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Chapter

The World Largest Focus of the Opisthorchiasis in the Ob-Irtysh Basin, Russia, Caused by *Opisthorchis felineus*

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Abstract

The world's largest focus of opisthorchiasis caused by cat fluke *Opisthorchis felineus* Rivolta, 1884, is associated with the Ob-Irtysh basin (Russia). The chapter provides data on the history of discovery and the study of opisthorchiasis. Features of the morphology and life cycle of *O. felineus* are described. Data on the infection of intermediate hosts (mollusks and cyprinids fish) are provided. Species of fish that have important epizootological significance are indicated. The incidence of opisthorchiasis in the people of different age and social groups, clinical manifestations, pathogenesis, and complications is discussed. The climatic and social factors that contribute to maintaining the focus of opisthorchiasis are described. The measures of personal and social prevention of the people are given.

Keywords: *Opisthorchis felineus*, history and study, intermediate hosts, important epizootological significance, epizootology and epidemiology, personal and social prevention

1. Introduction

The goal of this work was to assess the current epidemiological and epizootological situations in the world largest focus of opisthorchiasis; to clarify the specific features in its clinical course, pathogenesis, and complications; to determine the natural, climatic, and social factors that enhance preservation of this focus; and to propose an algorithm for preventive activities.

The tasks of this research are to study the epizootological situation and features of the circulation of *Opisthorchis felineus* in the Ob-Irtysh basin, assess the epidemiological situation of opisthorchiasis in Russia, and give recommendations on measures to prevent the disease.

The concept of sustainable development [1] sets the control of unattended diseases as one of the global goals in the area of public health care; these diseases include the helminthic invasions in hyperendemic foci. The ongoing changes in

all spheres of production and sale of raw materials and goods have led to serious violations of sanitary rules and norms, which deteriorate the epizootic situation for parasitic invasions in the world.

Opisthorchiasis, the trematodiasis caused by *O. felineus* Rivolta, 1884, is one of the relevant problems in both Russia (with its world largest Ob-Irtysh natural focus) and worldwide despite the implemented prevention measures. The relevance of this problem is determined by both its high incidence among adults and children, severity of the resulting pathology, and its chronic course.

The socioeconomic factors, such as active migration of population, unawareness of opisthorchiasis among the newcomers to the region, poor knowledge about the rules for disinfection of local population, all-year-round consumption of fish, and homemade fish products, increase in the number of amateur fishermen and poachers, and vending of fish and fish products on unauthorized markets creates the conditions for the stable preservation of opisthorchiasis.

One of the major factors that influence the level of *O. felineus* liver fluke invasion is a high rate of fish invasion by its metacercariae. The natural and climatic conditions that have established in the Ob-Irtysh basin support the active opisthorchiasis focus there.

A vast floodplain of the Ob-Irtysh basin, rich in lakes and meadows, and a developed network of first- and second-order tributaries enhance the maintenance of the Bithyniidae mollusks at a high level.

Close coexistence and cohabitation of the first intermediate host and cyprinid fish (second intermediate host) in the same habitats provide the implementation of liver fluke life cycle. In their abundance and species diversity, the cyprinid fish are the leader group in the Ob-Irtysh basin. A high infection rate of the prevalent fish species, which are of important commercial value, with *O. felineus* metacercariae is a major risk factor, influencing the incidence of this disease among local population.

2. Brief history of opisthorchiasis discovery and research

The liver fluke was for the first time described in 1884 by Sebastiano Rivolta, an Italian scientist. He isolated the parasite from the liver of a cat and a dog and named it the liver fluke, *O. felineus*, and the corresponding disease, opisthorchiasis. K.N. Vinogradov, a professor at the Tomsk University, discovered the liver fluke in the human liver in 1891. After the discovery by Vinogradov, human cases of opisthorchiasis were repeatedly recorded in 1892–1929 in Tomsk, Biysk, Novosibirsk, Tyumen oblast, Kuznetsk raion, and other localities. During WWII, a Russian soldier from Siberia died in one of the fascist concentration camps; his autopsy demonstrated 42,000 liver flukes in his liver and pancreas.

