Medical treatment versus “Watch and Wait” in the clinical management of echinococcal CE3b cysts of the liver.

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BACKGROUND. Available treatments for uncomplicated hepatic cystic echinococcosis (CE) include surgery, medical therapy with albendazole (ABZ), percutaneous interventions and the watch-and-wait (WW) approach. Current guidelines indicate that patients with hepatic CE should be assigned to each option based on cyst stage and size and patient characteristics. However, treatment indications for transitional CE3b cysts are still uncertain. These cysts are the least responsive to non-surgical treatment and often present as indolent, asymptomatic lesions that may not warrant surgery unless complicated. Evidence supporting indications for treatment of this stage is lacking. In the attempt to fill this gap before the advent of randomized clinical trials, we compared the clinical behavior of single hepatic CE3b cysts in 60 patients followed by the WHO Collaborating Center for Cystic Echinococcosis of the University of Pavia.

METHODS. We analyzed retrospectively 60 patients seen at our clinic over 27 years, who either received ABZ or were monitored with WW.

RESULTS. ABZ treatment was positively associated with inactivation (p<0.001), but this was not permanent, and no association was found between therapeutic approach and relapse (p=0.091). No difference was found in the rate of complications between groups.

CONCLUSIONS. In conclusion, our study shows that ABZ treatment induces temporary inactivation of CE3b cysts, while during WW cysts remain stable over time. As the rate of adverse events during ABZ treatment and WW did not differ significantly during the follow-up period considered in this study (median 43 months, IQR 10.7-141.5), we conclude that expectant management might represent a valuable option for asymptomatic CE3b cysts when strict indication for surgery is absent and patients comply with regular long-term follow-up.
INTRODUCTION

Cystic Echinococcosis (CE), caused by the zoonotic tapeworm Echinococcus granulosus, is a serious health problem in many regions of the world, but is among the most neglected parasitic diseases [1]. The liver is the most frequent location of echinococcal cysts (70% of cases), the larval metacestode stage, with a highly variable clinical presentation, ranging from asymptomatic to life-threatening manifestations [2, 3].

The current management of CE is based on quality of evidence III (evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of committees) with B-D recommendation strength (moderate to poor evidence to support recommendation). This results from the lack of longitudinal controlled studies, partly due to the chronicity of the disease, which requires years-long follow-up, and to the difficulty in comparing results from different studies [4].

The classification and clinical management of CE have been only recently addressed in a more harmonized manner [4]. The diagnosis of CE is based mainly on imaging methods and serology, with the latter having a complementary role [4]. Ultrasonography (US) is the mainstay of diagnosis of abdominal CE [5]. The WHO Informal Working Group on Echinococcosis (WHO-IWGE) classification, introduced in 2001, describes 5 CE stages based on US features (Figure 1): CE1 and CE2 are active cysts, CE3 are transitional, and CE4 and CE5 inactive cysts [6]. Observations on the response to non-surgical therapy and metabolic profiles using magnetic resonance spectroscopy have shown that this classification largely reflects the biological and metabolic activity of the cysts [7, 8]. Accordingly, CE3 cysts have been further divided into CE3a, which are equally likely to be active or inactive, and CE3b, which are active [7].

Cyst staging and the experience gathered in a number of referral centres allowed for a more rational allocation of uncomplicated cysts to the different available treatments (surgery, medical therapy, percutaneous interventions or “watch-and-wait” approach) (Figure 1) [4]. Treatment with albendazole (ABZ) is usually given continuously in courses of 3 to 6 months or longer, depending on cyst stage, activity and patient
characteristics [4, 9-11]. The “watch and wait” approach (WW) consists of regular US follow-up without interventions on the cyst in the absence of reactivation or complications. In our center, this approach is currently the choice for uncomplicated inactive CE4 and CE5 cysts [4, 6, 12-14]. CE3b cysts are poorly responsive to non-surgical treatment [8, 15] and often present as indolent, asymptomatic or pauci-symptomatic lesions that may not warrant surgery unless complicated. There is a lack of evidence supporting indications for treatment for these cyst stages. Often, after an attempted treatment with ABZ, which almost inevitably results in failure (i.e. relapse occurring shortly after inactivation obtained at the end of treatment) [16], in our centre CE3b cysts are allocated to the WW approach.

