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Medical Treatment of Liver Hydatidosis

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Abstract. There are currently three treatment options for liver hydatidosis: urgery, which remains the mainstay of radical treatment; ultrasound-guided aspiration (puncture/aspiration/injection/reaspiration—PAIR); and chemotherapy with benzimidazole compounds (albendazole and mebendazole). Chemotherapy is a noninvasive treatment and is less limited by the patient's status than surgery or PAIR but is not ideal when used alone. Albendazole, the drug most often used, appears to have the greatest efficacy of any agent used so far; nevertheless, apparent cure (shrinkage or disappearance of cysts) ranges only between 20% and 30% of cases. The possible contribution of perioperative chemotherapy offers the prospect of preventing recurrent disease, but it requires more clinical trials to establish that pre- or postoperative chemotherapy does prevent recurrence. The main adverse events are related to changes in liver enzyme levels and bone marrow suppression. About 10% to 20% of patients develop self-limited, reversible rises in transaminase levels; clinically severe pancytopenia or agranulocytosis is exceptional. Alopecia is observed during long-term treatment with albendazole. In all cases these events disappear once treatment is interrupted. According to the World Health Organization guidelines, chemotherapy is the preferred treatment when the disease is inoperable, when surgery or PAIR is not available, or when the cysts are too numerous. Another important indication for chemotherapy is the prevention of secondary echinococcosis. There is not yet formal consensus, as the efficacy and safety of some of the methods require further evaluation before we can establish comprehensive guidelines for the medical treatment of hydatidosis.

Surgery remains the cornerstone of radical treatment for cystic echinococcosis [1], with either removal of the whole cyst or destruction using ethanol, hypertonic saline, or cetrimide solution. The development of medical treatments is important for several reasons.

1. Completely curative surgery, whatever the method, is not always possible, and other interventions involve a 2% to 15% risk of relapse in hyperendemic areas [2–4]. (Most patients treated in France come from these regions and have often undergone operations beforehand.)
2. Even in ideal conditions the operative mortality rate ranges from 0.9% to 3.6% for the first operation with considerable additional morbidity. This risk increases with further surgery, reaching 6% for the second operation and 20% for the third operation in some series [2]. Postoperative hospitalization is often lengthy. Medical treatment might reduce the operative risks or even the need for further operations and hence the length of hospitalization.
3. Cyst rupture may also occur spontaneously; and surgical damage (accidental or deliberate) of the cyst(s) can lead to spillage and widespread dissemination in the peritoneal or pleural cavities. A major problem is recurrence due to incomplete removal or destruction of the cyst. It has been estimated that between 11.3% [5] and 30% [6] of patients have a recurrence within 5 years of the first surgical procedure.
4. There are both temporary and permanent contraindications to surgery, linked to the difficulty reaching the lesion, the poor condition of some patients operated on several times, some patients' refusal to undergo surgery, and in some highly endemic regions long hospital waiting lists and a lack of adequate medical structures or experienced staff (or both) [7].

Chemotherapy with benzimidazole compounds and the more recently developed PAIR method (puncture/aspiration/injection/reaspiration) with concomitant chemotherapy offer new options for the treatment of CE, especially for inoperable cysts and patients with a high surgical risk. The following short review discusses only noninvasive treatment of liver echinococcosis.

Chemotherapy of Cystic Echinococcosis

Until the early 1980s and the first treatment attempts with benzimidazole compounds—albendazole (ABZ) mebendazole (MBZ) [8–11]—surgery was the only treatment, and the general progress made in antiparasitic therapy (especially that of helminthiasis) had no beneficial impact on human echinococcosis. It has long been known that effective parasiticidal, or at least parasitostatic, chemotherapy is required. This objective ought to have been attained, but the use of the two drugs has expanded in such an empiric manner that it has become almost impossible to conduct controlled trials complying with the rules of good clinical practice. In most published papers on medical treatment it is only the responders who are documented, and it can be difficult to tell whether a given patient's status remained unchanged or deteriorated [12].

The choice of benzimidazole carbamates was primarily related to their mode of action and pharmacologic properties. The mode of action of benzimidazole carbamates includes a direct effect on

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Table 1. Clinical response to albendazole.

