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Medical Treatment of Cystic Echinococcosis

Irina Magdalena Dumitru

Abstract

Medical treatment in cystic echinococcosis is limited; albendazole remains the gold treatment for patients with low hydatid cysts or those with inoperable echinococcosis. Due to uncommon side effects, administration may be continuous (cycles of 28 days with a break of 14 days between courses) as well as discontinuous over long periods of time. In recent years, there have been many concerns for the testing of various substances and drugs against *Echinococcus granulosus*, both in vitro and in vivo, on the animal model, but the results have not been satisfactory. New clinical trials are required, as well as the development of an effective vaccine to limit the spread of echinococcosis in endemic areas.

Keywords: albendazole, hydatid cysts, medical treatment, vaccine, endemic areas

1. Introduction

Treatment of uncomplicated cystic echinococcosis (CE) is complex and consists of medical treatment, surgical and puncture, aspiration, injection, and reaspiration (PAIR), depending on the characteristics of the cyst. For some cases (CE4 and CE5), a conservative “watch and wait” approach is preferred (**Table 1**) [1, 2], because hydatid cysts may spontaneously regress with calcification without chemotherapeutic intervention [3].

Medical treatment has a role in reducing the size of cysts and stopping their development and reducing infectivity and is the only therapeutic option in inoperable cases. The combination of medical treatment with surgery (preoperative and postoperative administration) or PAIR plays a role in preventing recurrences [4].

2. The current state of knowledge

Mebendazole (MBZ) was the initial agent, but it has proven less effective than albendazole over time (10–15 mg/kg/day, maximum 800 mg orally in two doses) [5]. Because MBZ is insoluble in water and has a poor solubility and bioavailability, the drug is poorly effective [5]. The recommended regimen is 40–50 mg/kg/day, orally in three divided doses during meals, in long-term therapy (more than 2 years), and the success rate is 14–49% of cases [1]. MBZ is more effective in small cysts <5 cm in size, and the therapeutic response was superior in pulmonary (83%) than in hepatic (18%) locations [6]. MBZ treatment is well tolerated in long term therapy; adverse events have been described in 5–40% of patients—gastrointestinal distress, hair loss, neutropenia, anaphylactic reactions, glomerulonephritis, vertigo,

WHO classification	Suggested practice
CE1	Albendazole alone if <5 cm PAIR + albendazole if >5 cm
CE2	Surgery + albendazole or Non-PAIR PT + albendazole
CE3a	Albendazole alone if <5 cm PAIR + albendazole if >5 cm
CE3b	Surgery + albendazole Non-PAIR PT + albendazole
CE4 and CE5	Wait and watch

Table 1.
Treatment modalities stratified by cyst stage [1].

headache, psychic conspicuousness, hematotoxic effects, and abnormal levels of serum transaminases [7]—and so MBZ treatment is not recommended in pregnant women during the first trimester of pregnancy because it is associated with congenital abnormalities of the fetus [8].

The standard regimen of albendazole (ABZ) is cycles of 28 days with a break of 14 days between courses, but duration of treatment is different depending on many factors.

Velasco-Tirado et al. show that in a meta-analysis performed on 33 cystic echinococcosis treatment-related studies, there are insufficient data to standardize the results, and the optimal duration of therapy has not yet been established [9].

A study conducted by Dumitru et al., in Constanta, Romania, on 320 patients diagnosed with hydatid cyst, during 5 years (2008–2013), showed that six therapeutic cures were necessary before the first healing signs appeared [10] in most of cases and the response to treatment depends on the location of the cyst, size, and type according to Gharbi classification and immune status.

Related to location, albendazole treatment's efficiency is higher in the case of hepatic or pulmonary localization than in other localizations (7.428571 ± 1.886039 cures) [11]. Dimension <7 cm (especially <5 cm) responds better to medical treatment, and the number of therapeutic cures administered for the CE1 (6.739 ± 1.91 cures) is significantly smaller than the number of cures administered for the CE3 (8.181 ± 2.39 cures) [11]. Long-term treatment with albendazole (more than 6 months) was only used for multiple or inoperable CE [11].

In the same study, we concluded that patients with good immune status responded better to albendazole treatment than to patients with $CD4 < 500$ cells/ mm^3 ; also, the presence of comorbidities such as diabetes and chronic hepatitis was a negative predictive factor [11].

An additional study, conducted by the same team on a group of HIV-infected patients diagnosed with CE, with low $CD4 (<200$ cells/ mm^3), demonstrated that continuous therapy with albendazole 800 mg/day, administered more than 6 months, was not effective, and $CD4$ count can be a predictive factor for response to medical treatment [12].

