DOI: https://doi.org/10.17816/EID628865

An experimental model of liver echinococcosis in laboratory rats to study the effectiveness of anthelmintic drugs

Timofey V. Gavrilyuk[1], Andrey V. Saulevich[1], Sergei S. Kozlov[1, 2, 3], Yuri F. Zakharkiv[1], Konstantin V. Kozlov[1], Vladimir S. Turitsin[1, 4], Vadim E. Karev[3]

[1] Kirov Military Medical Academy, Saint Petersburg, Russia;
[2] Saint Petersburg State Pediatric Medical University, Saint Petersburg, Russia;
[3] Pediatric Research and Clinical Center for Infectious Diseases under the Federal Medical Biological Agency, Saint Petersburg, Russia;
[4] Saint Petersburg State Agrarian University, Saint Petersburg, Russia

ABSTRACT

BACKGROUND: The introduction into clinical practice of drug therapy with anthelmintic drugs from the carbamate-benzimidazole group has reduced the need for aggressive surgical interventions in the initial stages of parasitic cyst development. However, no consensus has been reached in which cases and for what size of cysts the use of monotherapy with carbamate benzimidazoles will be sufficient and in which cases a combination of surgical and therapeutic treatment methods is necessary. Experimental studies with human participants are impossible to solve this problem.

AIM: To evaluate the proximity of the developed experimental model of liver echinococcosis to real clinical practice, including the response to the use of carbamate benzimidazoles.

MATERIALS AND METHODS: Modeling of liver echinococcosis in laboratory animals was performed by suturing a part of an echinococcal bladder (*Echinococcus granulosus*) to the liver capsule. The model provides a high survival percentage of laboratory animals, in which after 60 days a typical hydatid cyst forms in the liver. The effects of albendazole and praziquantel were studied using this echinococcus model. One group of animals (n = 10) received albendazole through an intragastal tube for 28 days and the other (n = 10) received praziquantel for 15 days, after which the animals were autopsied.

RESULTS: When using albendazole, destructive changes were microscopically determined in the structure of the walls of the echinococcal cyst on day 28 of therapy. Similar changes were observed when using praziquantel; however, they were characterized by more massive cellular infiltration of all cyst layers.

CONCLUSIONS: The developed experimental model of liver echinococcosis in laboratory animals allowed us to experimentally examine the effect of various drugs on the larval stages of *E. granulosus* development and evaluate their effectiveness.

Keywords: *Echinococcus granulosus*; helminthiasis; echinococcosis; experimental model; albendazole; praziquantel.

To cite this article:
Gavrilyuk TV, Saulevich AV, Kozlov SS, Zakharkiv YuF, Kozlov KV, Turitsin VS, Karev VE. An experimental model of liver echinococcosis in laboratory rats to study the effectiveness of anthelmintic drugs. *Epidemiology and Infectious Diseases.* 2024;29(3):176–183. DOI: https://doi.org/10.17816/EID628865

Received: 07.03.2024 **Accepted:** 30.05.2024 **Published online:** 18.06.2024

DOI: https://doi.org/10.17816/EID628865

Экспериментальная модель эхинококкоза печени у лабораторных крыс для изучения эффективности антигельминтных препаратов

Т.В. Гаврилюк[1], А.В. Саулевич[1], С.С. Козлов[1, 2, 3], Ю.Ф. Захаркив[1], К.В. Козлов[1], В.С. Турицин[1, 4], В.Е. Карев[3]

[1] Военно-медицинская академия имени С.М. Кирова, Санкт-Петербург, Россия;
[2] Санкт-Петербургский государственный медицинский педиатрический университет, Санкт-Петербург, Россия;
[3] Детский научно-клинический центр инфекционных болезней Федерального медико-биологического агентства, Санкт-Петербург, Россия;
[4] Санкт-Петербургский государственный аграрный университет, Санкт-Петербург, Россия

АННОТАЦИЯ

Обоснование. Внедрение в клиническую практику лекарственной терапии препаратами антигельминтного действия из группы карбаматбензимидазолов снизило потребность в агрессивных хирургических вмешательствах на начальных стадиях развития паразитарных кист. Однако до сих пор нет единого мнения, в каких случаях и при каких размерах кист будет достаточным применение монотерапии карбаматбензимидазолами, а в каких необходима комбинация хирургического и терапевтического методов лечения. Экспериментальные исследования с участием людей для решения данной задачи невозможны.