In this study we compared the behavior of and occurrence of complications in CE3b cysts treated with ABZ with those managed with the WW approach, in a cohort of patients seen in our centre over 27 years.

MATERIAL AND METHODS

ETHICS STATEMENT

All patients gave their written informed consent to data treatment and the study was approved by the Ethics Committee of IRCCS San Matteo Hospital Foundation, Pavia, Italy.

DATA EXTRACTION AND INCLUSION CRITERIA

This is a retrospective, comparative study of medical treatment vs expectant management (Watch and Wait – WW- approach) of patients with hepatic CE3b cysts. Clinical and demographic data of CE patients seen in our WHO Collaborating Centre for Cystic Echinococcosis from January 1985 through December 2012 were extracted from the Echinococcosis Database (FileMaker Inc., Santa Clara, CA, USA) and double-checked in the paper-based archive. Only patients with at least one hepatic CE3b cyst on first consultation and with a minimum of two follow-up visits were included in the analysis. In the case of patients diagnosed with multiple CE3b cysts,
the most active cyst, i.e. the cyst with higher relapsing rate, was considered in the analysis. To reduce possible confounding factors, patients harboring a CE3b cyst together with CE1, CE2, or CE3a cysts were excluded from the study, while those harboring a CE3b cyst together with one or more CE4 or CE5 cysts were included. Follow-up was defined as more than one consultation independent of time between visits. Data extracted included patient’s demographic data, geographical origin, cyst number, size, stage and location, time to inactivation (i.e. evolution from CE3b to inactive CE4-CE5 stage), time to relapse (i.e. reappearance of daughter cysts in the cysts that had reached the inactive stages CE4 or CE5), treatments, and complications.

Patients not having had a consultation during the last two years of the studied period (i.e. in 2011 and 2012) or longer, were contacted by telephone to inquire about their condition and reason for not coming to follow-up. Data collected by telephone were not included in the statistical analysis.

**CYSTS CHARACTERISTICS AND CLASSIFICATION OF FOLLOW-UP EVENTS**

Patients were evaluated by US at each follow-up visit by an Infectious Diseases clinician with long-standing experience in clinical ultrasound (EB). For records post-2003, cysts were staged according to the standardized WHO-IWGE ultrasound classification [6]. Cysts diagnosed prior to this date were classified according to Gharbi classification [17]. In these cases, Type III cysts were considered as CE3b stage for the analysis (Figure 1). Cyst size at first consultation and before any complication event was classified as: S <5 cm, M = 5-10 cm, L >10 cm, based on the largest diameter and according to the WHO-IWGE classification [6].

The majority (58.33%) of CE3b cysts seen in our center were treated with several courses of ABZ followed by at least 24 months of WW. This length of observation in the absence of treatment (≥ 24 months) was considered long enough to avoid confounding effects (“carry-over effect”) of the ABZ treatment on the outcome due to the natural history of the cyst during
the WW period [18, 19]. Patients were therefore grouped as “ABZ only”, “ABZ/WW”, and “WW only” as schematized in figure 2.

Complications were divided into mild, severe and lethal. Complications considered unrelated with ABZ intake were: abdominal pain, gastrointestinal symptoms, and allergic cutaneous manifestations (mild), and cyst rupture, development of biliary fistula, infection of the cyst cavity, secondary dissemination, and anaphylactic shock (severe). Adverse events considered likely to be associated with ABZ treatment were: alopecia, self-limiting, up to 5-fold increase in liver enzymes, rash, abdominal pain, gastrointestinal symptoms, and headache (mild), and bone marrow suppression and liver damage [20, 21] (severe). To our knowledge, only one case of death related to ABZ treatment has been reported in the literature [22].

**STATISTICAL ANALYSIS**

For the statistical analysis, periods of ABZ treatment and periods of WW follow-up were considered separately. Thus, periods of ABZ intake by patients classified as “ABZ only” and as “ABZ/WW” were analyzed together and compared with periods of WW observation undergone by patients classified as “WW only” and “ABZ/WW” (“treated” vs “observed” periods, figure 2).

