Long-Term Evaluation of Patients with Hydatidosis Treated with Benzimidazole Carbamates

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Four hundred forty-eight patients with 929 *Echinococcus granulosus* hydatid cysts received 3- to 6-month continuous cycles of mebendazole or albendazole treatment and underwent prolonged follow-up by clinical visits and imaging studies (range, 1–14 years) to assess the long-term outcome of treatment. Degenerative changes and relapse were assessed by imaging techniques. At the end of therapy, 74.1% of the hydatid cysts showed degenerative changes. These were more frequent in albendazole-treated than in mebendazole-treated cysts (82.2% vs. 56.1%; $P < .001$). During long-term follow-up, 104 cysts (22%) had degenerative changes that progressed, whereas 163 cysts (~25%) relapsed. The percentages of relapses in the two drug-treated groups were almost the same. Relapses occurred more frequently in type II cysts of the liver. Cysts recurred most often (78.5%; $P < .001$) within the first 2 years after treatment ended. Further chemotherapy cycles induced degenerative changes in >90% of relapsed cysts without inducing more frequent or more severe side effects than those observed during the initial cycles.

Cystic hydatid disease caused by *Echinococcus granulosus* is still an important public health problem in many parts of the world, such as Mediterranean and South American countries. Furthermore, it is becoming more frequent in other countries, such as the United States, as an imported disease [1].

Benzimidazole carbamates (mebendazole and albendazole) are anthelmintic drugs that inhibit the assembly of tubulin into microtubules, thus impairing uptake of glucose and interfering with the homeostasis of the parasite [2]. Since their introduction in the 1970s, benzimidazoles have proved effective against the larval stages of *E. granulosus,* first in vitro, then in animals, and later in humans [3, 4].

See editorial response by Schantz on pages 310–1.

In the early 1980s, we began using chemotherapy with benzimidazole carbamates to treat hydatid disease caused by *E. granulosus.* At the end of treatment, more than two-thirds of the cysts showed degenerative changes, including a volumetric reduction, membrane detachment, increased solid component, and calcification [5].

In this work, we report the results obtained during long-term follow-up (at least 1 year) of a series of patients with hydatidosis treated with benzimidazole carbamates.

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All patients gave their informed consent to the study and the local ethical committee approved the procedures.

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Materials and Methods

Patients and cysts. From January 1982 until March 1997, in the II Chair of Infectious Diseases of the Department of Infectious and Tropical Diseases, University of Rome "La Sapienza," 448 patients (191 male and 257 female; mean age, 52 years; range, 4–86 years) with singly identifiable *E. granulosus* cysts located in various body organs underwent chemotherapy for hydatidosis: 125 patients received mebendazole and 323 received albendazole.

All of them attended the outpatient clinic for follow-up assessment for at least 1 year after the end of chemotherapy. Patients treated early in the series were randomly assigned to receive mebendazole or albendazole; patients treated from 1989 onwards received albendazole alone.

Because of the difficulty in identifying and counting the cysts, we excluded from the study patients who had multiple cysts that were difficult to identify singly or widespread hydatidosis or both disorders.

The diagnosis of hydatid disease was based on morphological features detected by imaging techniques (ultrasonography, chest radiography, CT, MRI) and immunologic tests (immunoelectrophoresis, immunoblotting, histamine release test).

Drugs. Of the total of 929 singly identifiable hydatid cysts, 289 (178 in the liver, 59 in the abdomen, and 52 in the lung) were treated with mebendazole and 640 (440 in the liver, 57 in the abdomen, and 143 in the lung) with albendazole. Because some patients received mebendazole and albendazole, their cysts were included in both series. Albendazole (SmithKline Beecham, London, UK), was given orally, twice daily, at a total dosage of 10–12 mg/(kg · day), and mebendazole (Janssen Pharmaceutica, Beerse, Belgium) was given orally, three times a day, at a total dosage of 50 mg/(kg · day). Patients received

Table 1. Results of treatment of 929 hydatid cysts with benzimidazole carbamates in patients infected with *Echinococcus granulosus.*

	Mebendazole (n = 289)			Albendazole (n = 640)		
Parameter	Liver	Abdomen	Lung	Liver	Abdomen	Lung
No. of cysts treated	178	59	52	440	57	143
No. of cysts evaluated	165	55	51	417	55	139
No. of cysts changed	77	34	41	342	37	123
% with degenerative changes	46.6	61.8	80.4	82.1	67.3	88.5

both drugs in continuous 3- to 6-month cycles, sometimes repeated.