Цель исследования — оценить приближённость разработанной авторами экспериментальной модели эхинококкоза печени к реальной клинической практике, в том числе реакцию на применение карбаматбензимидазолов.

Материалы и методы. Моделирование эхинококкоза печени у лабораторных животных осуществлялось путём подшивания к капсуле печени части эхинококкового пузыря (*Echinococcus granulosus*). Модель обеспечивает высокий процент выживания лабораторных животных, у которых через 60 дней в печени формируется типичная эхинококковая киста. На данной модели эхинококка было изучено действие албендазола и празиквантела. Одна группа животных (10 особей) получала албендазол через интрагастальный зонд в течение 28 дней, другая (10 особей) празиквантел в течение 15 дней, после чего проводили вскрытие животных.

Результаты. При использовании албендазола на 28-е сутки терапии в структуре стенок эхинококковой кисты микроскопически определялись деструктивные изменения. Подобные изменения наблюдались при применении празиквантела, но они характеризовались более массивной клеточной инфильтрацией всех слоёв кисты.

Заключение. Разработанная экспериментальная модель эхинококкоза печени у лабораторных животных позволяет изучать в эксперименте действие различных препаратов на личиночные стадии развития *E. granulosus* и оценивать их эффективность.

Ключевые слова: *Echinococcus granulosus*; гельминтозы; эхинококкоз; экспериментальная модель; албендазол; празиквантел.

Как цитировать:
Гаврилюк Т.В., Саулевич А.В., Козлов С.С., Захаркив Ю.Ф., Козлов К.В., Турицин В.С., Карев В.Е. Экспериментальная модель эхинококкоза печени у лабораторных крыс для изучения эффективности антигельминтных препаратов // Эпидемиология и инфекционные болезни. 2024. Т. 29, № 3. С. 176–183. DOI: https://doi.org/10.17816/EID628865

Рукопись получена: 07.03.2024 **Рукопись одобрена:** 30.05.2024 **Опубликована online:** 18.06.2024

BACKGROUND

More than two million new cases of echinococcosis are registered annually worldwide, representing a prevalence of 0.05%–1.5% within the broader context of infectious pathology. In recent years, the incidence of this helminthiasis has notably increased, with prevalence rates reaching 30%–95% in certain countries. The number of cases with complicated forms is increasing, 35%–40% [1, 2], with a mortality rate of 2%–5% [3]. Consequently, echinococcosis is included in the list of the most widespread human helminthic diseases requiring priority elimination by the World Health Organization [4–6].

The epidemiological situation with parasitic diseases in Russia, including echinococcosis, remains challenging. More than 500 cases of this larval helminthiasis are registered in the country annually. In 2021, the incidence increased by 18.75% compared with 2020 and amounted to 0.19 per 100,000 population [7].

The clinical diagnosis of echinococcosis is challenging because of its prolonged latent phase. Consequently, instrumental methods (ultrasonography, computed tomography, etc.) and serologic techniques, which are particularly effective when used in conjunction, are instrumental in establishing a definitive diagnosis [8, 9].

Currently, the primary method of treatment for echinococcosis remains surgical. However, the feasibility of this approach is severely constrained in cases of multiple invasions or inoperable cases [10]. The initial attempts to develop a method of specific chemotherapy for echinococcosis were made in the 1980s, with mebendazole (a drug of the carbamate-benzimidazole group) as the basis for these early investigations. In the late 1990s, the structural analog of mebendazole, albendazole, was widely used in the treatment of echinococcosis. The inefficacy of both oral preparations is largely attributed to their relatively low bioavailability. Attempts to enhance their bioavailability by developing experimental oil dosage forms have not produced the anticipated outcomes. The use of praziquantel as a tissue antihelminthic medication is constrained by the distinctive characteristics of its pharmacokinetics, particularly by its brief half-life and a considerable range of adverse reactions that emerge during prolonged use [11].