Univariate and multivariate analysis were performed using a Cox proportional hazard model to investigate the effect of the variables age, sex, origin, type of treatment (“treated” or “observed”), cyst size and presence of other echinococcal hepatic cysts on outcome (inactivation or relapse). Differences in cumulative time to inactivation and time to relapse between “treated” and “observed” groups were investigated using the Kaplan-Meier estimator. Incidence of complications were calculated together with their 95% CI and compared between treatment groups using an exact binomial test. All analyses were performed using STATA software (Stata Corporation, College Station, TX, USA). A p-value <0.05 was considered significant.
RESULTS

Data from 60 patients, seen over 27 years (1985-2012) in our centre and fulfilling the inclusion criteria, were extracted from the database. Median follow-up was 43 months (IQR 10.7-141.5, range 2-306). Patients included 34 males and 26 females, with a mean age of 43.63 years (range 8-75).

Forty-six (76.6%) patients were from Italy, of whom 28.2% were from the endemic region of Sicily, while 14 (23.3%) were immigrants, mainly from North Africa and Eastern Europe. The most frequent hepatic location was the VII segment (19 cysts, 31.6%). Seventeen (28%) patients had also hepatic inactive cysts (CE4 and CE5) in addition to the CE3b considered for the analysis. Only one patient harbored two CE3b cysts. Size at diagnosis was available for 50 CE3b cysts: S = 7 (14%); M = 29 (58%); L = 14 (28%).

Patient classification according to clinical management is detailed in figure 2. Median cumulative length of ABZ intake was 12.2 months (IQR 4.2-38.3), while median WW observational period was 48.8 months (IQR 30.8-116.9). Of the 17 patients who received ABZ throughout the follow-up, 7 reached stable inactivation, 1 became inactive but relapsed once and then remained CE3b, and 9 remained unchanged. One of the patients with a cyst that reached inactivation had been also treated with PAIR while receiving ABZ. Of the 8 patients who received WW only, none became spontaneously inactive. Of the 35 patients who received periods of ABZ interspaced by periods of ≥ 24 months WW, 3 reached stable inactivation, 19 became inactive but relapsed (once n=10, twice n=4, three times n=4, four times n=1) and 13 remained CE3b. Of the patients who reached stable inactivation, one had also been treated with percutaneous drainage. Of the patients who relapsed, one received PAIR, one received PAIR followed by surgery, and one underwent radiofrequency thermal ablation during the observation period [23]. Of the patients who remained CE3b, one also underwent PAIR and one was surgically treated. Median time to inactivation and time to relapse are shown in table 1.

The univariate and multivariate analysis showed that ABZ treatment was positively associated with inactivation (hr 5.50, CI 2.61-11.60; p < 0.001 univariate analysis; hr 7.18; CI 2.66-19.40; p = 0.001 multivariate
analysis), while Italian origin was negatively associated with inactivation (hr 0.26; CI 0.09-0.76; p=0.01 univariate analysis; hr 0.29; CI 0.08-0.96; p=0.04 multivariate analysis). None of the variables analyzed were associated with relapse. The influence of ABZ treatment and WW approach on inactivation and relapse are depicted in Kaplan-Meier survival plots (Figure 3). Significantly, more cysts reached inactivation during ABZ intake and in a shorter time than during WW periods. Additionally, no difference was found in rate and time to relapse between cysts during ABZ or WW periods.

Multiple complications were experienced by 6 patients, while 8 patients had a single occurrence of a complication. The most common complication was abdominal pain (6 patients, 12 episodes), followed by biliary tree communication with jaundice or compression of biliary vessels (4 patients, 7 episodes). Other complications were allergic reactions (4 cases with 2 reporting rash and 2 anaphylactic shock episodes, of difficult interpretation and without available documentation), cyst rupture (2 cases), bacterial infection of the cyst (1 case), and increased liver enzymes (2 cases) and anaemia (1 case) while on ABZ.