Clinical and imaging assessment and follow-up. Patients with lung cysts had chest radiographic examinations before treatment and after 1, 3, or 6 months of treatment. Patients with liver and abdominal hydatid cysts underwent ultrasonography before treatment and after 1, 3, or 6 months. Some patients also underwent CT or MRI. Assessments were repeated every 6–12 months during follow-up.

As an index of degeneration of the hydatid cysts induced by the two benzimidazole carbamates, we assessed the following morphological changes: volumetric reduction (>10% until disappearance), detachment of parasitic membranes, pseudosolidification, reduction or disappearance of daughter cysts, and calcification.

For the sonographic classification of the hydatid cysts, we followed the criteria proposed by Caremani et al. [6]: type I, simple cyst; type II, cyst with daughters; type III, cyst with membrane detachment; type IV, mixed-type cyst (with partial solidification); type V, heterogeneous cyst; type VI, hyperechoic cyst; and type VII, calcified cyst.

Table 2. Side effects observed during the first cycle of chemotherapy for hydatid cysts in patients infected with *Echinococcus granulosus.*

Side effect	Mebendazole (n = 125)	Albendazole (n = 323)
Elevated alanine aminotransferase and aspartate aminotransferase	16	67
Abdominal pain	14	40
Headache	3	8
Distention	5	7
Vertigo	1	5
Urticaria	3	5
Jaundice	1	1
Alopecia	5	4
Thrombocytopenia	0	2
Dyspepsia	4	2
Fever	0	3
Asthenia	0	2
Tachycardia	0	2
Patients who stopped treatment for side effects	8	6

NOTE. Data are no. of patients. Some patients experienced more than one side effect.

During therapy, all patients underwent clinical, blood chemical, and immunologic assessment. Liver, kidney, and hematopoietic function were tested every 10–15 days during treatment. World Health Organization protocols were used to determine indications and contraindications for chemotherapy: chemotherapy was used for patients who could not undergo surgery or who had nonradical surgery. Contraindications for chemotherapy included complications of hydatid cyst(s) (e.g., infection, rupture); pregnancy; impaired liver, hemopoietic, and/or kidney function; and lack of cooperation of the patient [7, 8]. In addition to patients with compulsory indications for chemotherapy, patients who had refused surgery and chosen medical treatment as the first approach also received chemotherapy [9].

Imaging techniques were used to detect relapse, or reactivation of parasitosis, defined as the appearance of new cysts, evidence of exogenous vesiculation from the cyst, volumetric increase, appearance or increase in the liquid component of the matrix, and disappearance of membrane detachment.

The mean duration of follow-up among the 448 patients was 22 months (range, 12–170 months).

Statistical analysis. Rates and means of differences within each group of cysts and patients were compared by two-tailed Student's t test and the χ^2 test. P values of $\leq .001$ were considered to indicate statistical significance. The Bonferroni correction was used to correct for multiple statistical tests [10].

Cysts from patients who failed to complete therapy were excluded from the statistical analysis. Because both drugs have the same mechanism of action, long-term follow-up data for cysts from patients treated with both benzimidazoles were pooled.

Results

Degenerative changes at the end of treatment. Evaluation of the 929 hydatid cysts (from 448 patients) at the end of the first 3- to 6-month continuous cycle of therapy with benzimidazole carbamates showed degenerative changes in 74.1% of the 882 evaluable cysts. Degenerative changes were significantly more frequent in albendazole-treated than in mebendazole-treated cysts (82.2% vs. 56.1%; $P < .001$) (table 1). The most frequent sonographic finding (329