As has been observed, the liver fluke is not met far and wide but rather near freshwater bodies. Brown in 1893 assumed that fish consumption is the source of liver fluke infection, which was later (1904) experimentally confirmed by M. Askanazy (Germany). In 1891, Vinogradov postulated the first intermediate host of liver fluke, which was experimentally confirmed by H. Vogel (Germany): he demonstrated that the first intermediate host was the mollusk *Bithynia leachii* (Sheppard, 1823).

The study of opisthorchiasis commences in 1929 after publication of the information that 100 opisthorchiasis patients were admitted to the Tobolsk hospital over 6 months. This initiated organization of specialized helminthological expeditions to the Ob-Irtysh basin, headed by K.I. Skryabin. Numerous experiments have demonstrated that this region houses the largest opisthorchiasis focus. Russian

helminthologists under the guidance of Skryabin paid significant attention to the study of *O. felineus* (1927–1929). The liver fluke larvae were for the first time discovered in the muscle of fish individuals inhabiting Siberian water bodies by N.N. Plotnikov and L.K. Zerchaninov in 1932.

All these efforts allowed for discovery of a considerable incidence of opisthorchiasis among people, cats, and dogs along the Irtysh and Ob rivers up to the polar circle. In 1973, a cat was autopsied by an expedition organized by Skryabin in the north of the Tomsk oblast; eight cysts containing liver flukes were found in its liver; one of the cysts, medium in its size (similar to a walnut), contained 654 parasites.

The following scientists contributed to the studies of the epidemic situation of opisthorchiasis: S.D. Titova (publications of 1946–1980), V.S. Myasoedov (publications of 1953, 1959, and 1960), M.P. Miroshnichenko (1954, 1955, and 1956), T.A. Bocharova (1971–2005), G.I. Golovko (1981–1986), and so on. The population migration to the oil and gas areas in the north of the Tomsk oblast increased the attention to this disease [3, 18–22, 24, 43].

3. Life cycle of *O. felineus*

The liver fluke *O. felineus* has an intricate life cycle, which involves three hosts: the definitive host and two intermediate hosts; the life cycle comprises two free-living stages, the egg and cercaria (**Figure 1**).

Infected domestic and wild animals that fed on fish and infected people, which are the definitive host of the liver fluke, are the sources of invasion. One trematode lays approximately 2000 eggs per day. The eggs are not viable when dry and are rapidly killed by sunlight but retain their viability for 15 months in a water body at a temperature of 4–7°C; all eggs die after 29 months [2].

When entering water with human and animal feces, the liver fluke eggs can be ingested with detritus by the first intermediate host, a Bithyniidae (genera *Codiella* and *Opisthorchophorus*) mollusk [2].

In the Ob-Irtysh basin, the mollusks susceptible to the invasion inhabit only standing perennial silt water bodies. The mollusks are unable to migrate for a long distance and form local clusters. Presumably, the infection rate of mollusks depends on the population density and the distance from human dwellings [3].

The infection rate of Bithyniidae mollusks in the upper reaches of Ob and Irtysh rivers within the Altai Krai is 2%, amounts to 6.1% within the Novosibirsk oblast, and varies in the range of 0.3–20.2% in the Irtysh basin in the Omsk oblast [4, 5]. The density of the mollusk population in the floodplain water bodies in the Tomsk oblast is 8100 individuals/m^3; however, the prevalence of invasion is extremely low (3.7%), and the intensity is very high (on the average, 8130 ± 470 cercariae/mollusk). Coinvasions are extremely rare [6]. The infection rate of mollusks in the Tura and Pyshma river floodplains varies from 4 to 9%; the infection characteristics in the Khanty-Mansiysk Autonomous Okrug are also low, to 6.7% [7].

