

# Comparative analysis of anti-relapse treatment regimens in 110 patients with hepatic and pulmonary hydatid echinococcosis

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**Abstract. – OBJECTIVE:** Hydatid echinococcosis is worm disease caused by *Echinococcus granulosus*, that is primarily detected in the liver and lungs. This study aimed at determining the clinical tolerance and efficacy of albendazole in patients with cystic echinococcosis, depending on the volume of the previous one.

**PATIENTS AND METHODS:** We retrospectively (from 2016 to 2020 years) analyzed patients who have been treated with two treatment regimens (28-day courses with a 14-day break and continuous drug intake for 60 days), which are used in the Russian Federation. There were 110 patients (after surgery) who had hydatid echinococcosis of the liver and lungs; the diagnosis of these patients was confirmed morphologically (intra-vitam). A retrospective analysis was carried out on the following matters: (1) the duration of anti-relapse chemotherapy depending on the localization of the parasitic cyst; (2) chemotherapy's side effects and long-term relapses after treatment. We evaluated patients' tolerability of albendazole according to the level of blood cells count and hepatic enzymes. The effectiveness of anti-parasitic treatment was evaluated by imaging studies that did not reveal the growth of new parasitic cysts even in the presence of serum antibodies to echinococcal antigens.

**RESULTS:** A correlation was found between the choice of antiparasitic treatment regimen and the frequency of adverse reactions in lab tests: more often adverse reactions (drug-induced hepatitis, anemia, granulocytopenia) occurred in patients who received a continuous treatment regimen for 60 days ( $p < 0.05$ ). The frequency of relapses reached 4.5% and was more often observed in patients who received treatment for 28 days with a 14-day break.

**CONCLUSIONS:** Continuous drug intake for 60 days is the most effective.

*Key Words:*

Hydatid echinococcosis, Side effects, Tolerability, Chemotherapy.

## Introduction

Echinococcosis is one of the most dangerous zoonoses caused by *Echinococcus granulosus*, its diagnosis and treatment remain a pressing medical and social issue in many countries, including Russia<sup>1-3</sup>.

*Echinococcus granulosus* is a cestode that consists of a head with four suckers and a double crown of hooks, a neck and 3-6 segments, 7 mm long. A mature segment and eggs, together with feces, enter the soil and inseminate pastures, forests, reservoirs, as well as premises for animals and people<sup>20</sup>. A human becomes infected by contact with a sick animal (most often a family of canids), or by eating wild berries, as well as unwashed vegetables, fruits contaminated with echinococcus eggs.

Echinococcus eggs do not differ from those of other teniids and easily lose their shell; therefore, they are present in the feces and in the external environment as a mature invasive larva. Some of the larvae, entering the host organism, can overcome the hepatic and pulmonary barriers, therefore, they can be localized in any organ, where they turn into a larvocyst – a cyst filled with fluid, which slowly expands due to concentric increase. The formed cyst contains elements of both the parasite, including antigenic substances, and the host<sup>21</sup>.

The wall of the cyst consists of two layers: chitinous (external) and germinal (internal). The thickness of the outer shell can reach 2000 microns. The germinal layer itself produces brood capsules connected by a stalk to the cyst wall. Inside the cyst, there is a cystic fluid that may contain protoscolices. The latter are formed from a small bubble that has grown from the germinal layer. This blister may separate from the cystic fluid within the cyst or daughter cysts. Inside single-chamber bubbles, daughter bubbles can

form, from which grandchildren are born, having the same structure as the mother ones. The liquid contains hydatid sand, consisting of brood capsules and protoscolexes<sup>22-23</sup>.

In some cases, it is possible to develop a sterile echinococcal blister without brood capsules and scolexes. Then, they are called acephalocysts, which are considered viable, but are not pathogenic to the host. From cysts containing protoscolexes, an adult helminth can develop when it enters the body of the final host. If a cyst ruptures in an intermediate host, the cysts can spread to other tissues. Daughter larvocysts can grow endogenously (into the cavity of the maternal blister) and exogenously, which is extremely rare in humans. Also, larvocysts can bud off and continue to develop independently<sup>23,24</sup>.