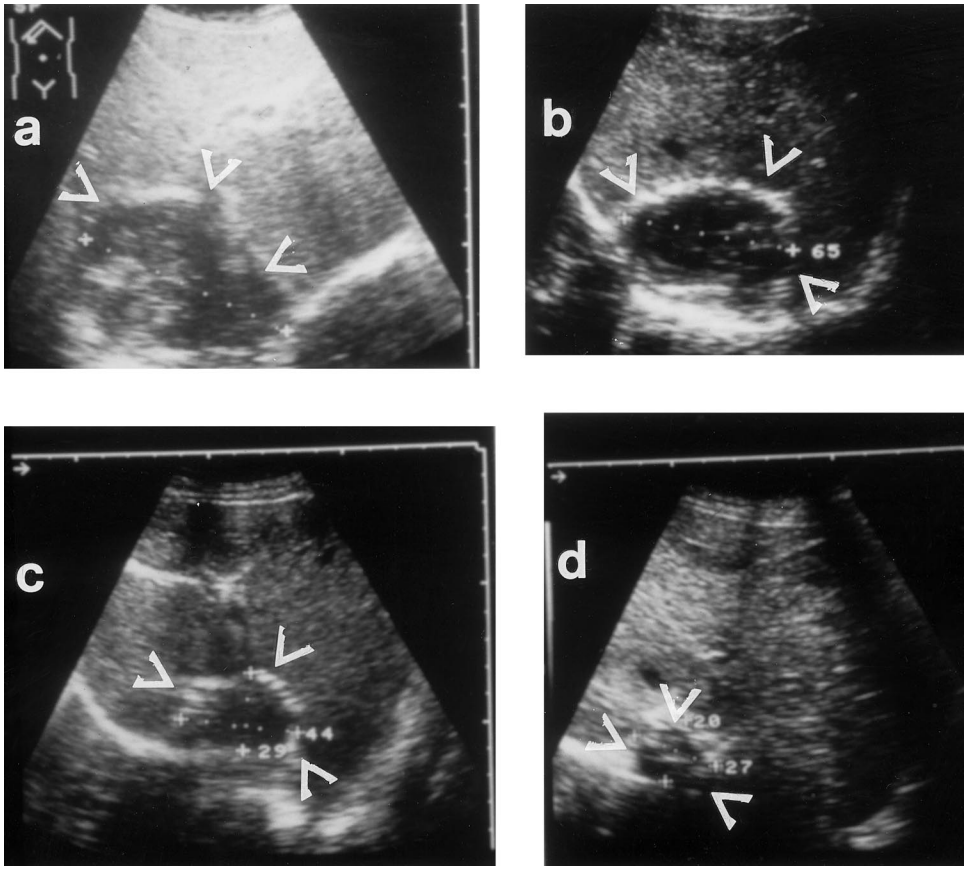

Figure 1. Sonographic scan of a liver hydatid cyst (*arrowheads*): *a,* before treatment; *b,* at the end of treatment with albendazole; *c,* 1 year after discontinuing treatment; and *d,* 3 years after discontinuing treatment. Progressive volumetric reduction and solidification can be observed.

[37.3%] of the 882 evaluable cysts) was a degenerative cystic change consisting of a reduction in the liquid component and the appearance of a pseudosolid component. Sonographic pseudosolidification occurred most frequently in cysts with daughters (type II cysts) and probably corresponded to drug-induced aseptic inflammation on the parasitic membranes of mother or daughter cysts [11]. In both benzimidazole treatment groups, volumetric reduction and membrane detachment (29% and 15.6%, respectively) were less frequent than pseudosolidification; they occurred most frequently in simple cysts (type I) and probably corresponded to altered parasite homeostasis with a reduction in the ratio between the hydatid fluid produced by the parasite and the fluid reabsorbed by the host [11].

Table 3. Long-term evaluation of hydatid cysts treated with benzimidazole carbamates in patients infected with *Echinococcus granulosus.*

Parameter	Mebendazole	Albendazole	Total
Treated cysts	289	640	929
Evaluable cysts treated with benzimidazole carbamates	271	611	882
Cysts with degenerative modifications at the end of treatment	152	502	654 (74.1%)
Cysts with further degenerative modifications after the end of treatment	34 (22.4%)	110 (21.9%)	144 (22%)
Cysts that relapsed after the end of treatment	37 (24.3%)	134 (26.7%)	163 (24.9%)

NOTE. Data are no. of cysts.

Benzimidazole carbamate–treated cysts rarely became calcified soon after treatment (3.1%); calcification occurred long after the end of treatment (1–3 years). Few cysts in either drug treatment group (~10%) completely disappeared. Most of these were lung cysts in young patients and were often expectorated.

Side effects. In some patients (~20%), the initial cycles of chemotherapy induced side effects, such as abdominal pain, meteorism, headache, alopecia, and increased serum transaminase levels (table 2).

All of these side effects were spontaneously reversible, even without discontinuation of treatment. We stopped treatment because of side effects for 14 patients only.