However, no unified approach to therapeutic techniques has been established for the management of patients with echinococcosis among surgeons, infectious disease specialists, and physicians of other specialties. The introduction of drug therapy with anthelminthic drugs from the carbamate benzimidazole group into clinical practice has reduced the need for aggressive surgical interventions at the initial stages of parasitic cyst development. Nevertheless, no consensus has been made on whether the use of carbamate benzimidazole monotherapy is sufficient in all cases and at all sizes of cysts or whether a combination of surgical and therapeutic methods of treatment is necessary in some cases. According to several authors, the ineffectiveness of monotherapy is primarily caused by the inability to follow a full course of treatment with albendazole because of the pronounced polymorphism of genes encoding enzymes of albendazole biotransformation and various side effects of the drug. Furthermore, the disease often recurs after surgical intervention not accompanied by subsequent carbamate-benzimidazole therapy.

At present, data derived from clinical studies and proposed experimental models on laboratory animals are insufficient to fully assess the histologic changes in the structure of echinococcal cysts and the viability of the parasites during etiotropic therapy [12]. Thus, we have developed a new, simpler technical execution model of liver echinococcosis in experimental animals, which allows for the assessment of the dynamics of histological changes during therapy with antihelminthic drugs.

This study aimed to evaluate the proximity of the developed experimental model of liver echinococcosis to real clinical practice, including the response to the use of carbamate benzimidazoles.

MATERIALS AND METHODS

The experimental work on animals was approved by the independent Ethics Committee of the Kirov Military Medical Academy (Minutes No. 258, dated December 21, 2021). The maintenance and care of experimental animals were conducted in accordance with the requirements outlined in the Law of the Russian Federation dated May 14, 1993, No. 4979-1, "On Veterinary Medicine", as well as the recommendations outlined by the Ethics Committee for Conducting Expertise in Biomedical Research.

The study included 30 male Wistar rats, weighing 250±50 g, in which liver echinococcosis was modeled according to the developed method. The experimental hepatic echinococcosis was performed as follows: In the operating room, the animals were anesthetized with Zoletil 100 (tiletamine hydrochloride and zolepam hydrochloride 250 mg each) at a dose of 20 mg/kg body weight. After the onset of anesthesia, the animal's abdominal and thoracic hairs were shaved off, and the animals were then fixed on the operating table. The surgical field was treated with an antiseptic solution in accordance with the methodology proposed by Filonchikov-Grossikh. The sternum and edge of the right rib arch were then palpated. A midline laparotomy was performed using a scalpel. A portion of the wall of the echinococcal bladder obtained from an echinococcus-affected sheep was placed on the capsule of the right liver lobe ensuring that the germinative layer was adjacent to the capsule. This portion of the larvocyst, measuring approximately 10×10 mm, was fixed to the liver using a ligature with a single suture. The abdominal wound was then sutured tightly.

On the 60th day of the experiment, the formation of a liver cyst was confirmed in all animals by ultrasound examination.