It should be noted that a person is a dead-end host for *Echinococcus granulosus*, on which the development cycle of this parasite ends; therefore, it does not pose an epidemiological danger to others. At the same time, more than 70 species of mammals, including farm animals, can be intermediate hosts of this helminth<sup>24</sup>.

*Echinococcus* spp. is characterized by intraspecific variability; therefore, some time ago, *E. granulosus* was subdivided into strains depending on the range, morphology, and pathogenicity. However, it is now more appropriate to use the term "genotype" because intraspecific polymorphism is based on genotyping rather than other diagnostic methods (especially morphological) that were previously used to distinguish between strains<sup>25</sup>.

Echinococcosis is a widespread disease that occurs on all continents except Antarctica. Currently, about 1 million people in the world are affected by echinococcosis<sup>26</sup>. The incidence of rural residents in some areas of South America (Argentina, Peru), East Africa and Asia (Central Asia and China) reaches 10%. Infected people from the listed regions are often involved in breeding domestic animals (mainly the canine family and cattle) or hunting, which involves butchering carcasses of wild animals such as wolves, jackals, foxes<sup>28</sup>. Mortality due to cystic echinococcosis was approximately 1,200 cases in 2010 compared to 2,000 cases in 1990. The annual economic cost of echinococcosis is estimated at about US \$3 billion<sup>27</sup>.

It should be noted that the average incidence of echinococcosis in some regions, including Russia, is high. The annual human incidence of *E. granulosus* in endemic areas can exceed 50 cases per 100,000, and in parts of Central Asia, China, Peru, Argentina and East Africa, the prevalence of this

disease can reach 5-10%. The leader in the incidence of cystic echinococcosis is South America, which is considered a hyperendemic continent, where the infection of farm animals with this parasite reaches 95%<sup>28</sup>. According to the latest data from "Rosspotrebnadzor"<sup>29</sup> (an organization dealing with sanitary and epidemiological aspects in the field of infectious diseases in the Russian Federation), the prevalence of echinococcosis in the Russian Federation has been at the level of 1 case per 100,000 population for a long time.

The absence of a specific picture of the disease, late diagnosis and untimely treatment, as a rule, ends with surgical removal of a parasitic cyst, although the effectiveness of conservative treatment with albendazole (ABZ) has been proved, and, according to WHO recommendations, it can be used as an independent method<sup>4-7</sup>. In case of surgical removal of an echinococcal cyst, many authors<sup>8-11</sup> agree on the need for postoperative antiparasitic chemotherapy, especially in complicated forms.

There are two groups of the drugs for treatment cystic echinococcosis (CE): Benzimidazoles (in particular ABZ) and praziquantel (PZQ) are effective against CE<sup>12,13</sup>. Although numerous trials<sup>14,15</sup> have been performed in search of novel therapeutic options to curb the neglected zoonosis, no other nonsurgical options are currently available to replace the licensed antiechinococcal drugs ABZ and mebendazole (MBZ). In recent years, drugs of the benzimidazole group have become widespread, with ABZ being the most acknowledged and popular. Albendazole is better adsorbed from the gastrointestinal tract than MBZ, which makes it easy to achieve the required concentration in the blood at various doses<sup>16</sup>. The positive feature of this drug is that its main metabolite (ABZ sulfoxide) is highly effective in echinococcosis<sup>17</sup>. In the Russian Federation, treatment with ABZ at a dose of 10 mg/kg of the patient's body weight is carried out in courses of 28 days at 14-day intervals and/or continuously for 60 days.

The purpose of the study is to optimize the treatment schemes for patients with echinococcosis of liver and lungs.