Data source	No. of patients	Cured	Improved	No change	Worse
European data	253	72 (28.5%)	129 (51.0%)	46 (18.1%)	6 (2.4%)
Publications	1116	372 (33.3%)	469 (42.0%)	275 (24.6%)	
Total	1369	444 (32.4%)	598 (43.7%)	327 (23.9%)	

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the cumulus oophorus and perhaps also on the wall of the cyst, whose permeability might be increased [13]. Factors influencing the efficacy of benzimidazoles have not been well defined, but it is conceivable that the size and the age of the parasite, the calcification, and the fibrosis correlate with the outcome of the therapy. The penetration of drugs across cyst walls depends on the nature of the cyst. "Recent" cysts and those with thin walls inside the hepatic parenchyma showing little or no appreciable pericystic fibrosis are more accessible to drugs than "old" cysts with thick, partially "cartilagenous" or calcified walls. For the same reasons, extrahepatic cysts (e.g., those in lung and peritoneum) are probably more accessible to these drugs.

The pharmacology of these drugs [14, 15] also influences their action. MBZ was designed as a broad-spectrum anthelminthic drug active against intestinal nematodes. To limit the risk of adverse reactions, it had to be poorly absorbed. ABZ proved to be a more interesting product showing better absorption and tissue distribution than previous benzimidazole molecules [13–15]. It differs from MBZ in two respects: It is absorbed at a higher rate than MBZ [16], and it undergoes almost total first-pass metabolism to its effective protoscolicide metabolite ABZ sulfoxide [13, 17], whereas liver metabolism of MBZ leads to inactive metabolites and a loss of antiparasitic activity [15, 18]. ABZ sulfoxide is found in plasma and cyst fluid, and its plasma concentration in hydatid-infested patients is about 10 to 40 times higher than that of mebendazole [19, 20]. Cyst fluid concentrations of ABZ sulfoxide are much lower than plasma levels but are considerably higher than those obtained with MBZ [20], which may explain the better clinical response seen with ABZ. It was suggested that tissue, cystic, and intracystic concentrations of the drug and its metabolite show a better correlation with therapeutic efficacy than peripheral or portal levels [10], but more recently no significant correlation could be found between ABZ sulfoxide or the parent drug in the cyst and cyst nonviability [21]. The failure of the MBZ fluorinated analog flubendazole to penetrate hydatid cysts suggested that it did not offer a viable alternative to MBZ or ABZ for treatment of echinococcosis [20, 22].

The first published results on the treatment of hydatid cysts with mebendazole appeared spectacular, but these data were obtained in trials involving a small number of patients and were not confirmed subsequently [23]. The difficulties interpreting the studies that followed were primarily due to their heterogeneity: Indications frequently differed from one series or one patient to the next (or even in one individual over the course of time); the doses and duration of administration varied from single to repeated courses; monitoring varied from several weeks to several years; and the end points were often solely clinical (74% of patients in the initial studies showed a "subjective improvement"). Moreover, the natural history of echinoccocosis remains poorly understood [24]. During the natural course of infection some cysts may grow and then persist unchanged for many years, whereas others spontaneously collapse and disappear, as exemplified by results showing that most asymptomatic liver hydatid patients (in Argentina) remain symptom-free for more than 10 years regardless of the cyst size or type (and echographic features), and that such carriers are at a low risk of developing complications; hence it is difficult to establish specific rules for their therapy, if any [25]. Consequently, one should keep in mind that a "cure" or apparent stabilization during medical treatment may be the result of spontaneous resolution.

Because individual studies undertaken since 1977 produced inconsistent results, in 1981 the World Health Organization (WHO) set up a multicenter clinical study to improve the evaluation of chemotherapy with potential efficacy in human echinococcosis. A standard methodology, introduced in 1985 in the WHO working group and the European compassionate use programs, formed the basis of almost all published data [26–28].

Two trials were conducted between 1982 and 1987. The first was an open, nonrandomized trial involving 121 patients. The success rate (partial or total) was 14% in the MBZ group and 30% in the ABZ group [27]. The second trial analyzed results from 112 patients and suggested that ABZ was more effective than MBZ (39.1% vs. 16.7% of "successes"), but there were few patients and the difference was not statistically significant at the 5% level [28].