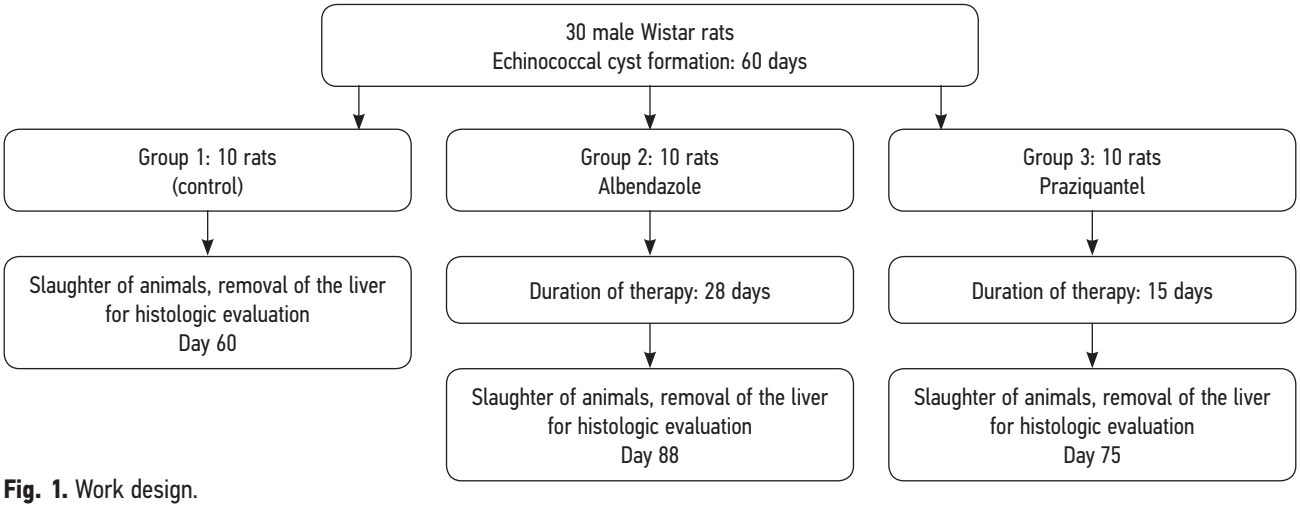

Fig. 1. Work design.

After that, the rats were randomly divided into three groups: the first control group (10 rats) and two experimental groups of 10 rats. The animals of the second group were given albendazole suspension intragastrically for 28 days through a tube at a daily dose of 5 mg, which was divided into two doses. To increase bioavailability, 100 mg of liquid butter was added to the drug. The third group received praziquantel suspension, which was prepared from the tablet form of the drug. The drug was administered by intragastric tube at a daily dose of 15 mg in two administrations for 15 days. The study design is presented in Fig. 1.

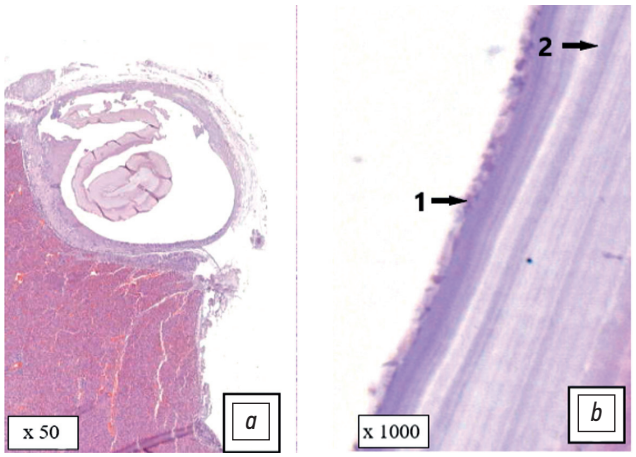

Fig. 2. Echinococcal cyst with fibrous and germinal membranes: *a* — echinococcal cyst (magnification ×50); *b* — part of the cyst with inner membranes (magnification ×1000): 1 — germinative shell; 2 — cuticle shell.

During the experiment, all animals were fed a standard rodent diet (Nuvilab CR1s, Brazil) containing 22% protein, 4% fat, and 4% crude fiber, for a total of 290 kcal/100 g. Each animal received 12 g of food per day. At the end of the experiment, the animals were killed, and their livers were extracted for further study. Its fragments with parasitic cysts were fixed in a 10% neutral formalin solution for 24 h. After fixation, they were dehydrated by incubation in isopropyl alcohol and then embedded in paraffin according to the generally accepted method. Paraffin blocks were used to prepare 4-μm thick tissue sections, which were stained with hematoxylin–eosin and Van Gieson picrofuchsin and then placed under coverslips. Histologic preparations were examined under a binocular microscope in transmitted light at total magnifications of ×50, ×200, and ×2000.

