving certain cyst types untreated and just monitoring them over time is a logical consequence of two main findings: 1) a good proportion of cysts are consolidating and calcifying (i.e., become completely inactive) without any treatment\(^ {74,109} \) and 2) cysts that have arrived at this stage and behave quietly (i.e., do not compromise organ functions or cause discomfort) seem to remain like this or stabilize even further.\(^ {110}\)

Long-term follow-up of patients with imaging, in particular ultrasound, which does not use ionizing radiations and is easily repeatable, has increased our confidence that we have to offer something spectacular to quite a substantial group of patients: no treatment at all. This decision must, however, be accompanied and verified by long-term ultrasonographic follow-up. Ten years seem to be an adequate time frame. Again, the published evidence for this approach is far from adequate. In recent years, however, substantial positive experience with “watch and wait” is accumulating in various centers.\(^ {111}\) This attractive approach to patients with advanced cyst stages needs and deserves formal evaluation to define its indications and limitations [strength of recommendation B, quality of evidence III] (Tables 5 and 6).

**DISCUSSION**

CE is difficult to treat and, even more so, to cure for a number of reasons. The disease is complex and dynamic with an evolving phase and quietly growing cysts. This is followed by an involution process during which the parasite is gradually dying off, leaving behind a solidified, often calcified cyst or a scar. Each successive active cyst stage carries its own risks for serious and even life-threatening complications. For complex diseases, no “one size fits all” approach is available, and clinicians must take a stage-specific approach. This leads to a wide range of treatment modalities with an equally wide range of technological and training backgrounds necessary for implementation and delivery. This, in turn, clashes with technical and economic difficulties in countries with limited resources where the patient load is greatest and problems in acquiring clinical competence in countries where few patients suffer from the disease.

**Imaging is crucial to new treatment approaches.** Progress in managing patients with CE is greatly facilitated by consensus on cyst stages and reliable correlation of ultrasound-defined cyst stages and parasite viability. Substantial research efforts are needed to establish this firmly.\(^ {112}\) Predicting complications, in particular those related to cysto-biliary/bronchial fistulas, is essential.\(^ {113}\) Furthermore, availability of ultrasound machines and training may be a problem in countries with limited resources. Well-trained and equipped mobile teams might be an option. In resource-rich countries, instead, the problem lies in the difficulty of acquiring experience because of the rarity of the disease. Center-based management of patients seems to be the appropriate answer here.

**Imaging-based, stage-specific approach to treatment.** Most clinicians around the world continue to rely exclusively on surgery, and most patients in endemic countries do not receive any treatment at all until complications intervene. Prospects for wider use and accessibility of medical treatment (albendazole, mebendazole), percutaneous techniques, and “watch and wait” are poor at the current level of investment into this neglected disease.

A few groups of clinicians around the world, under the umbrella of WHO IWGE, try to keep track of the developments in clinical management of CE.\(^ {114}\) Sample sizes of studies are small, there is overlapping of patient cohorts in successive publications, many studies are retrospective, and problems related to the design and conduct of studies are frequent. Pooling published studies for meta-analysis is difficult because of unbridgeable heterogeneity of study design and conduct. Nevertheless, the IWGE released guidelines in 1996.\(^ {114}\) The ranking of the WHO guidelines according to the Infectious Diseases Society of America grading system\(^ {3} \) shown in Tables 5 and 6, is B-C for strength of recommendation and II-III for quality of evidence.

In certain areas, the WHO guidelines have fallen behind current treatment practice of various clinical groups and centers, particularly with respect to expanding indications for percutaneous and medical treatment and “watch and wait.”

**Table 5**

<table>
<thead>
<tr>
<th>Strength of recommendation</th>
<th>Infectious Diseases Society of America grading system (strength of recommendation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Good evidence to support a recommendation for use</td>
</tr>
<tr>
<td>B</td>
<td>Moderate evidence to support a recommendation for use</td>
</tr>
<tr>
<td>C</td>
<td>Poor evidence to support a recommendation</td>
</tr>
<tr>
<td>D</td>
<td>Moderate evidence to support a recommendation against use</td>
</tr>
<tr>
<td>E</td>
<td>Good evidence to support recommendation against use</td>
</tr>
</tbody>
</table>

**Table 6**

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>Infectious Diseases Society of America grading system (quality of evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence from at least one properly randomized, controlled trial</td>
</tr>
<tr>
<td>II</td>
<td>Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies; from multiple time series; or from dramatic results from uncontrolled experiments</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of committees</td>
</tr>
</tbody>
</table>
Asking our aim here is to provide best practice therapy options to individual patients until more formally tested algorithms are available and to facilitate the design of appropriate clinical trials.