In the mollusk gut, miracidia, free-swimming larvae, hatch from the eggs (**Figure 1**). A miracidium hatched from the egg enters the mollusk body cavity by passing through the gut wall to undergo a regressive metamorphosis there. It loses its larval organs (glands, epidermal plates, cilia, etc.) preserving only the germline cells and protonephridia to change into a mother sporocyst with a length up to 2 mm [2].

Young sporocysts are transversely constricted to give smaller sporocysts, which propagate and form rediae. Rediae are sack-like structures with a large mouth and gut. When leaving the mother sporocyst, rediae migrate to the liver of mollusk to parthenogenetically reproduce.
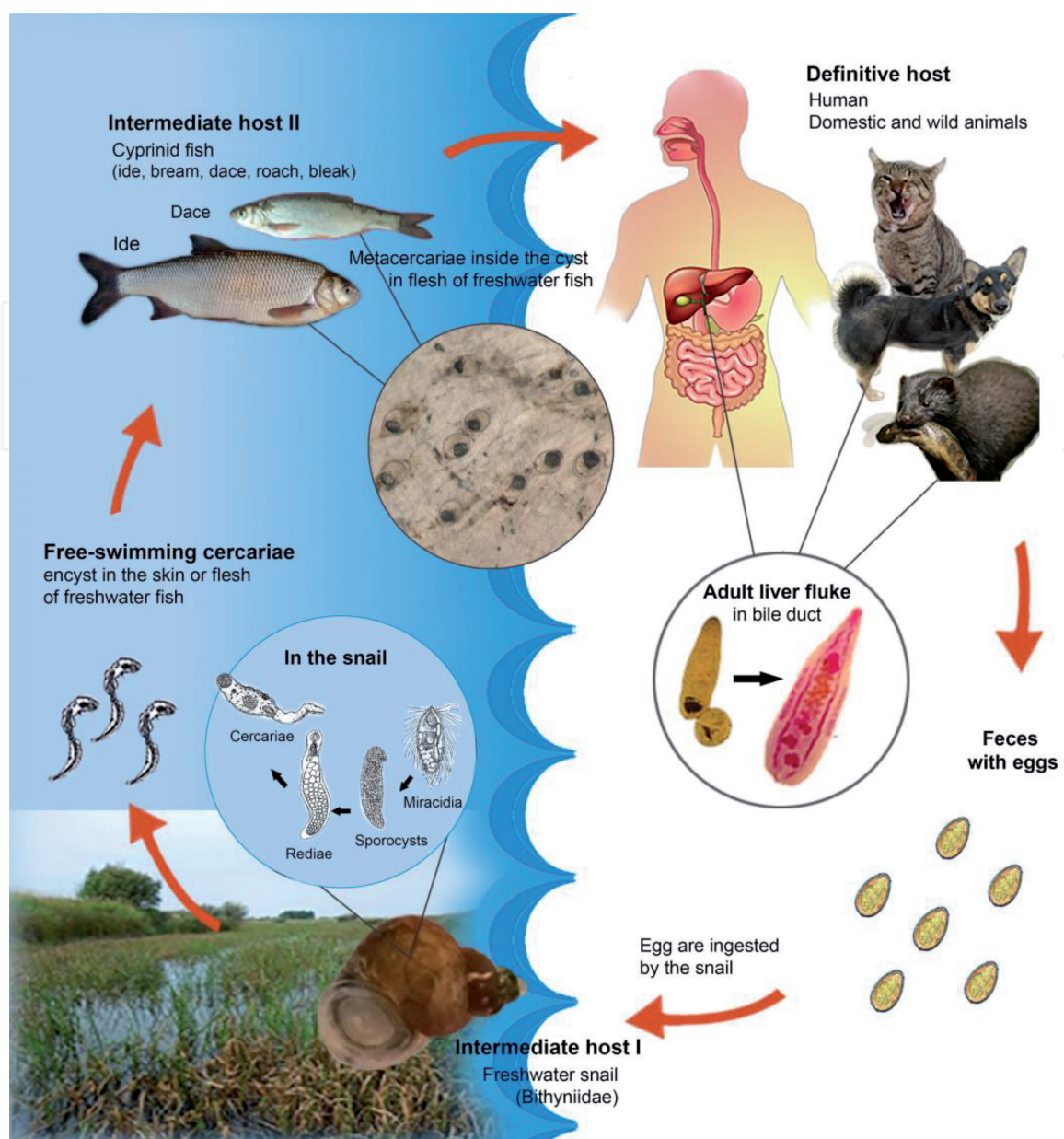
Figure 1.
Life cycle of O. felineus.