RESULTS

In the first group (n=10, control), without antihelminthic drug treatment, microscopy of histological sections revealed an outer fibrous sheath of a specific structure with an organ-like structure, which contained blood vessels providing nutrient transport to the parasitic cyst. Near the fibrous sheath, inflammatory polymorphocellular infiltration including segmented neutrophils, eosinophils, macrophages, and fibroblasts with occasional lymphocytes, was detected in the liver tissue (Fig. 2).

Table 1 presents the comparative characteristics of morphologic changes in echinococcal cysts in experimental

Table 1. Morphological characteristics of cysts

Morphological characteristics of cysts	Day 28 of albendazole treatment	Day 15 of praziquantel treatment
Germinative membrane	Detachment and fragmentation	Severe fragmentation
Cuticular membrane	Destructive changes	Severe destructive changes
Fibrous membrane	Perifocal cellular infiltration	Massive cellular infiltration
Detritus in the cyst cavity	Detritus accumulation	Detritus accumulation
Protoscolexes	No	No
Acephalocysts	No	No

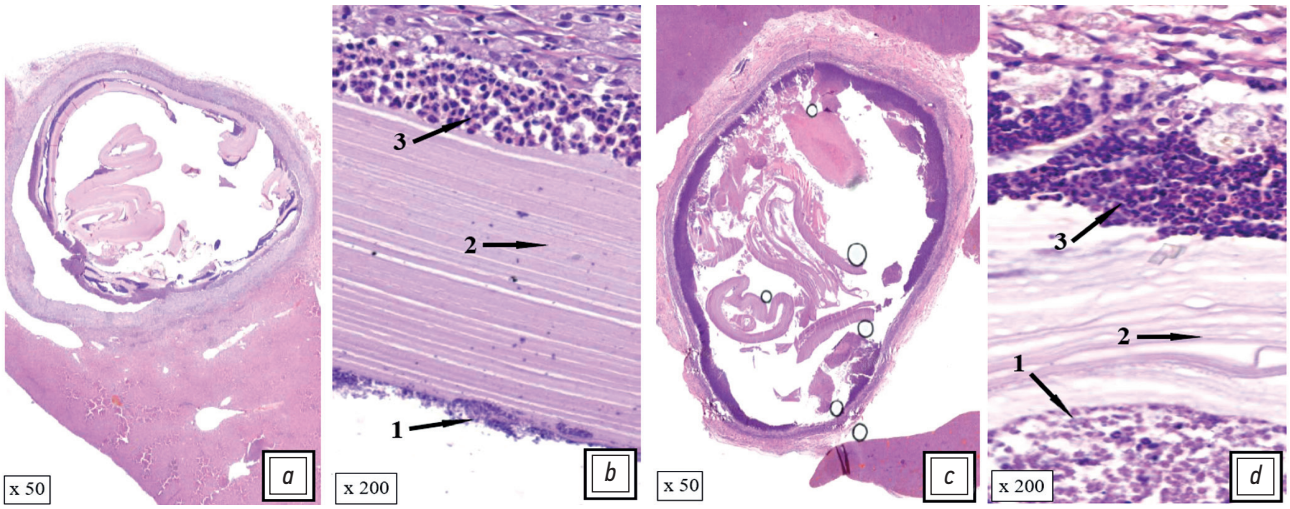

Fig. 3. Destructive changes in the cuticle and germinal membrane of an echinococcal cyst during therapy with albendazole (*a, b*) and praziquantel (*c, d*): 1 — destructive changes in the germinal membrane; 2 — destructive changes in the cuticle membrane; 3 — massive leukocyte infiltration.

animals on days 28 and 15 of albendazole and praziquantel treatments, respectively.

In echinococcal cysts of the liver of the second group (*n*=10) treated with albendazole, destructive changes in the cuticular and germinative membranes developed on day 88 of the experiment (day 28 of therapy). The histological picture was characterized by germinative membrane detachment and fragmentation, and detrital masses accumulated in the cyst cavity, indicating parasite death. In addition, perifocal cellular infiltration, which was represented by lymphocytes, neutrophils, eosinophils, macrophages, and mast cells, was detected in the fibrous membrane and adjacent tissues (Fig. 3, *a, b*).