As a whole, in studies comparing the response to ABZ and MBZ [27–31] 75.5% of patients responded to ABZ, and 58.2% to MBZ, using a lower daily dose of ABZ and a much shorter treatment period. In two of these studies analyzing the individual cyst response, 48.1% and 24.2% of cysts disappeared or shrank, respectively (giving a total of 72.3% of "successes"), on ABZ, compared with 27.9% and 29.7% with MBZ (57.6% of "successes") [29, 31].

Today ABZ is the drug most often used. In 1997 Horton reviewed the data collected or published during 12 years of experience with ABZ (1983–1995) [12] since the initial publications [9, 10]. Among the data collected through the compilation of European compassionate-use results from SmithKline Beecham files [12] and published data, the number of evaluable patients (n = 1369) was approximately 38% of the total (n = 3532).

Clinical Response

As with WHO method of evaluation, clinical outcome is classified as cure, improvement, no change, or worsening, irrespective of the number of organs with cysts (Table 1). A degree of response was observed in more than 75% of patients. According to the WHO working group, when evaluated up to 12 months about 30% of patients showed cyst disappearance (cure), 30% to 50% showed cyst degeneration or a significant size reduction (improvement), and 20% to 40% exhibited no change (i.e., failure), although it is unclear whether in this group the patient's status remained unchanged or worsened [32]. Chemotherapy seems to be more

Table 2. Cyst response to albendazole.

Data source	Evaluable cysts	Cure	Improved	No change	Worse
European data	435	160 (35.2%)	187 (41.1%)	102 (22.4%)	6 (1.3%)
Publications	2912	663 (22.8%)	1418 (48.7%)	831 (28.5%)	
Total	3347	823 (24.6%)	1605 (48%)	919	

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effective in young than in older patients. Small cysts with a thin wall, without infection or communication, and secondary cysts are mostly susceptible to chemotherapy; chemotherapy may, however, be less effective on daughter cysts within a mother cyst.

Cyst Response and Viability

The available data (until 1997) give an overall cyst response rate (cured or improved) of 72.6% (Table 2). A detailed analysis of the two sets of data shows that the best efficacy is observed with liver, lung, and peritoneal cysts (about 76% success). Surgical data suggests that only 50% of cysts are viable at surgery [3, 4, 21].

There is only one prospective, controlled, randomized, open study of ABZ in patients with liver hydatid disease that assessed parasite viability after treatment in all patients. Two groups of patients received ABZ for 1 or 3 months, respectively; surgery alone was used in a control group; and all patients underwent surgery on completion. Altogether, 50% of cysts in the control group were found to be nonviable versus 72% and 94% in the 1-month and 3-month ABZ groups, respectively. Protoscolex and cyst viability were significantly lower in treated patients than in controls. Treatment was also associated with total cyst membrane disintegration. This study confirmed that the echographic response (increase in echogenicity) correlates with cyst nonviability: 68% of cysts treated for 3 months showed changes ultrasonographically, and only 1 of 20 cysts that showed changes during treatment was judged viable [21].

Treatment Duration

In general, treatment was administered in three or four courses lasting 4 weeks separated by 14-day intervals. With treatment lasting less than 3 months (i.e., one or two cycles) 59% of patients responded, compared to 74% and 83% with 3 to 5 months or more than 6 months of therapy, respectively. The proportion of responders rose slightly with the duration of treatment, but the additional benefit from more than 6 months of treatment was marginal for most patients. Three courses are routinely recommended, in agreement with viability data suggesting that a maximum benefit is not reached with less than 3 months of therapy; more than 6 months of treatment is rarely necessary [32]. Cyclic treatment was originally recommended, but more recent data on uninterrupted treatment show that this approach could have better efficacy over 3 to 6 months or longer with no increase in adverse events [31–35].

Recurrence

Four published studies evaluated recurrences after medical therapy in series of patients followed for a significant number of years [31, 36–38]. A wide range of recurrence rates was observed, from less than 3% to as high as 30% of cases. In a 5-year follow-up study, 22.7% of patients relapsed, but they had received short courses of treatment [36]. A similar high recurrence rate of individual cysts was recorded in a study of 337 patients [31], in which relapses after therapy with MBZ or ABZ were observed in approximately 30% of cases, but is is unclear how many recurred during the 2 years after the first course of treatment. The lowest recurrence rate was 2.9% (two cases) among 68 patients followed for up to 7 years [38]. About 95% of the recurring cysts showed good susceptibility to retreatment.