The way ahead. Awareness for CE must be raised under the umbrella of orphan disease (rich countries) and neglected disease (poor countries) initiatives to stimulate funding for much needed clinical research, involvement of private-public partnerships in the development of new drugs and other treatment aids and commitment of health authorities to stepping up the care for CE patients.

It is also important that more reliable epidemiologic data are made available if one has to gauge correctly the burden of this disease.2 This may come from population-based surveys and from analysis of hospital records, where available.115

Until major breakthroughs are seen, medium-term solutions need to be found. In countries where the disease has orphan disease status (i.e., where the disease occurs at low incidence and prevalence), patients should be managed by interdisciplinary teams in referral centers.

Few centers per country will suffice. Only then will patients benefit from accumulating experience, and long-term follow-up can be achieved, which is essential to control relapse.

The task is much more difficult in high prevalence countries because of the wide, almost unbridgeable discrepancy between medical demands to treat CE and available resources. A referral center approach might be the best solution in this setting, supplemented by mobile teams to bring diagnosis and management, including long-term follow-up, as close as possible to the community.

Again, large, well-designed clinical trials are essential to develop treatment algorithms adapted to the specific requirements in a wide range of health care settings where patients need treatment.

CE shares these problems with other neglected diseases. Getting CE on the agenda of the most neglected health problems is overdue.

### Table 7
Complications requiring interventions other than standard protocol

<table>
<thead>
<tr>
<th>Cysto-biliary fistulas</th>
<th>Cysto-bronchial fistulas</th>
<th>Secondary bacterial infection</th>
<th>Cyst rupture</th>
<th>Cyst with detached membranes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plus biliary obstruction/obstructive cholangitis</td>
<td>Plus bronchial obstruction</td>
<td>Liver abscess (can be treated percutaneously)</td>
<td>Plus anaphylaxis</td>
<td>* Cyst with detached membranes (<em>“water-lily”</em> sign).</td>
</tr>
<tr>
<td>Bacterial abscesses</td>
<td></td>
<td>Lung abscess (can be treated with antibiotics and surgical drainage if necessary)</td>
<td></td>
<td>* * Cyst with detached membranes (<em>“water-lily”</em> sign).</td>
</tr>
<tr>
<td>Cysto-bronchial fistulas</td>
<td></td>
<td></td>
<td></td>
<td>* * Cyst with detached membranes (<em>“water-lily”</em> sign).</td>
</tr>
<tr>
<td>Plus biliary obstruction</td>
<td></td>
<td></td>
<td></td>
<td>* * Cyst with detached membranes (<em>“water-lily”</em> sign).</td>
</tr>
<tr>
<td>Bacterial abscesses</td>
<td></td>
<td></td>
<td></td>
<td>* * Cyst with detached membranes (<em>“water-lily”</em> sign).</td>
</tr>
</tbody>
</table>

### Table 8
Treatment modalities stratified by cyst stage (uncomplicated) and level of health care

<table>
<thead>
<tr>
<th>WHO classification 2001</th>
<th>Current practice</th>
<th>Suggested</th>
<th>Resource setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Percutaneous techniques</td>
<td>Medical treatment</td>
<td></td>
</tr>
<tr>
<td>CE1</td>
<td></td>
<td></td>
<td>PAIR + ABZ, if &gt; 5 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ABZ alone, if &lt; 5 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rich</td>
</tr>
<tr>
<td>CE2</td>
<td></td>
<td></td>
<td>Non-PAIR PT + ABZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Surgery + ABZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rich</td>
</tr>
<tr>
<td>CE3a*</td>
<td></td>
<td></td>
<td>PAIR + ABZ, if &gt; 5 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ABZ alone, if &lt; 5 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rich</td>
</tr>
<tr>
<td>CE3b†</td>
<td></td>
<td></td>
<td>Non-PAIR PT + ABZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Surgery + ABZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rich</td>
</tr>
<tr>
<td>CE4 and 5</td>
<td>Regarded as inactive and, unless complicated, they should not be treated</td>
<td>Watch and wait</td>
<td></td>
</tr>
</tbody>
</table>

* Cyst with detached membranes (*“water-lily”* sign).
† Cyst with daughter cysts in solid matrix.
‡ All three current suggestions (i.e., percutaneous treatment, surgery, and albendazole) are, for obvious reasons (see text), equally difficult to implement in resource-poor settings at acceptable quality and affordable cost. CE shares these problems with other neglected diseases, and this urgently calls for setting specific development of treatment approaches and strategies.

\* = practiced; \* = rarely practiced.
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