## Patients and Methods

From 2016 to 2020, 110 patients with CE turned to the Clinical Department of Medical Parasitology and Tropical Medicine of Sechenov

**Table I.** Distribution of patients by localization of hydatid cysts.

| Location        | Male |      | Female |      | Total |        |
|-----------------|------|------|--------|------|-------|--------|
|                 | Abs. | %    | Abs.   | %    | Abs.  | %      |
| Liver           | 30   | 27.2 | 38     | 34.8 | 68    | 62     |
| Lungs           | 13   | 11.8 | 18     | 16.2 | 31    | 28     |
| Liver and lungs | 6    | 5.4  | 5      | 4.6  | 11    | 10     |
| Total           | 49   | 44.4 | 61     | 55.6 | 110   | 100.00 |

University. Among them there were 59 (53%) women and 51 (47%) men; the sex distribution (women/men) was 1:1.15.

The distribution of patients by location of hydatid cysts is presented in Table I. According to the data presented in this study, the liver was most often affected by hydatid cysts, found in 68 patients (62% cases); lungs were affected in 31 patients (28% cases), and combined liver and lung lesions were found in 11 patients (10% cases).

Thus, the vast majority of patients (79 patients) had liver lesions – 72% (79 patients out of 110), of which 68 patients (86% of all liver lesions) had isolated liver lesions, 11 patients (14% of all liver lesions and 10% of all patients) had hydatid cysts in liver and lungs. Isolated lung lesions were observed only in 31 patients (28% of all patients) (Figure 1).

Concomitant diseases that burden the general condition of patients were detected in 64 (58%) out of 110 people. Patients with diabetes mellitus, hypertensive and ischemic heart disease deserved special attention. There were no immunosuppressive conditions in the patients treated in our department.

The diagnosis of CE was based on physical examination: ultrasound scans (USs), magnetic resonance imaging (MRI), or multispiral computed

tomography (MSCT), as well as data from morphological studies of biopsy material in previously operated patients, as determined by the World Health Organization Informal Working Group on Echinococcosis (WHO-IWGE) criteria<sup>18</sup>. Serum antibodies (Ab) against Echinococcus antigens (Ag) were determined using an Enzyme-Linked Immunosorbent Assay (ELISA) (Echinococcus-IgG, kit, Vector-best, Russia), which is the only test system licensed in our country. The results were considered positive or negative according to the manufacturer’s recommendations and the proven effectiveness of the test system for CE<sup>19</sup>.

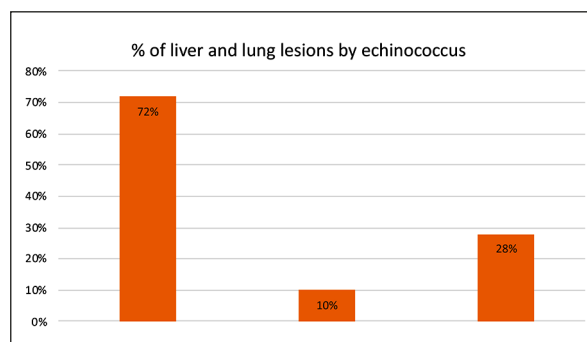
All patients had a parasitic cyst with a diameter of 5 cm or more, which was an indication for surgical treatment. They have been operated in various hospitals of the Russian Federation, such as Sklifosovsky Clinical and Research Institute for Emergency Medicine, Vishnevsky Institute of Surgery, Petrovsky Russian Research Center of Surgery, Sechenov University Moscow, etc. and the diagnosis of hydatid echinococcosis was confirmed morphologically (intra-vitam).

Surgical treatment of hydatid echinococcosis consists of cyst removal, destruction of the parasite, prevention of pleural cavity infestation, and elimination of the residual cavity with maximum preservation of tissue.

There are three main types of surgical interventions:

1. Removal of only hydatid cyst elements without fibrous cap (hydatid surgery);
2. Removal of the parasite together with the fibrous capsule (pericystectomy);
3. Removal of hydatid cyst by resection of the organ.