Table 3. Adverse reactions in 780 patients with cystic echinococcosis treated with albendazole.

Reaction	%
Elevation of transaminases	14.7
Abdominal pain	5.7
Loss of hair	2.8
Vertigo/dizziness	1.3
Nausea	1.3
Reversible leukopenia	1.2
Abdominal distension	0.6
Urticaria	0.5
Jaundice	0.5
Thrombopenia	0.3
Allergic shock	0.3
Bone marrow toxicity	0.1
Cyst pain	0.1

Adapted from the World Health Organization (WHO) guidelines [32].

Adverse Events

The main adverse events are related to changes in liver enzyme levels (Table 3). Approximately 10% to 20% of patients develop rises in transaminases at some time during treatment, but these rises are mild to moderate, self-limiting, and reversible on cessation of treatment. Values usually normalize during the drug-free interval between courses. In a recent review, aminotransferases increases (ranging from two- to fourfold the normal values in most patients) were observed in 12.9% of 448 patients without other risk factors who were treated with ABZ or MBZ [39]. The enzymatic increase was always reversible and slight, even without stopping treatment; it was less frequently observed during further cycles of therapy. The increase in transaminases correlated with the effectiveness of therapy and with the earlier occurrence of degenerative cyst modifications. Although liver enzyme evaluations could be due to pericystic inflammation secondary to the marked host immune reaction or cyst release of material toxic to the liver (a drug–parasite interaction) [40], direct hepatocyte toxicity cannot be excluded. During treatment of neurocysticercosis with ABZ, liver enzyme abnormalities were noted in only 0.3% of

cases [41], suggesting that the site of the cyst is the determinant factor rather than the drug [12]. Only 12 of 316 patients in the European data (3.8%) had treatment withdrawals for liver enzyme abnormalities.

The second major event is bone marrow suppression of unknown origin. This toxicity has also been reported with MBZ and is probably linked to a benzimidazole class effect. Clinically, severe pancytopenia, neutropenia, or agranulocytosis is exceptional, although two deaths attributed to ABZ agranulocytosis have been reported [12].

Less severe adverse events are relatively frequent, the most noteworthy being alopecia during long-term treatment with ABZ followed by regrowth after treatment cessation. The other common events reported during echinococcosis treatment with ABZ have included abdominal pain, loose stools, nausea, vomiting, and headache.

In summary, the commonest recorded events leading to withdrawal are liver function abnormalities and alopecia. In all cases these events disappeared once treatment was interrupted.

Drug Treatment Concomitant with Surgery

Preoperative treatment with benzimidazoles has been reported to soften the cysts, thereby reducing intracystic pressure and simplifying their removal. It has also been shown to reduce significantly the protoscolex and cyst viability and hence the risk of secondary echinococcosis and recurrence [42]. The required duration of such treatment has not been definitively determined, but it is no less than 3 months [21].

The possible contribution of perioperative chemotherapy offers the prospect of preventing recurrent disease [43, 44], but there are no published data on the added benefit of postoperative ABZ in patients undergoing a complete surgical cure. It requires more long-term controlled clinical trials to establish that pre- or postoperative chemotherapy prevents recurrence. Currently it is recommended only when there is cyst spillage at surgery, partial cyst removal, or biliary rupture. According to the WHO guidelines, preoperative treatment with benzimidazoles should begin at least 4 days before surgery and last 1 month (ABZ) or 3 months (MBZ) [32].