While on ABZ, the incidence of mild events was 0.053 (IC 0.0194–0.1154) events per year and that of severe events was 0.0176 (IC 0.0021–0.0638) events per year. While on WW, the incidence of mild events was 0.0403 (CI 0.0193-0.0741) per year and that of severe events was 0.0403 (CI 0.0193-0.0741) per year. No statistically significant differences were found in the incidence of adverse events between the two treatment groups.

Of the 60 patients included in the study, 24 (40%) did not have a consultation during the last two years of the studied period (i.e. in 2011 and 2012) or longer. Of these, 11 (46%) could not be reached at the telephone number provided at the time of the visit. Of the 13 patients (54%) who could provide information, 4 (31%) returned for a visit in late 2013: one patient was diagnosed with a relapse seven years after the last visit, one remained a stable CE5, and two remained CE3b three years after the last visit. Of the 9 patients who were only interviewed by telephone (69%), one underwent surgery in another hospital as he wanted
the cyst removed) and was not evaluated further since then, one patient died for reasons unrelated to CE, two patients declared to be followed in another hospital closer to their residence, and all other patients did not seek further medical advice because they declared to be asymptomatic and deemed further visits unnecessary.

**DISCUSSION**

The introduction of the WHO-IWGE classification of echinococcal cysts, followed by the expert consensus for CE diagnosis and treatment, has provided a long needed framework for the clinical management of this condition [4, 6]. Nevertheless, the current management of CE is still largely based on expert opinion and moderate to poor evidence [4]. Four treatment modalities are currently available for CE (surgery, percutaneous treatments, medical therapy with benzimidazole derivatives such as albendazole, and a watch and wait approach). However, longitudinal controlled studies comparing the efficacy and effectiveness of the different treatment options for specific clinical stage are lacking. As a consequence, the issue of “best” treatment for echinococcal cysts of the liver is still controversial [4].

CE3b cysts are the least responsive to non-surgical treatments and relapse almost invariably occurs soon after ABZ discontinuation [15, 16]. However, in our experience they often show an indolent behavior with infrequent development of complications and as such they are often assigned to a “watch-and-wait” approach when a surgical intervention does not appear to be necessary. We analyzed treatment outcome and incidence of complications in patients with hepatic CE3b cysts managed with either albendazole or watch-and-wait approach to evaluate their effectiveness and safety.

Our results show that ABZ treatment was positively associated with inactivation, while reactivation after initial response to treatment was not associated to either approach. Thus, during ABZ treatment cysts showed a higher probability to become inactive and inactivation occurred in a shorter time period compared to cysts that were managed expectantly. In addition, the probability of and time to relapse after
initial ABZ-induced inactivation did not significantly differ during ABZ or WW periods. This is unlikely to be related to any percutaneous interventions, as the final outcome of the 5 patients who received this treatment was indeed stable inactivation in only 1 case. These results indicate that treatment with ABZ does not induce permanent inactivation of CE3b cysts, at least not in our cohort. There should be caution in drawing conclusions on the feasibility of WW as an approach for CE3b cysts due to the limitations of our study and by the complete absence of other studies on this subject in the literature.

While temporary response to ABZ treatment was predictable, the correlation between outcome and geographical origin of patients is difficult to explain. This different behaviour is likely not due to the presence of different CE genetic strains in different areas as recent investigations have shown that the G1-G3 E. Granulosus sensu stricto genotype complex is largely prevalent in all endemic areas [24-29]. Cyst size was unrelated to treatment outcome, in contrast with what reported by Stojkovic et al. [30].

We found no statistically significant difference in the rate of complications during ABZ or WW. Thus, the decision not to treat uncomplicated CE3b cysts seems to be unrelated to an increased risk of developing a mild or severe adverse event in our series, at least over a median observation period without treatment of 48.8 months. One of the two patients who reported an anaphylactic reaction (undocumented) during WW was receiving Amoxicillin-Clavulanate at that time, a drug that might have caused this event [31]. As for the second patient reporting an episode of shock, this occurred before she presented to our clinic. Because we never witnessed the event, the actual occurrence of a true anaphylactic shock should be taken cautiously.