In the redia, tailed motile larvae—cercariae—are formed of the germ balls. The developmental stage in the mollusk takes 2–2.5 months (**Figure 1**) [2].

With the maturation, cercariae leave the redia through the pore to migrate in the mollusk body leaving it for water, where they swim for 30–50 h. Up to 3500 cercariae can leave the mollusk during 24 h. The release of cercariae has two peaks, namely a pronounced midsummer peak and a flat spring one [2].

When encountering a cyprinid fish (ide, dace, roach, bream, Siberian roach, Caspian roach, tench, common rudd, common carp, asp, common bleak, etc.), the cercaria attaches to it; detaches its tail; loses its eyes and sensory organs; and penetrates into the muscles to form the inner and outer (a capsule of connective tissue) membranes and to transform into the next phase, metacercaria (**Figure 1**).

The metacercariae have a size of 0.23–0.38 × 0.18–0.28 mm and are very survivable. The metacercariae become invasive 3–6 weeks after entering the fish and now are able to infect the definitive hosts—domestic and wild carnivores and omnivorous animals and humans. Metacercariae retain their viability in the fish body for 1–3 years and even to 9 years according to some data [8].

As is known, only cyprinid species are suitable intermediate hosts for the metacercariae. Approximately 20 species of both aboriginal and alien cyprinid species of commercial or noncommercial value inhabit the rivers and lakes of the Ob-Irtysh basin, the most important fish species of commercial significance are the ide, bream, crucian carp, roach, and, to a lesser degree, dace [2].

The rate of the fish infection by liver fluke metacercariae has been studied with different intensities in different periods. A large volume of data on the prevalence of fish infection in the Ob-Irtysh basin was accumulated in the 1990s to 2000s. Our data and the earlier results suggest high rates of infection of the ide, dace, and roach. The prevalence of ide and dace infection amounted to 20–100% and of roach, 2–80% with the intensity of infection of 1–1780 metacercariae per individual. These fish species are among the major carriers of *O. felineus* metacercariae and significantly contribute to the preservation of the opisthorchiasis focus. In addition, the bream and common bleak, alien species for this region, also appeared to be susceptible to the infection by liver fluke metacercariae and, correspondingly, have been involved in the maintenance and spreading of opisthorchiasis in Western Siberia [8–25].

The definitive hosts are infected orally by consuming the cyprinid fish muscles infected by liver fluke. The metacercarial membrane is finally destroyed in the host stomach, and the young helminth migrates along bile ducts to the liver and gall bladder to reach the sexual maturity in 20–25 days (**Figure 1**) [2].

The intensity of invasion of definitive hosts and their role in maintaining the strength of opisthorchiasis focus are different. As is assumed, in addition to humans who account for 56.6% of the invasion, cats (15.8%), dogs (3.6%), and pigs (to 0.9%) are also significant contributors to opisthorchiasis [26]. The total prevalence of cat invasion in the opisthorchiasis focus of the Khanty-Mansiysk Autonomous Okrug in the 2000s amounted to 48.2% (males were more frequently affected than females). The prevalence of dog invasion was lower, amounting to 17.14% [27]. An analogous study in Novosibirsk demonstrated the total prevalence of cat invasion of 7.9% with the intensity of 69.9 flukes and of dog invasion of 3.4% with the intensity of 23.8 flukes. Males appeared more affected among cats and females among dogs. The invasion parameters increase with animal age [28].