Long-term follow-up. Long-term follow-up of the 654 cysts that degenerated after the first cycle of chemotherapy showed that in 22% these degenerative changes advanced spontaneously, even after treatment ended (figure 1). However,

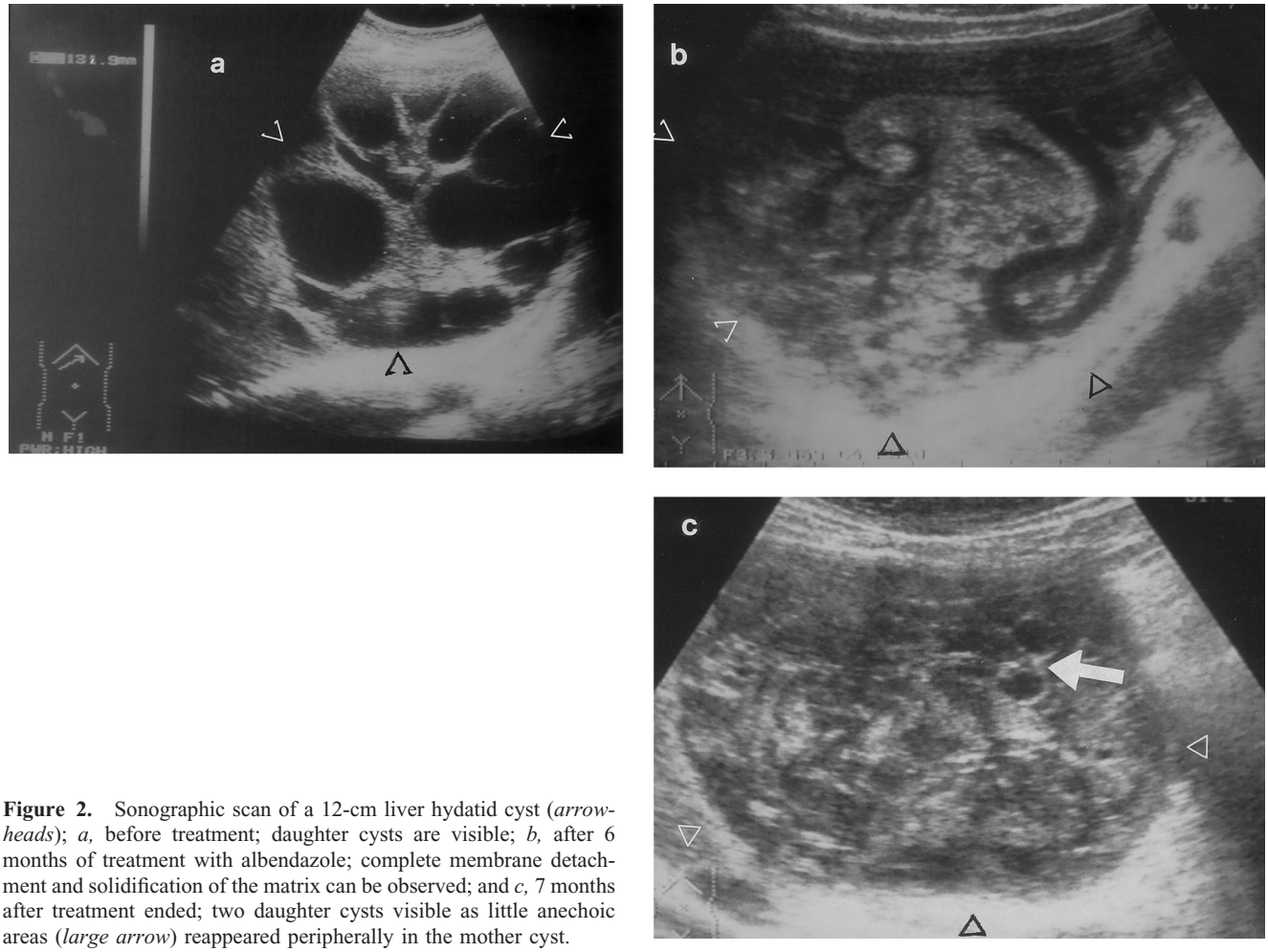

Figure 2. Sonographic scan of a 12-cm liver hydatid cyst (*arrowheads*); *a,* before treatment; daughter cysts are visible; *b,* after 6 months of treatment with albendazole; complete membrane detachment and solidification of the matrix can be observed; and *c,* 7 months after treatment ended; two daughter cysts visible as little anechoic areas (*large arrow*) reappeared peripherally in the mother cyst.

in ~25% (163 cysts in 107 patients), imaging studies showed signs of relapse (table 3; figure 2).