Types of surgical interventions performed on analyzed patients with hydatid echinococcosis who sought medical care at the clinical department of medical parasitology and tropical medicine are presented in Table II.



**Figure 1.** Percentage of liver and lung lesions by echinococcus.

**Table II.** Types of surgical interventions performed for hepatic and pulmonary echinococcosis.

| Type of surgical intervention                          | Number of surgical interventions | Percentage of operations, % |
|--|----------------------------------|-----------------------------|
| Video-assisted thoracoscopic hydatid surgery           | 38                               | 34.5                        |
| Enucleation of hydatid cyst                            | 2                                | 1.8                         |
| Thoracoscopic single-port sublobar pulmonary lobectomy | 2                                | 1.8                         |
| Subtotal pericystectomy                                | 2                                | 1.8                         |
| Pulmonary lobectomy                                    | 1                                | 1.2                         |
| Laparoscopic hydatid surgery                           | 34                               | 30.9                        |
| Open hydatid surgery                                   | 31                               | 28.1                        |
| Total  | 110                              | 100.00                      |

Despite the perfect instrumentation, great experience of the surgeon, and even complete cleanliness of the operation with observance of all rules regarding parasites does not exclude the possibility of disease recurrence. In addition, modern diagnostic methods still do not allow detecting small echinococcal seeding. In this regard, the need for contradictory chemotherapy for all patients with a diagnosis of echinococcosis is now indisputable.

All patients who applied for anti-relapse chemotherapy received ABZ (10 mg/kg/day) for 60 days continuously and 28 days continuously with a 14-day break. Consequently, patients were divided into two groups: Group 1 – patients who received a continuous regimen: 51 patients (46.4%), and the Group 2 – patients who received treatment with a 14-day break: 59 people (53.6%). Anti-Relapse treatment was prescribed with normal hepatic enzymes, hemograms and leukocytosis of at least  $4 \times 10^9$  and with the normal patient's body temperature.

The time interval between diagnosis and anti-relapse chemotherapy varied significantly from patient to patient. ABZ treatment began 2-6 weeks after any surgical treatment. Various courses of ABZ were recommended as anti-relapse chemotherapy. The number of chemotherapy courses was determined by the severity and extent of the process, as well as individual tolerance of the drug, and uncomplicated courses ranged from 2 to 11 courses, which could consist of courses from 60 days of continuous use to regimens of 28 days of continuous treatment with a further 14-day break. After each course of ABZ laboratory and instrumental parameters were monitored. Success in the treatment of cystic echinococcosis was determined as the absence of re-growth of parasitic cysts in the liver and lungs throughout the entire observation period, even with positive

antibodies to echinococcal antigens, which were regarded as immunological memory ("trace" remaining after the disease cured). Immunological memory is the ability of the immune system to quickly and specifically recognize an antigen previously encountered by the body, and therefore, the ability to initiate a corresponding immune response. In other words, immunological memory is producing secondary (tertiary etc.) immune responses to the same antigen.

Throughout the observation period, we evaluated our patients' tolerability of ABZ according to the level of hepatic enzymes (AST, ALT), total bilirubin, and blood cells count. In cases where such levels went 3-4 times beyond the reference values and/or there was a decrease in the number of leukocytes below  $2.5 \times 10^9$ , level of hemoglobin below 110 g/l drug treatment with ABZ was adjusted, and symptomatic treatment was prescribed, with ABZ being resumed after normalization.

A number of patients who received chemotherapy lived not only in Moscow, but also in different regions of Russia, which made it difficult for them to return for follow-up examinations, so treatment of patients from other cities was carried out *via* telemedicine.

Ethical approval was not required for this retrospective study. All patients were informed and give their consent to this study.