In addition to domestic carnivores, wild carnivores (common fox, wolf, brown bear, lynx, polecat, sable, mink, muskrat, bank vole, and others) also contribute to the liver fluke circulation in natural foci. These animals play different roles in the epizootic process in opisthorchiasis: the animals living in the floodplain and constantly "supplying" the infectious material to the biotopes of the first intermediate host are actual players of the opisthorchiasis circulation in the Ob-Irtysh basin, whereas the remaining animals are potential sources of invasion. In general, foxes and muskrats account for the largest number of invaded wild animals. The rate of invasion in the floodplain of Ob river and its tributaries reaches 77% on the background of a growth in the prevalence characteristics from the upper to lower reaches. The intensity of invasion amounts to 10–500 liver flukes per individual. The invasion of the muskrat in Western Siberia reaches 33% [29]; however, this issue requires further studies.

Thus, a complex multihost life cycle of this parasite enhances its long-term retention in wildlife and preservation of the natural opisthorchiasis focus in the Ob-Irtysh basin.

4. Epidemiology of opisthorchiasis in Russia

Opisthorchiasis is an important social problem in Russia. Two-thirds of the world distribution range of this pathogen concentrates in this country [30]. Opisthorchiasis

accounts for approximately 80% of all helminthic diseases. According to the official statistical data, up to 26,000 cases are annually recorded. The actual number of opisthorchiasis patients taking into account the correction factor is 15-fold higher [31].

In total, 106,362 cases of invasion were detected in 2014–2018. The maximum number of cases was recorded in 2014 (25,545 cases) and minimum, in 2017 (18,755 cases). The incidence rate of opisthorchiasis among population in 2018 decreased by 25.3% as compared with 2014, varying from 12.79 to 17.51 per 100,000 population (**Table 1**).

The natural foci of opisthorchiasis are adjacent to the Ob, Irtysh, Ural, Volga, Kama, Don, Dnepr, Severnaya Dvina, and Biryusa rivers [32–42].

Approximately 80% of the opisthorchiasis cases are recorded in the territories adjacent to the Ob, Irtysh, and Tom river basins and their tributaries [43], housing the administrative centers of the Omsk, Novosibirsk, Tyumen, Tomsk, and Kemerovo oblasts and Khanty-Mansiysk and Yamalo-Nenets Autonomous Okrugs. Most part of the local population is affected (80–95%) [44–46]. The total incidence rate over 2014–2018 was 84,331 opisthorchiasis cases, accounting for 79.3% of the total cases in the Russian Federation.

The Khanty-Mansiysk Autonomous Okrug heads the list of percentage of opisthorchiasis incidence (2.6–4.6) followed by Yamalo-Nenets Autonomous Okrug (1.2–2.3%), Novosibirsk oblast (1.1–1.5%), Tomsk oblast (1.0–1.6%), Tyumen oblast (0.9–1.3%), Omsk oblast (0.7–1.0%), Kemerovo oblast (0.5–0.7%), and Altai Krai (0.3–0.5%) [47–51].

The incidence rate of opisthorchiasis in the analyzed regions varies, with the maximum exceeding 1.3–1.8-fold the minimal value. The highest incidence rates are recorded in the hyperendemic regions of Yamalo-Nenets (124.2–226.7) and Khanty-Mansiysk (259.2–461.5) Autonomous Okrugs, Tyumen oblast (90.7–132.2), Tomsk oblast (104.7–158.4), Novosibirsk oblast (112.2–148.8), and Omsk oblast (72.8–103.3). The Kemerovo oblast (49.8–66.23) and Altai Krai (33.09–45.48) are the regions with a high level of invasion. The incidence of opisthorchiasis in these regions severalfold exceeds the mean level for the Russian Federation with the Khanty-Mansiysk Autonomous Okrug heading the list (19–26-fold) followed by Yamalo-Nenets Autonomous Okrug (9–13-fold), Tomsk and Novosibirsk oblasts (7–10-fold), Omsk and Tyumen oblasts (5–8-fold), Kemerovo oblast (3–5-fold), and Altai Krai (2–3-fold).