Preoperative treatment with albendazole begins 1–3 months (average 14 days) before surgery and/or PAIR and continues for 1–3 months posttreatment [1, 3].

Because absorption of albendazole in humans is very variable, it is considered that concomitant administration of fatty meal would increase the absorption [13].

In recent years, the occurrence of resistance to albendazole has been frequently discussed, which greatly limits the medical treatment of echinococcosis [14]. Recent study conducted by Mortezaei et al. has shown that genetic makeup and miRNA

profile of helminths affect their response to albendazole sulfoxide (ABZ-SOX) and revealed significant differential expression of let-7 and miR-61 at different drug concentrations [14]. This may explain the poor response to ABZ-SOX in some patients and requires the emergence of more effective new therapies.

A large meta-analysis conducted on 711 patients from 5 countries shows that multivesicular, multi-septated, and transitional cysts responded poorly to benzimidazoles (BMZ) and were associated to a high rate of relapses and BMZ are effective only in small cysts (diameter < 6 cm) [4]. Other factors that influence the response to therapy with benzimidazoles are age, because young patients respond much better to treatment than older people, and on the other hand, cyst localization influences the response to treatment; bone cysts were less susceptible to BMZ than hepatic or pulmonary echinococcosis [11, 15].

Albendazole long therapy is well tolerated; therefore, many clinicians prefer continuous therapy more than discontinuous therapy.

Because ABZ is nowadays considered a relatively safe drug, continuous therapy is preferred over discontinuous treatment protocols. The reported side effects were more frequent hepatotoxicity, alopecia, and gastrointestinal disturbances and less common jaundice, severe headache, cough, jaundice, vertigo, and itching [16]. ABZ is embryotoxic and teratogenic in pregnant women [17].

Recent studies have shown that concomitant administration of ABZ with certain drugs has a synergistic effect. Adding metformin to classical treatment with ABZ (an antidiabetic drug) has increased the efficacy of ABZ in vitro and in vivo (mouse models) [18, 19]. ABZ-mefloquine combined treatment seems a promising combination, with results slightly superior to monotherapy with ABZ [20].

In recent years, researchers' efforts have focused on new ABZ formulations that lead to better tissue and organ penetration, including liposomes, biodegradable microspheres, and polymer conjugates. In this manner the drug is released for prolonged periods of time, improving the therapeutic effect [21].

Praziquantel (PZQ) is a less effective antiparasitic drug than albendazole in the treatment of CE but in combination with ABZ might be helpful than ABZ alone in disseminated and inoperable cases [22, 23]. PZQ 40 mg/kg once a week in combination with ABZ 800 mg/day has proven more effective than ABZ alone, both before surgical intervention or PAIR and in the treatment of inoperable cases [23, 24]. Also, a combined therapy with ABZ 10 mg/kg/day and PZQ 25 mg/kg/day is effective as a prophylactic, preoperative treatment [25].

Isolated studies have demonstrated the antiparasitic properties of some drugs in vivo or only in vitro, but all studies have concluded that there is no alternative drug to albendazole to treat echinococcosis and it needs more research to discover new drugs [26, 27].

- **Ursodeoxycholic acid** had some scolicidal effects and can be administered to patients with poor response to albendazole therapy, in combination [28].
- ***Lawsonia inermis* and *Achillea millefolium* extracts** are a potent protoscolicidal which may be used as a scolicidal agent during the surgery. *Achillea millefolium* extracts at the concentration of 3 mg/ml after 5 minutes of exposure killed all of the protoscolices, and *Lawsonia inermis* extracts at concentration of 3 mg/ml after 10 minutes of exposure killed also all the protoscolices [28].
- **Sodium arsenite (NaAsO₂)** administered in combination with albendazole significantly increases sensitivity of *Echinococcus granulosus* protoscoleces to ABZ, and the maximum protoscolicidal effect was seen with the combination 20 μM NaAsO₂ + 80 μM ABZ [29].