### **Statistical Analysis**

The obtained data were processed using the SPSS 20.0 statistical software package for Windows (SPSS Corp., Armonk, NY, USA). Information from patients' clinical data registration cards and test results were entered into special tables and further subjected to automatic analysis. The significance of differences between parametric

**Table III.** Course duration in Group 1 depending on the extent of surgical treatment

| Extent of surgical treatment                           | Number of patients | Course duration             |
|--|--------------------|-----------------------------|
| Video-assisted thoracoscopic hydatid surgery           | 16                 | 120 days (2 60-day courses) |
| Enucleation of hydatid cyst                            | 2                  | 180 days (3 60-day courses) |
| Thoracoscopic single-port sublobar pulmonary lobectomy | 2                  | 120 days – 2 courses        |
| Laparoscopic hydatid surgery                           | 18                 | 240 days (4 60-day courses) |
| Open hydatid surgery                                   | 13                 | 180 days (3 60-day courses) |
| Total  | 51 patients        | 840 days                    |

values with normal distribution was assessed using Student's *t*-criterion. If the *t*-criterion value is 2.0 or more, we can state that the difference in the indices is not random, depends on a certain cause, and the probability of error to detect non-existent differences does not exceed 5% ( $p < 0.05$ ).

### Results

Group 1 included 51 patients (46.4%) out of 110 patients studied, who were treated with ABZ for 60 days continuously, including 2 patients (1.8% of the total) after enucleation of hydatid cyst and thoracic sublobar resection by the extent of surgical treatment, 18 patients (16.4%) after laparoscopic hydatid surgery, 13 patients (11.8%) after open hydatid surgery, and 16 (14.5%) who underwent thoracic hydatid surgery. The duration of courses depending on the extent of surgical treatment is presented in Table III.

The patients listed in Table III received a continuous 60-day course of ABZ at intervals of 1-2 months, depending on complications, as shown in Table IV.

Thus, we considered the most frequent complications to be drug-induced hepatitis arising in the background of ABZ administration, which required the administration of a hepatoprotective agent. In blood biochemical analysis, there

was periodically observed a short-term increase of aminotransferases activity, not exceeding 110  $\mu\text{mol}/(\text{min}\cdot\text{L})$ . Only five patients in this cohort had anemia with hemoglobin below 115 g/L (9.8% of 51 patients), which required cancellation of ABZ, and six cases (11.7% of the total Group 1) had granulocyte reduction up to a critical level (1200 cells in absolute value), which also required temporary cancellation of antiretroviral therapy. In addition, this group of patients reported subjective side effects of chemotherapy: headache, dizziness, liquid stools, hair loss, and BP instability.

Group 2 included 59 patients (53.6%) out of 110 studied patients who received chemotherapy with a break of 14 days: 16 patients (27.1% of Group 2) after laparoscopic hydatid surgery, 18 patients (30.5%) who underwent open hydatid surgery, 22 patients (37.2%) after thoracoscopic hydatid surgery and 2 patients with subtotal pericystectomy (3.4%), and 1 patient (1.7%) after lower lobe lobectomy. All patients received a treatment regimen: 28 days of continuous treatment, followed by a 14-day break and 28 days of retreatment with ABZ.

The duration of courses in Group 2 depending on the extent of surgical treatment is presented in Table V.

Complications of chemotherapy are presented in Table VI.

**Table IV.** Results of basic blood parameters in Group 1 after the first and second courses of treatment ( $p < 0.05$ ).

| Parameter                                 | Reference values         | Course 1          | Course 2          |
|---|--------------------------|-------------------|-------------------|
| Hb, g/L                                   | 120-180                  | 115.85 $\pm$ 2.14 | 123.81 $\pm$ 2.05 |
| WBC                                       | 4-9 $\times 10^9$        | 4.72 $\pm$ 0.33   | 4.16 $\pm$ 0.22   |
| RBC                                       | 3.7-5.0 $\times 10^{12}$ | 4.51 $\pm$ 0.21   | 4.81 $\pm$ 0.23   |
| PLT                                       | 180-360 $\times 10^9$    | 284.87 $\pm$ 7.29 | 256.44 $\pm$ 6.71 |
| ALT, U/L                                  | < 40                     | 97.63 $\pm$ 4.25  | 82.64 $\pm$ 3.51  |
| AST, U/L                                  | < 40                     | 78.90 $\pm$ 3.14  | 65.32 $\pm$ 3.05  |
| Total bilirubin, $\mu\text{mol}/\text{L}$ | 3.4-21                   | 20.44 $\pm$ 1.01  | 22.56 $\pm$ 1.12  |