Surgery was performed on 3 patients during WW period, due to biliary communication (n = 2) and cyst infection (n = 1). However, we observed biliary communication with jaundice also during ABZ intake periods, although this did not result in the decision to refer patient to surgery due to patient-related issues.
The loss of CE patients to follow-up is a problem commonly faced by clinicians. In our series, of those patients who did not have a consultation during the last two years of the studied period (i.e. in 2011 and 2012) or longer and could be reached by telephone, 38% declared that they did not seek further medical advice because they were asymptomatic and they did not consider a control visit necessary. However, it is extremely important to stress that a constant, long-term follow-up of patients with CE3b cysts is mandatory when surgery is not considered the first choice based on a patient-tailored approach, and clearly, an improvement in the doctor-patient relationship and a better explanation of the necessity of regular follow-up of even asymptomatic CE cysts has to be sought. Indeed, major complications such as rupture into the biliary tree may develop during both WW and ABZ treatment, therefore non-surgical approaches, including WW, should be considered only for those patients who adhere strictly to the follow-up schedule.

CONCLUSIONS

In conclusion, our study shows that ABZ treatment does induce inactivation of CE3b cysts, but this is only temporary. Additionally, during WW CE3b cysts remain stable over time. As the rate of adverse events during ABZ treatment and WW observation did not differ significantly, we conclude that expectant management might represent a viable option for patients with asymptomatic CE3b cysts that do not warrant surgery and who can comply with follow-up. In the majority of cases, patients with CE3b cysts have been receiving treatment(s) with ABZ interrupted by observation periods without treatment. Therefore, a direct comparison between those treated with ABZ and those untreated was not possible. Longer prospective observation of a larger cohort after assignment to clearly distinct management options is needed to confirm our findings.
ABBREVIATIONS


COMPETING INTERESTS

All the authors declare no competing interests exist.

AUTHORS’ CONTRIBUTIONS

Drafting of study protocol writing and data extraction: FR, FC, RL; data analysis: ADS; drafting and revisions of paper: FT, EB, FR.

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Figure 1. Schematic representation of the natural history of hepatic CE and suggested treatments. Black arrows: proposed cyst natural history based on clinical observation (Brunetti E., unpublished) Solid black arrow indicates natural evolution toward inactivation; black dashed arrows indicate evolution of therapy-unresponsive chronic stages. US images: cyst ultrasound classifications according to WHO-IWGE (in bold) and Gharbi[17]. WHO stage CE3b had not been explicitly described by Gharbi but could be classified as Type III[32]. Gray boxes: suggested stage-specific approach to uncomplicated hepatic CE [4, 15, 33]. ABZ = Albendazole; PAIR = Puncture, Aspiration, Injection of scolecidal agent, Re-aspiration; PC = Permanent Catheterization

Figure 2. Patients grouped by clinical management

Figure 3. Kaplan Meier Survival Curve of Inactivation and Relapse
REFERENCES


<table>
<thead>
<tr>
<th>Outcome</th>
<th>ABZ (n=17)*</th>
<th>ABZ/WW (n=35)*</th>
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<td>N</td>
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<td>Relapse</td>
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<td>6 (5-30.5)</td>
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<td>Unchanged</td>
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<td>5 (3.5-7)</td>
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<td></td>
<td>3</td>
<td>4 (4-20)</td>
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**Table 1. Evolution of cysts according to treatment approach over time.**

*Time in months is expressed as median (IQR).*
<5 cm ABZ; 5-10 cm PAIR + ABZ; >10 cm PC + ABZ

Watch-and-Wait

CE1 Gharbi I

CE3a Gharbi II

CE4 Gharbi IV

CE5 Gharbi V

Chronicization

Inactivation

CE2 Gharbi III

CE3b Gharbi III

<5 cm ABZ (?) ; >5 cm Surgery + ABZ

Figure 1
Figure 2

INACTIVATION

Percent of active (CE3b) cysts

p < 0.001

RELAPSE

Percent of inactive (CE4) cysts

p = 0.091

Days

WW
N = 43

ABZ
N = 52
Figure 3

CE3b

ABZ only
N=17
ABZ throughout follow-up OR follow-up without ABZ < 24 months

ABZ/WW
N=35
ABZ treatment AND WW ≥24 months

WW only
N=8
No ABZ treatment

TREATED
Periods of ABZ

OBSERVED
Periods of WW