In the echinococcal cysts of the liver of the third group (*n*=10) treated with praziquantel, destructive changes in the cuticular and germinative membranes were also observed on day 75 of the experiment (day 15 of therapy). However, these changes were more pronounced than in the albendazole group, manifested by more massive leukocytic infiltration and germinative membrane fragmentation (Fig. 3, *c, d*).

Thus, significant destructive changes in the cuticular and germinal membranes of echinococcal cysts were observed on day 28 of albendazole treatment. When praziquantel was administered as early as day 15, the histological picture was characterized by a more pronounced cellular infiltration of all cyst layers. However, during praziquantel administration, side effects clearly emerged, such as decreased motor activity and hair loss.

DISCUSSION

In the scientific literature, studies have performed experimental modeling of echinococcal cysts by intraperitoneal injection of germinal elements directly into the liver parenchyma or into the vessels supplying blood to the organ. However, common disadvantages include the multistep and complexity of the techniques, longer time of echinococcal cyst modeling, and high lethality in experimental animals [12]. Intravenous or intraperitoneal introduction of germinal elements does not guarantee the formation of an echinococcal cyst. In addition, intravenous or intrahepatic injection of germinal elements in most cases leads to the obstruction of large vessels or organ infarction. In surgery, the use of three-dimensional (3D) technologies in hepatic echinococcosis enables the assessment of the anatomical features of the affected organ and the determination of the localization of the echinococcal bladder, which allows for the selection of the most optimal surgical technique [13]. However, 3D polymer modeling does not allow us to study the morphological changes in echinococcal cysts against treatment using various antihelminthic drugs because it is possible only on a living experimental model.

CONCLUSIONS

The developed model of hepatic echinococcosis does not have any of the abovementioned drawbacks and is simple to execute. This model provides a high survival rate of experimental animals and the formation of parasitic cysts, which allows its use in experimental studies for the evaluation of the effectiveness of various antihelminthic drugs while considering the histological changes in echinococcal cysts.

ADDITIONAL INFORMATION

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declare that they have no competing interests.

Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree

to be accountable for all aspects of the work. T.V. Gavrilyuk — preparation, development and implementation of modeling of liver echinococcosis in laboratory animals; A.V. Saulevich, Yu.F. Zakharkiv, V.S. Turitsin — participation in the development and practical assistance in modeling liver echinococcosis in laboratory animals; S.S. Kozlov, K.V. Kozlov — editing research materials; V.E. Karev — production of histological preparations and their description.

REFERENCES

1. Zarivchatskiy MF, Mugatarov IN, Kamenskikh ED, Kolyvanova MV, Teplykh NS. Surgical treatment of liver echinococcosis. *Perm Medical Journal.* 2021;38(3):32–40. (In Russ.) doi: 10.17816/pmj38332-40

2. Gorbachev DS, Kulikov AN, Kozlov SS, et al. Clinical Case of Echinococcosis of the Orbit. Modern Approaches to Diagnosis and Treatment. *Ophthalmology in Russia.* 2022;19(1):215–228. (In Russ.) doi: 10.18008/1816-5095-2022-1-215-228

3. Akbarov MM, Ruzibaev RYu, Sapaev DSh, Ruzmatov PYu, Yakubov FR. Modern approaches in the prevention and treatment of liver echinococcosis. *Problems of Biology and Medicine.* 2020;120(4): 12–18. (In Russ.) doi: 10.38096/2181-5674.2020.4.00181

4. The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2017. *EFSA Journal.* doi: 10.2903/j.efsa.2018.5500

5. *World Health Organization: Echinococcosis* [Internet]. 2021. Available from: https://www.who.int/ news-room/fact-sheets/detail/echinococcosis/

6. *On the state of sanitary and epidemiological well-being of the population in the Russian Federation in 2021: State Report.* Moscow: Federal Service for Supervision of Consumer Rights Protection and Human Welfare; 2022. 233 p. (In Russ.)