**Table V.** Course duration in Group 2 depending on the extent of surgical treatment.

| Extent of surgical treatment                 | Number of patients | Course duration                               |
|--|--------------------|---|
| Video-assisted thoracoscopic hydatid surgery | 22                 | 252 days (9 courses: 28 days × 14-day break)  |
| Subtotal pericystectomy                      | 2                  | 112 days (4 courses: 28 days × 14-day break)  |
| Pulmonary lobectomy                          | 1                  | 112 days (4 courses: 28 days × 14-day break)  |
| Laparoscopic hydatid surgery                 | 16                 | 280 days (10 courses: 28 days × 14-day break) |
| Open hydatid surgery                         | 18                 | 308 days (11 courses: 28 days × 14-day break) |
| Total  | 59 patients        | 1064 days                                     |

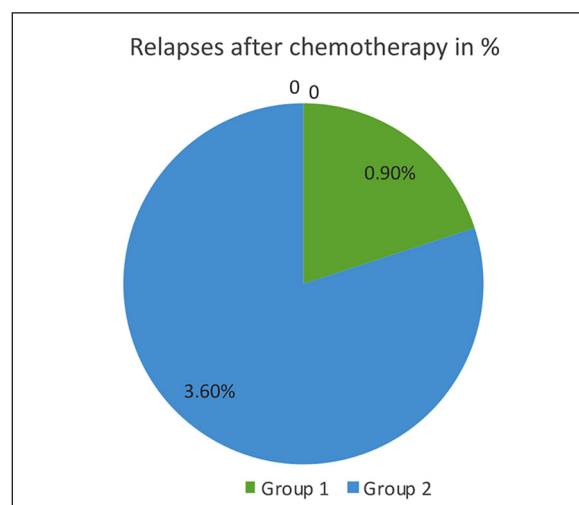
**Table VI.** Basic blood parameters in Group 2 after the first and second course of treatment with ABZ ( $p < 0.05$ ).

| Parameter               | Reference values           | Course 1      | Course 2      |
|-------------------------|----------------------------|---------------|---------------|
| Hb, g/L                 | 120-180                    | 115.92 ± 2.06 | 123.84 ± 2.12 |
| WBC                     | 4-9 × 10 <sup>9</sup>      | 4.26 ± 0.29   | 8.66 ± 0.43   |
| RBC                     | 3.7-5.0 × 10 <sup>12</sup> | 4.22 ± 0.21   | 7.72 ± 0.38   |
| PLT                     | 180-360 × 10 <sup>9</sup>  | 276.48 ± 4.82 | 264.61 ± 4.41 |
| ALT, U/L                | < 40                       | 71.91 ± 3.82  | 71.73 ± 3.79  |
| AST, U/L                | < 40                       | 66.35 ± 2.15  | 67.61 ± 2.41  |
| Total bilirubin, μmol/L | 3.4-21                     | 19.56 ± 0.95  | 18.89 ± 0.88  |

In the second group of patients, we also observed drug-induced hepatitis in all patients, but the cytotoxicity level did not exceed 80 μmol/(min.L). This cohort of patients was also given a hepatoprotective agent to prevent liver fibrosis. 13 patients with normal leukocytes showed a steady increase in granulocytopenia (up to 20%, absolute number of granulocytes up to 1200) by the end of the treatment course, which was compensated by a further two-week break in treatment. Subjectively, this group of patients complained of mild dizziness, minor headaches, mushy stool, and BP instability. The patients had no other complaints.