Analysis of the long-term results for the two drug-treated groups showed that the percentages of relapses were almost the same (24.3% for mebendazole and 26.7% for albendazole) (table 3).

The reappearance of liquid areas on sonograms showed that cysts with daughters (type II) relapsed more frequently than did simple cysts (type I) (55.2% vs. 30.6%; $P < .001$; figure 3).

The elapsed time between the end of treatment and onset of the first recurrence ranged from 1 month to 100 months. Cysts recurred most often (78.5%; $P < .001$) within the first 2 years after treatment ended, the period of highest risk (figure 4).

Cysts in younger patients (<30 years) relapsed less frequently than did cysts in older patients (14% vs. 86%; $P < .001$; table 4). Cysts located in the liver relapsed more frequently than did cysts located in the lung (33.9% vs. 9.7%; $P < .001$; table 5). Patients whose cysts relapsed underwent further cycles of chemotherapy with benzimidazole carbamates until the fifth recurrence (table 6). Further benzimidazole cycles induced degenerative changes in >90% of relapsed cysts. Some cysts relapsed more than five times (in two patients as many as eight times) but continued to respond well to chemotherapy.

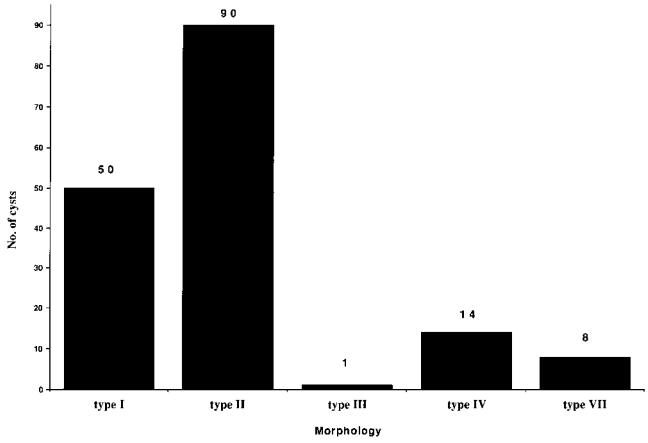

Figure 3. Correlation between relapse of hydatid cysts and their morphology [6] among patients infected with *Echinococcus granulosus.*

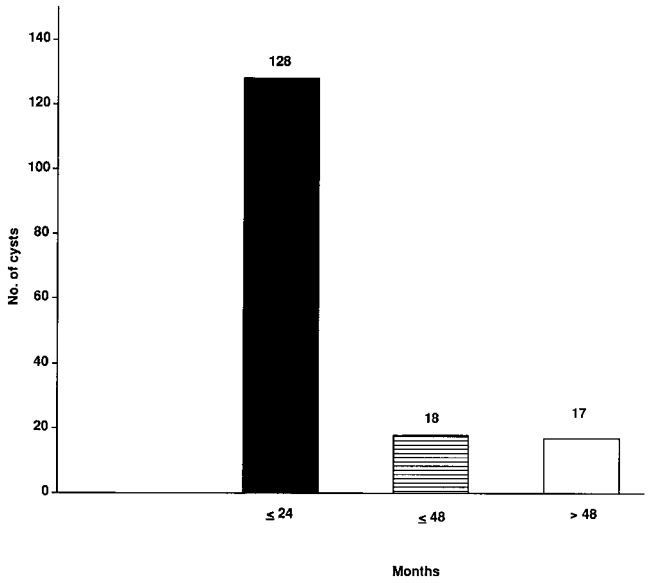

Figure 4. Times of appearance of relapse of hydatid cysts after discontinuing treatment with benzimidazole carbamates in patients infected with *Echinococcus granulosus.*

Further cycles of chemotherapy for treatment of relapsed cysts induced similar side effects that were neither more frequent nor more severe than those induced by the initial cycles. Elevation of transaminase levels occurred less frequently during further chemotherapy cycles than during the first cycle of treatment. No aftermath of adverse effects was observed during long-term follow-up.

Discussion

In imaging studies obtained after therapy, ~74% of the hydatid cysts treated with mebendazole and albendazole showed detectable degenerative changes, whereas ~26% remained unchanged (table 1). In agreement with others, we found that in some treated cysts without degenerative imaging changes, histological examination of the operative specimen disclosed evidence of drug-induced degeneration or sterilization or both effects [5, 12]. Despite being the most readily available and commonly used data, as in our study, imaging findings are therefore not entirely reliable for evaluating the outcome of chemotherapy [5, 8]. Most other assessment methods are unethical or unduly invasive.