7. Arakelyan RS, Shendo GL, Maslyaninova AE, et al. Serological Research Methods in the Diagnosis of Parasitic Diseases. *International Research Journal.* 2021;(8-2(110)):78–82. (In Russ.) doi: 10.23670/IRJ.2021.110.8.051

8. Wen H, Vuitton L, Li J, et al. Echinococcosis: advances in the 21st century. *Clinical Microbiology Reviews.* 2019;32(2):e00075-18. doi: 10.1128/CMR.00075-18

9. Ikramov RZ, Zhavoronkova OI, Botiraliev ASh, et al. Modern treatment of the liver echinococcosis. *Vysokotekhnologicheskaya meditsina*. 2020;7(2):14–27. (In Russ.) EDN: MVGWUE

10. Flohr C, Tuyen LN, Lewis S, et al. Low efficacy of mebendazole against hookworm in Vietnam: two randomized controlled trials. *Am J Trop Med Hyg.* 2007;76(4):732–736.

11. Shkolyar NA. *Development of new methods of experimental chemotherapy for larval echinococcosis* [abstract of dissertation]. Moscow; 2015. 22 p. (In Russ.) EDN: ZPNYZH

12. Patent RUS №2222052, МПК G09B 23/28, 2000.01. *Method of modeling solitary echinococcosis of the liver in experiment.* Applicant: Dagestan State Medical Academy. (In Russ.)

13. Gerasimenko IN. *Improvement of operative and conservative treatment of abdominal echinococcosis in children* [dissertation]. Stavropol; 2022. 239 p. (In Russ.) EDN: STHPNZ

СПИСОК ЛИТЕРАТУРЫ

1. Заривчацкий М.Ф., Мугатаров И.Н., Каменских Е.Д., Колыванова М.В., Теплых Н.С. Хирургическое лечение эхинококкоза печени // Пермский медицинский журнал. 2021. Т. 38, № 3. С. 32–40. doi: 10.17816/pmj38332-40

2. Горбачёв Д.С., Куликов А.Н., Козлов С.С., и др. Клинический случай эхинококкоза глазницы. Современные подходы к диагностике и лечению // Офтальмология. 2022. Т. 19, № 1. С. 215–228. doi: 10.18008/1816-5095-2022-1-215-228

3. Акбаров М.М., Рузибаев Р.Ю., Сапаев Д.Ш., Рузматов П.Ю., Якубов Ф.Р. Современные пути лечения и профилактики эхинококкоза печени // Проблемы биологии и медицины. 2020. Т. 120, № 4. С. 12–18. doi: 10.38096/2181-5674.2020.4.00181

4. The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2017 // EFSA Journal. doi: 10.2903/j.efsa.2018.5500

5. World Health Organization: Echinococcosis [Internet]. 2021. Режим доступа: https://www.who.int/ news-room/fact-sheets/detail/echinococcosis/

6. О состоянии санитарно-эпидемиологического благополучия населения в Российской Федерации в 2021 году: государственный доклад. Москва: Федеральная служба по надзору в сфере защиты прав потребителей и благополучия человека, 2022. 233 с.

7. Аракельян Р.С., Шендо Г.Л., Маслянинова А.Е., и др. Серологические методы исследования в диагностике паразитарных болезней // Международный научно-исследовательский журнал. 2021. № 8-2 (110). С. 78–82. doi: 10.23670/IRJ.2021.110.8.051

8. Wen H., Vuitton L., Li J., et al. Echinococcosis: advances in the 21st century // Clinical Microbiology Reviews. 2019. Vol. 32, N 2. P. e00075-18. doi: 10.1128/CMR.00075-18

9. Икрамов Р.З., Жаворонкова О.И., Ботиралиев А.Ш., и др. Современные подходы в лечении эхинококкоза печени // Высокотехнологическая медицина. 2020. Т. 7, № 2. С. 14–27. EDN: MVGWUE

10. Flohr C., Tuyen L.N., Lewis S., et al. Low efficacy of mebendazole against hookworm in Vietnam: two randomized controlled trials // Am J Trop Med Hyg. 2007. Vol. 76, N 4. P. 732–736.