- **Garlic chloroformic extract** had high protoscolicidal effects in recent study conducted by Barzin et al. in 2019 and could substitute other agents. The study compared the effectiveness of garlic extract with sodium chloride and silver nitrate and demonstrated that the protoscolicidal effects of the garlic extract at 1 ($P < 0.001$) and 2 ($P < 0.001$ and $P = 0.003$) minutes of exposure were higher than those of sodium chloride and silver nitrate. At 5 minutes of exposure, there was no difference between the garlic extract and sodium chloride ($P = 0.36$) [30].
- Anti-theilerial drugs **MMV689480 (buparvaquone)** and **MMV671636 (ELQ-400)** have demonstrated a cytotoxic effect [29]. Buparvaquone impaired parasite mitochondria, and with an IC_{50} of $2.87 \mu\text{M}$ and $0.02 \mu\text{M}$, respectively, against in vitro cultured *E. multilocularis* metacestodes, buparvaquone can be an effective therapeutic choice [31].
- *Myrtus communis* methanolic extract and *Tripleurospermum disciforme* have proven a scolicidal effect [30]. They can be used during hydatid surgery and could prevent the secondary infection. The results indicated that the highest scolicidal effect (100%) of *M. communis* was obtained at 100 and 50 mg/ml concentrations and LC_{50} in 10, 20, and 30 minutes were 11.64, 7.62, and 6.47 mg/ml, respectively. Further studies are required for identification of the active ingredients in the extracts [32].
- **Chitosan nanoparticles containing curcumin (Ch-Cu NPs)** had a good activity against *Echinococcus granulosus* in study published by Napooni et al. and can be considered an anti-protoscolex agent [33].
- **Mebendazole C1 (M-C1)** and **mebendazole C2 (M-C2)**, two isoforms obtained from the reaction of mebendazole with epichlorohydrin, have superior efficacy on *Echinococcus multilocularis* protoscoleces and metacestodes compared to mebendazole [34]. It was also found that the introduction of an epoxy group to mebendazole reduced its cytotoxicity in rat hepatoma (RH) cells. The conclusion of the study was that introduction of an epoxy group to mebendazole improved the solubility of mebendazole, increased the parasiticidal effects on *E. multilocularis*, and reduced its cytotoxicity in RH cells [34].
- **Anacardic acid (AA)** is a natural product isolated from the Brazilian cashew-nut shell liquid and presented a high activity against metacestodes of *Echinococcus multilocularis* (*E. multilocularis*) and *Echinococcus granulosus sensu stricto* (*E. granulosus* s.s.) in vitro and in vivo [35]. Yuan et al. demonstrated that anacardic acid (AA) has better efficacy than albendazole (ABZ) in vitro against *Echinococcus* metacestode and has similar efficacy to albendazole in vivo and the researchers concluded that AA may be an effective anti-*Echinococcus* drug in the future [36].
- **Pentamidine** (MMV000062), **alpha-difluoromethylornithine** (MMV001625), and **suramin** (MMV637953) were all tested in vivo against *E. granulosus*, but did not show any effects [36, 37].
- **Rifampicin** (MMV688775) and **miltefosine** (MMV688990) were ineffective in vivo against *E. granulosus* [36, 38].

- **Amphotericin B** (MMV689000) which is an antifungal drug has demonstrated a good activity against *E. multilocularis* metacestodes in vitro at 2.7 μ M [39–41]. Reiter et al. concluded that in some cases, amphotericin B therapy may be a salvage treatment in patients with progressive human alveolar echinococcosis [39] but is considered a limited therapy and is administered to well-selected patients due to increased nephrotoxicity [40, 42].
- **Nitazoxanide** (MMV688991) has been studied by Stettler et al. who demonstrated that it has a good activity against *E. granulosus* metacestodes and protoscoleces in vitro [43–46]. Nitazoxanide was also tested in vivo in mice and in human patients with cystic (CE) and alveolar (AE) echinococcosis, but no beneficial effects were observed compared to ABZ [43–46].
- **Auranofin** (MMV688978) is a thioredoxin-glutathione reductase inhibitor and has the property of killing *E. granulosus* protoscoleces and is also active against *E. multilocularis* metacestodes [47, 48]. The studies reported a good efficacy in vitro at 2.5 μ M after 48 h [49, 50].
- **Mefloquine** (MMV000016) is an antiparasitic drug used in malaria, active on *Plasmodium* spp., which has proven to be effective against *Echinococcus multilocularis* metacestodes in vitro and in vivo [51–54]. In a study conducted by Küster (2011), oral administration of mefloquine (25 mg/kg of body weight administered twice a week for a period of 8 weeks) was compared with albendazole (200 mg/kg/day) or mefloquine intraperitoneally compared with albendazole. The study was performed on mice infected with *Echinococcus multilocularis* and showed similar efficacy of mefloquine administered intraperitoneally, compared to oral albendazole [52]. Oral administration of mefloquine at higher doses and over a long period of time (200 mg/kg, 5 days per week, during 4 weeks followed by treatments of 100 mg/kg during the last 7 weeks) had superior efficacy [53].
- **Pomegranate peel aqueous extract** (PGE) in combination with albendazole has anti-hydrating and anti-inflammatory effects in vivo, in mice infected with *Echinococcus granulosus* [55]. The researchers consider that PGE has a significant additive anti-hydatid effect and is beneficial in the preventive treatment of recurrences [55].
- ***Pelargonium roseum*** and ***Ferula gummosa*** are essential oils with scolical properties, without side effect [56]. Tabari et al. have shown that protoscoleces of *E. granulosus* have a high potential against their two main constituents, citronellol and β -pinene, and toxic effect on *E. granulosus* in intraoperative use in hydatid cyst patients.
- BMZ analogs like **fenbendazole**, **flubendazole**, **oxfendazole**, and **triclabendazole** have been evaluated in the last years, in vitro and in vivo studies (animal models), but did not provide superior efficacy compared to mebendazole or albendazole [57].
- **Ivermectin** is an antiparasitic drug which is used against nematodes and has scolical activity if injected directly into the cyst during laparoscopy in a rodent but has a poor activity if administered orally due to low cyst penetration [58].
- **Cyclosporine A** is an immunosuppressant drug and described scolical activity in vitro and can be used for pre- and posttreatment in surgery or aspiration techniques [59].