During the periods of anti-relapse therapy in 110 patients with echinococcosis, five patients (4.5%) had a recurrence of the disease. In one patient from Group 1 (0.9%) after enucleation of the echinococcal cyst from the right lobe of the liver and completion of the third course of countercurrent chemotherapy, a parasitic cyst appeared one year later in the left lobe of the liver. Parasitic cysts in other liver segments were found in three patients from group 2 (2.7%) after laparoscopic hydatid surgery and 10 courses of ABZ with a two-week break. One of the patients from Group 2 (0.9%) still had cysts in the lower lobe of the right lung (previously localized in the middle lobe of the same lung) after video-assisted thoracoscopic hydatid surgery and 9 courses of ABZ with a two-week break. Percentage of relapses of those patients after complete chemotherapy course is shown in Figure 2.

In 110 patients operated in different hospitals of the Russian Federation, the treatment regimen was prescribed depending on age, presence of concomitant pathology, and the choice of surgical treatment and lasted from 120 to 380 days of ABZ administration (total irrespective of the choice of a treatment regimen). All patients tolerated the drug differently, as reflected in their complaints during chemotherapy, and in no case, it required withdrawal. Patients were explained the treatment adherence and explained that in case of refusal of ongoing therapy there may be a

**Figure 2.** Summary relapses after chemotherapy in Groups 1 and 2.

growth of a parasitic cyst with the development of complications, as well as distant recurrences. In a retrospective analysis of 110 records of patients observed in the clinical department of the Institute of Medical Parasitology and Tropical Medicine for the period from 2016 to 2020, the most effective regimen of anti-relapse chemotherapy after surgical treatment of hydatidosis echinococcosis was a 60-day continuous regimen (regardless of cyst location), as it resulted in the least number of long-term recurrences of the disease, and the safest was with a 14-day break. Patients had fewer shifts in general clinical and biochemical blood tests, which did not require temporary discontinuation of therapy to reduce side effects, but after this therapy, there were more relapses (4.5%) compared to continuous therapy (0.9%). The number of courses required for patients with operated hepatic and pulmonary hydatid echinococcosis depending on the choice of treatment regimen shows that fewer days of treatment were required for patients who received ABZ continuously for 60 days and for those patients who underwent radical operations: lobectomy, pericystectomy, resection of lobe/segment of the organ. Both for the continuous regimen and when 28-day continuous ABZ administration was chosen, the most frequent complications were drug hepatitis and granulocytopenia, which required administration of a hepatoprotective agent to prevent liver fibrosis due to the development of drug hepatitis, or temporary withdrawal of ABZ in case of development of granulocytopenia and anemia.

## Conclusions

During the retrospective analysis, the most effective was a continuous 60-day treatment regimen (recommended by WHO), requiring the administration of additional medications (hepatoprotective and mucosal protective agents) to relieve complications arising from prolonged chemotherapy, especially in comorbid patients. This regimen is the most convenient, because it does not require a break in treatment, and control of laboratory and instrumental parameters can be performed remotely during the entire period of therapy (through telemedicine), which does not require a second visit to consult an attending physician, which is important for patients from other cities. Our study also shows the relevance of the “old” treatment regimen with 14-day breaks,

which can be used in comorbid patients, as well as elderly patients suffering from hydatid echinococcosis. As a rule, the regimen of anti-relapse chemotherapy is chosen by the attending physician depending on the volume of surgical treatment, which has not been previously covered in scientific papers. In addition, the role of Abs in cystic echinococcosis in the dynamics of treatment, which remains in patients even after recovery, is still not known, which is regarded as immunological memory, which requires further research.

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### Conflict of Interest

The Author declares that he has no conflict of interests.

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### Ethical Approval

Ethical approval was not required for this retrospective study.

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### Informed Consent

Informed consent was obtained from all individual participants included in the study.

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