During the long-term follow-up in our study, ~22% of the hydatid cysts that showed benzimidazole-induced degenerative changes continued to degenerate, whereas ~25% of the treated cysts relapsed. These findings suggest that benzimidazole carbamates acted more strongly in some cysts (or patients) than in others, sometimes acting as only parasitistatic drugs. In the other cysts, the degenerative changes observed after treatment neither progressed nor regressed.

Cysts with daughters (type II) relapsed more frequently than

Table 4. Characteristics at the first relapse of the 107 patients and 163 hydatid cysts that relapsed after treatment with benzimidazole carbamates.

Parameter	No.	%
Sex		
Male	55	51.4
Female	52	48.6
Age (y)		
1–30	15	14
31–60	70	65.4
>60	22	20.6
Site		
Liver	142	87.1
Lung	16	9.8
Abdomen	5	3.1

did other cysts (usually seen as the reappearance of peripheral liquid areas within the cysts), possibly because they are the most active hydatid cysts. Hence, we propose that in patients with type II hydatid cysts, especially large-sized cysts (diameter of >8–10 cm), benzimidazole administration should be prolonged. However, no morphological type of hydatid cyst is wholly safe from relapse, as shown by the occasional relapsed calcified cysts (type VII) in our patients.

The frequent relapses that we observed after treatment ended suggest the need for periodic clinical and imaging surveillance, initially at short intervals (every 3–6 months during the first 2 years of follow-up, the highest risk period for relapse) and thereafter at longer intervals (once a year). Exactly how long follow-up should continue remains unclear. Our data imply lifelong follow-up: some patients' cysts relapsed even 8 years after treatment ended.

In our patients, liver cysts relapsed more frequently than did cysts in other sites, presumably because of differences in the chemical and antigenic composition of hydatid fluid and the greater fertility and more intense metabolic activity of parasitosis in hepatic localizations than in hydatid cysts in other organs [13].

Benzimidazole carbamate treatment was significantly more effective in treating relapsed cysts than in treating the whole hydatid cysts submitted to the first cycle of therapy (90% vs. 74.1%; $P < .001$). This difference suggests that the more intense metabolic activity in cysts that have recently relapsed makes them more susceptible to the action of benzimidazole

Table 5. Correlation between relapse of hydatid cysts and their localization in patients infected with *Echinococcus granulosus.*

Localization of cyst	No. of modified cysts after one cycle of therapy	Relapsed cysts, no. (%)
Liver	419	142 (33.9)
Lung	164	16 (9.7)
Abdomen	71	5 (7)

Table 6. Outcome of further cycles of treatment with benzimidazole carbamates in the hydatid cysts with multiple relapses.

	Relapse no.				
	1	2	3	4	5
Relapsed cysts	163	69	28	18	12
Evaluable cysts	140	56	28	14	10
Cysts with degenerative modifications after further cycles of therapy	136 (97.1%)	53 (94.6%)	26 (92.8%)	12 (85.7%)	9 (90%)
Unchanged cysts	4	3	2	1	1
Worsened cysts	0	0	0	1	0

carbamates, as has already been reported for schizomycetes in the active proliferative phase and antibiotics.

Further cycles of benzimidazole treatment of patients with recurrence were safe and well-tolerated: No increase in adverse effects nor aftermaths were observed during long-term follow-up.

The choice of treatment for hydatid disease (medical or surgical) must be carefully individualized [14, 15]. The relationship between surgical and medical treatment is even more problematic in patients with hydatid cysts that relapse after chemotherapy. Whereas treatment of the first or second relapse is normally straightforward (for patient and physician alike), treatment of further relapse is not. Not only does patient compliance decrease, but also the physician is more reluctant to propose further cycles of chemotherapy.

In conclusion, the relapse of hydatid cysts after chemotherapy with benzimidazole carbamates is a growing problem because the numbers of patients treated and the follow-up periods are increasing. However, the high susceptibility of the relapsed cysts to further cycles of chemotherapy suggests that drug resistance is not developing. More data are needed from larger case series of patients with hydatid cysts to better identify factors influencing the long-term outcome of treatment with benzimidazole carbamates.

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