According to the statistical data for 2014–2018, a decrease in the absolute characteristics and incidence rate was in general observed in all hyperendemic regions, which is explainable by inadequate diagnosing, registration, and recording of the cases as a result of decreased attention to the problem of opisthorchiasis.

Opisthorchiasis is mainly diagnosed among the adult population (over 90% cases in people aged 39–59); however, the level of child morbidity is rather high. Opisthorchiasis has been recorded in all age cohorts of children up to 17 years, with the age cohort of 7–14 years accounting for 60–80% of all cases recorded in children. In the Tomsk oblast, the children to 17 years old are the most affected as compared with other regions (29.7% in 2014–40.8% in 2018). In the mid-Ob river region, opisthorchiasis is detectable in children starting from 3 years (25–30%) with an increase at the age of 12–14 years (50–60%) to 100% in the adults [52]. In the child population of the city of Urai (Khanty-Mansiysk Autonomous Okrug), the most affected cohort is 7–14 (38%) and 14–17 (34%) years old versus 23 and 5% for the cohorts of 3–6 and 2–2 years [53]. An increase in the prevalence of infection among the children of 1–2 years (from 3.8 to 6.1%) is observed in the Tomsk oblast. Cases of opisthorchiasis in the children under 1 year have been recorded in Khanty-Mansiysk Autonomous Okrug (six cases in 2017).

Region of Russian Federation	2018		2017		2016		2015		2014	
	Total[*]	IR[**]	Total[*]	IR[**]	Total[*]	IR[**]	Total[*]	IR[**]	Total[*]	IR[**]
Russian Federation	19,077	12.99	18,755	12.79	20,846	14.24	22,139	15.15	25,545	17.51
Yamalo-Nenets Autonomous Okrug	838	155.6	666	124.2	766	143.4	875	162.0	1228	226.7
Khanty-Mansiysk Autonomous Okrug	5046	299.6	4309	259.2	4454	272.5	6024	374.0	7370	461.5
Tyumen oblast	1483	98.9	1341	90.7	1384	95.1	1518	106.2	1831	132.2
Tomsk oblast	1129	104.7	1251	116.0	1336	124.1	1557	145.5	1686	158.4
Novosibirsk oblast	3252	116.6	3118	112.2	4109	148.8	3930	143.1	3505	128.3
Kemerovo oblast	1386	51.43	1704	62.91	1800	66.23	1357	49.8	1547	56.58
Omsk oblast	1427	72.8	1450	73.27	1469	74.24	1622	81.99	2035	103.1
Altai Krai	869	36.7	818	34.3	959	40.2	791	33.09	1091	45.48

[*]Morbidity data according to Form 2 "Data on infectious and parasitic diseases" approved by Order 52 of the Russian Federal State Statistics Service of January 28, 2014.
[**]IR is the incidence rate of disease per 100,000 population.

Table 1.
Absolute values and incidence rate of opisthorchiasis in the Russian Federation and Western Siberian region in 2014–2018.

In 2008–2017, 43 cases of acute opisthorchiasis were recorded in the middle Ob basin. Among those infected, the proportion of women and men was 48.8 and 51.2%, respectively. In terms of age, the maximum number of cases of acute opisthorchiasis was recorded among people aged 20–39 years (74.4%), followed by those aged 40–49 and 50–59 years (9.3% each group), and people aged 15–19 years (7.0%).

The largest number of cases of opisthorchiasis was recorded in May (20.9%) and June (32.6%), and less often opisthorchiasis was recorded in September and November (11.6% each). In other months, the infection was observed sporadically (1–2 cases). In 2008–2017, from 52.8% (2011) to 80.9% (2017) of people with recorded opisthorchiasis underwent dehelmintization (original data).