- **Imatinib and pyridinylimidazoles** (anti-neoplastic drugs, kinase inhibitors) show therapeutic effects on the parasite, both in vitro and in vivo, on the animal model [60].
- Natural compounds like **thymol, menthol, and plant extracts** (*Trachyspermum ammi* L. fruit essential oil, *Zataria multiflora* and *Origanum vulgare* essential oils, *Salvia officinalis*, *Mentha* spp. essential oil, *Rosmarinus officinalis* essential oil, *Allium sativum* methanol or chloroform extract, *Berberis vulgaris* aqueous extract, *Cnidium monnieri* osthole, *Corylus* spp., *Curcubita* spp. hydroalcoholic extracts, *Curcuma longa* ethanol extract, *Mallotus philippinensis* fruit methanol extract, *Nigella sativa* seed essential oil, *Olea europaea* leaves aqueous extract, *Penicillium* extracted chitosan, *Penicillium aculeatum* in silver particles, *Pestalotiopsis* spp. ethyl acetate extract, *Pistacia atlantica* fruit methanol extract, *Punica granatum* peel aqueous extract, *Salvadora persica* root ethanol extract, *Sambucus ebulus* fruit methanol extract, *Satureja khuzestanica* leaves hydroalcoholic extract, *Trametes robiniophila* Murr. aqueous extract, and *Zingiber officinale* ethanol extract) have protoscoleces effects in vitro or in vivo, in different administrations such as oral or intragastric administration [57].

Recent studies have also tried to make albendazole more effective through nanotechnology. Ullio Gamboa et al. have demonstrated that ABZ lipid nanocapsules (ABZ-LNCs) are more effective than ABZ in vivo, in *Echinococcus granulosus* infected mice, in oral administration [61]. These results suggest that ABZ-LNCs could be a promising drug in the treatment of cystic echinococcosis in patients who are poorly responsive or nonresponsive to classical therapy with albendazole.

3. Future directions

In the future, vaccination could prevent the spread of echinococcosis in endemic regions. Zhao et al. identified six dominant T-cell epitopes and five dominant B-cell epitopes in the EgA31 protein structure and six dominant T-cell epitopes and three dominant B-cell epitopes in EgG1Y162 which may represent a beginning for multi-epitope vaccines against *Echinococcus granulosus* [62]. Miles et al. identified 9 novel proteins and 14 peptides to be further tested as potential cystic echinococcosis vaccine candidates [63]. Pilot field trial of the EG95 vaccine against ovine cystic echinococcosis conducted by Larrieu et al. in Argentina demonstrated a decrease in EC incidence and a good surveillance and control tool in the epidemiological chain of the parasite [64].

The development of recombinant bi-vaccines expressing EG95 *Echinococcus granulosus* antigen is a new orientation in the future. Goatpox (GPV) disease and cystic hydatidosis can be prevented by live-attenuated GPV AV41 vaccine; the GPV is an ideal vector for expressing the EG95 antigen [65]. The same group of researchers have developed another recombinant, bivalent vaccine using morbillivirus (SRMV) which expresses EG95 antigen [66], preventing both morbillivirus infection and *Echinococcus granulosus* infection.

Given that treatment in the CE is limited, new clinical trials are needed to find potential drugs and new strategies to limit transmission of infection.

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