ABZ Treatment Concomitant with PAIR

Ultrasound-guided cyst puncture with aspiration of cyst fluid and injection of protoscolicidal substances, introduced in 1986, is minimally invasive and less risky than surgery [45–47]. It confirms the diagnosis and removes a larger number of protoscolices and antigens with the aspirated cyst fluid. In a randomized study comparing percutaneous drainage with ABZ to ABZ or drainage alone, Khuroo et al. showed that a maximum size reduction was observed in cysts treated with a combination of percutaneous drainage and ABZ [48]. In a subsequent randomized study they demonstrated that percutaneous drainage combined with ABZ therapy is an effective, safe alternative to surgery for treating uncomplicated liver cysts (including multivesicular cysts) and requires a shorter hospital stay [49]. In the WHO guidelines PAIR is indicated for inoperable disease and in those who refuse surgery; it must be accompanied by chemotherapy to minimize the risk of recurrence. As for surgery, 4 days of treatment with benzimidazoles before PAIR is considered mandatory, and it should continue 1 month (ABZ) or 3 months (MBZ) after the procedure. Nevertheless, Filice and Brunetti thought that because the peak serum level of ABZ is reached 4 hours after administration it is sufficient to start treatment 4 hours before the procedure; they noted that a maximum of 4 weeks after drainage is necessary only for large cysts (>7 cm in diameter) [50].

Other Drugs

Use of praziquantel (PZQ), an isoquinoline derivative, has been proposed at a dose of 40 mg/kg once a week concomitant with benzimidazole. In a study of the effect on protoscolices' viability using a combination of ABZ plus PZQ (25/mg/kg/day) compared to ABZ alone as preoperative treatment in patients with intraabdominal hydatidosis, ABZ plus PZQ was more effective than monotherapy with ABZ [51]. PZQ might also be useful in cases of operative spillage, but the rationale behind such treatment needs to be confirmed. Another benzimidazole compound, oxfendazole, has been tested for cystic echinococcosis in naturally infected animals and seems at least as effective as ABZ and is easier to administer; determination of its relative efficacy warrants a comparison with ABZ [52].

WHO Guidelines

According to the WHO guidelines, chemotherapy is indicated for inoperable primary liver or lung echinococcosis and for patients with multiple cysts in two or more organs and peritoneal cysts. Another important indication for chemotherapy is the prevention of secondary echinococcosis. Presurgical use of ABZ or MBZ can reduce the risk of recurrence of cystic echinococcosis and facilitate the operation [42]. Concomitant chemotherapy is also recommended for PAIR. Chemotherapy is contraindicated for large cysts that are at risk of rupture (superficially situated, infected cysts) and for inactive or calcified cysts. Patients with chronic liver diseases and with bone marrow depression should not undergo benzimidazole treatment. Early pregnancy is a contraindication, and chemotherapy during the later stages of pregnancy is rarely indicated.

The usually recommended oral dosage of ABZ (Eskazole, SmithKline Beecham, England) is 10 to 15 mg/kg/day in two divided doses for several 1-month courses separated by 14-day intervals. This cyclic method of treatment was originally recommended because of the limited toxicology data available at the time of the first treatment attempts [9, 10]. More recent data show that continuous treatment could have better efficacy over 3 months or longer with no increase in toxicity [31, 33, 35], but this strategy remains to be validated by further clinical trials. The usual oral dosage of MBZ (Vermox, Janssen Pharmaceutica, BorgoSan Michele, Italy) is given as 500 mg tablets in daily doses of 40 to 50 mg/kg (in three divided doses) for at least 3 to 6 months. Better intestinal absorption of benzimidazole compounds is gained by administering it with a fat-rich meal [53] or by combining it with cimetidine [54]. Medical and laboratory examinations for adverse reactions are initially necessary every 2 weeks and then monthly. Ideally, serum drug concentrations are monitored after 2 and 4 weeks of therapy, respectively, to identify levels that are possibly toxic (too high) or ineffective (too low); but few laboratories have the capability to assay ABZ sulfoxide or the

MBZ parent compound, and those are mainly in Western countries.

Conclusions

There are currently three treatment options for hydatid disease: surgery, ultrasound-guided aspiration, and chemotherapy. Each of these therapeutic modalities has limitations depending on the individual case. Chemotherapy is a noninvasive treatment that can be used in patients of any age (although there is little experience in children); it is less limited by the patient's status than is surgery or PAIR. Chemotherapy is the preferred treatment when the disease is inoperable whatever the reason (e.g., patient's status, multiple cysts in several organs, peritoneal cysts), when surgery or PAIR is not available, or if the cysts are too numerous. In humans, benzimidazole treatment is a useful advance in the management of hydatid disease but is not ideal when used alone. ABZ appears to have the greatest efficacy of any agent used so far, although the apparent cure (shrinkage or disappearance of cysts) rate is only 20% to 30%. The above WHO guidelines, published in 1996, were based on the results of two earlier meetings of the WHO Informal Working Group on Echinococcosis [55] held in 1992 and 1994, but there is not yet formal consensus, as the efficacy and safety of some of the methods require further evaluation to establish comprehensive guidelines for the medical treatment of hydatidosis.