11. Школяр Н.А. Разработка новых методов экспериментальной химиотерапии ларвальных эхинококкозов: автореф. дис. ... канд. мед. наук. Москва, 2015. 22 с. EDN: ZPNYZH

12. Патент РФ № 2222052, МПК G09B 23/28, 2000.01. Способ моделирования солитарного эхинококкоза печени в эксперименте. Заявитель: Дагестанская государственная медицинская академия.

13. Герасименко И.Н. Совершенствование оперативного и консервативного лечения абдоминального эхинококкоза в детском возрасте: дис. ... д-ра мед. наук. Ставрополь, 2022. 239 с. EDN: STHPNZ

AUTHORS' INFO

*** Timofey V. Gavrilyuk**;
address: 6 Akademik Lebedev street,
194044 Saint Petersburg, Russia;
ORCID: 0000-0001-7102-0672;
eLibrary SPIN: 9515-3727;
e-mail: Gtv-25@mail.ru

Andrey V. Saulevich, MD, Cand. Sci. (Medicine);
ORCID: 0000-0001-6756-3105;
eLibrary SPIN: 9356-8410;
e-mail: saulevich_andrei@mail.ru

Sergei S. Kozlov, MD, Dr. Sci. (Medicine), Professor;
ORCID: 0000-0003-0632-7306;
eLibrary SPIN: 5519-6057;
e-mail: infectology@mail.ru

Yuri F. Zakharkiv, MD, Cand. Sci. (Medicine), Assistant Professor;
ORCID: 0000-0002-3453-7557;
eLibrary SPIN: 6541-9803;
e-mail: zufbiology@gmail.com

Konstantin V. Kozlov, MD, Dr. Sci. (Medicine), Assistant Professor;
ORCID: 0000-0002-4398-7525;
eLibrary SPIN: 7927-9076;
e-mail: kosttiak@mail.ru

Vladimir S. Turitsin, Cand. Sci. (Biology), Assistant Professor;
ORCID: 0000-0001-9066-0026;
eLibrary SPIN: 2022-1869;
e-mail: turicin_spb@mail.ru

Vadim E. Karev, MD, Dr. Sci. (Medicine);
ORCID: 0000-0002-7972-1286;
eLibrary SPIN: 7503-3253;
e-mail: vadimkarev@yandex.ru

ОБ АВТОРАХ

*** Гаврилюк Тимофей Васильевич**;
адрес: Россия, 194044, Санкт-Петербург,
ул. Академика Лебедева, д. 6;
ORCID: 0000-0001-7102-0672;
eLibrary SPIN: 9515-3727;
e-mail: Gtv-25@mail.ru

Саулевич Андрей Валерьевич, канд. мед. наук;
ORCID: 0000-0001-6756-3105;
eLibrary SPIN: 9356-8410;
e-mail: saulevich_andrei@mail.ru

Козлов Сергей Сергеевич, д-р мед. наук, профессор;
ORCID: 0000-0003-0632-7306;
eLibrary SPIN: 5519-6057;
e-mail: infectology@mail.ru

Захаркив Юрий Федорович, канд. мед. наук, доцент;
ORCID: 0000-0002-3453-7557;
eLibrary SPIN: 6541-9803;
e-mail: zufbiology@gmail.com

Козлов Константин Вадимович, д-р мед. наук, доцент;
ORCID: 0000-0002-4398-7525;
eLibrary SPIN: 7927-9076;
e-mail: kosttiak@mail.ru

Турицин Владимир Сергеевич, канд. биол. наук, доцент;
ORCID: 0000-0001-9066-0026;
eLibrary SPIN: 2022-1869;
e-mail: turicin_spb@mail.ru

Карев Вадим Евгеньевич, д-р мед. наук;
ORCID: 0000-0002-7972-1286;
eLibrary SPIN: 7503-3253;
e-mail: vadimkarev@yandex.ru

* Corresponding author / Автор, ответственный за переписку