Résumé

A présent, il existe trios options thérapeutiques pour l'hydatidose hépatique: la chirurgie, qui reste le traitement radical de référence, la ponction aspiration echo-guidée (PAEG) et la chimiothérapie (composés à base de benzimidazole (albéndazole et mebendazole)). La chimiothérapie est un moyen non invasif dont l'utilisation est moins limitée par l'état du patient en comparaison avec la chirurgie ou la PAEG, mais cette option n'est pas idéale lorsqu'elle est utilisée seule. De tous les agents utilisés jusqu'à présent, l'albendazole, utilisé le plus souvent, semble être le plus efficace; néanmoins, on ne constate la cure apparente, (rétrécissement ou disparition des kystes) qu'entre 20 et 30% des cas. La chimiothérapie offre la possibilité théorique de prévention des récidives mais il faut pour cela plus d'essais cliniques afin de confirmer si la chimiothérapie pré et/ou postopératoire prévient réellement la récidive. Les effets secondaires principaux de ces médicaments sont en rapport avec les variations du taux d'enzymes hépatiques et les effets sur la moelle osseuse. Dix à 20% des patients développent une élévation, habituellement limitée mais réversible, des transaminases; une pancytopénie ou une agranulocytose sont par contre exceptionnelles. On peut observer une alopécie lors du traitement au long cours par l'albendazole. Dans tous les cas, tous ces effets secondaires disparaissent lorsqu'on arrête le traitement. Selon les recommandations de l'OMS, la chimiothérapie représente le traitement préféré pour les patients qui ne sont pas opérables, lorsque la chirurgie ou la PAEG ne sont pas possibles ou lorsque les kystes sont trop nombreux. Une autre indication importante de la chimiothérapie est la prévention de l'échinococcose secondaire. Il n'y a pas encore de consensus formel puisqu'il faut encore évaluer l'efficacité et la sûreté de certaines méthodes thérapeutiques avant de pouvoir ériger des recommandations globales pour le traitement médical de l'hydaditose.

Resumen

En la actualidad, para el tratamiento de la hidatidosis hepática existen 3 posibles opciones: 1) la cirugía, que constituye la única terapéutica radical; 2) la aspiración del contenido quístico previa punción guiada mediante ecografía (p AIR); 3) la quimioterapia con compuestos de bencimidazol (albendazol y mebendazol). La quimioterapia por sí sola no constituye el tratamiento ideal; es una terapia no invasiva que debe prescribirse cuando el estado del paciente desaconseje el acto quirúrgico o la p AIR. El albendazol es el medicamento más empleado pues constituye la droga terapéutica más eficaz. Sin embargo, sólo se observa la desaparición o reducción del tamaño de los quistes en el 20-30% de los casos. Se ha descrito que el tratamiento perioperatorio con esta droga podría prevenir las recidivas, pero se precisan más estudios clinicos para evaluar si este tratamiento médico pre y postoperatorio es o no efectivo. Las reacciones adversas del medicamento son: modificaciones de los niveles séricos de las enzimas hepáticas e inhibición de la función de la médula ósea. En 10-20% de los pacientes aumentan transitoriamente las transaminasas; pancitopenias graves o agranulocitosis son excepcionales; tratamientos prolongados ocasionan alopecia. En todos los casos estas complicaciones son reversibles, remitiendo al interrumpir el tratamiento. De acuerdo con las directrices de la WHO, la quimioterapia es el tratamiento de referencia, siempre y cuando se juzgue que el paciente es inoperable, cuando no se disponga ni de cirugía ni de p AIR o cuando los quistes sean muy numerosos. La indicación "princeps" de la quimioterapia es la prevención de la equinococosis secundaria. En la actualidad, no hay consenso por lo que a la eficacia y seguridad del tratamiento médico se refiere. Se necesitan más estudios para establecer las directrices del tratamiento médico de la hidatidosis. Clinical response to albendazole. Cyst response to albendazole. Adverse reactions in 780 patients with cystic echinococcosis treated with albendazole.

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