Since most rural population, including children, are involved in fishing, regular consumption of frozen and slightly salted freshwater fish is widespread; correspondingly, the incidence rate increases with age, and the cases of superinvasion are observable [54, 55].

The morbidity patterns in the municipal entities of autonomous okrugs and oblasts are considerably different. However, the corresponding levels observed in the municipal entities of the north are higher by an order of magnitude. The significant differences in morbidity in different municipal entities of oblasts and autonomous okrugs are associated with different quality of clinical diagnostics, recording, and registration of opisthorchiasis cases rather than with the difference in diet pattern [56]. The facts that the child morbidity rate is higher than that in adults are explainable by that adult population rarer seeks medical help. Since the diet of children and adults does not significantly differ, it is likely that the adult population is highly affected with the prevalence of chronic disease courses [56].

The urban population on the average accounts for 75–78% of the opisthorchiasis cases [31, 57]. However, the incidence among the rural population is higher than the urbane population. Characteristic of the urban life style is rarer consumption of freshwater fish and better adherence to good cooking practice [54].

5. Clinical manifestations, pathogenesis, and complications of human opisthorchiasis

Opisthorchiasis is a food-borne disease, with the pathogen transmission via eating the fish infected with the liver fluke metacercariae. The susceptibility to invasion is ubiquitous. The duodenal content induces larvae to excyst there wherefrom they migrate through the ampulla of Vater to the bile excretory ducts owing to a positive chemotaxis to bile. In 3–5 h, liver flukes (100%) are detectable in the liver, pancreas, and gall bladder (20–40%) [58, 59].

After 3–4 weeks, liver flukes turn into sexually mature maritae, producing eggs [58].

Clinical manifestations of opisthorchiasis are manifold and depend on individual specific features of the host organism as well as infection intensity and duration [34, 60, 61]. Humans are unable to develop immunity to this pathogen; correspondingly, repeated consumption of the fish carrying metacercariae merely increases invasion [62, 63]. The counts of maritae in an individual can vary from solitary parasites to several tens and even hundreds [63].

The incubation period of opisthorchiasis is on the average 2–3 weeks [58, 61]. The early (acute) and late (chronic) phases of this disease are distinguished [64]. The early phase lasts from several days to 4–8 weeks and longer [60], while the chronic phase may last for 10–20 and more years [64]. The disease may have unapparent or overt manifestations [58, 61, 65, 66].

Characteristic of the subclinical case of opisthorchiasis early phase is a subfebrile temperature and insignificant eosinophilia on the background of normal leukocyte counts [58]. A subclinical course is observed in the children who have received the antigen during their embryonic development or the antibodies with mother's milk [67–69]. This is the explanation why the manifestation of opisthorchiasis in the indigenous population of the north (Khanty and Mansi) is primary chronic with poor symptomatics and aggravation under adverse conditions, such as stress, infections, or surgery [58, 60, 61, 70, 71].

An overt course of opisthorchiasis is usually observable in the patients who moved to the opisthorchiasis focus from the regions not endemic for the disease [58]. The acute phase starts abruptly and continues for 1–3 months or rarer, for 6–9 months [58, 62, 63]. A systemic allergic response determines development of inflammation in the lungs, gastrointestinal tract, musculoskeletal system, skin, and cardiovascular system [64]. The patients experience fever (from subfebrile to febrile for 1–3 weeks), eosinophilia (20–40%; sometimes, to 90%), intoxication, dyspeptic disorders (nausea, vomiting, and epigastric burning), moderate arthralgia and myalgia, and exanthems of various types [58, 60, 61, 64]; hepatocholangitic syndrome (right subcostal pain, increased liver, elevated transaminase activities, and elevated alkaline phosphatase activity) [58, 64], bronchopulmonary syndrome (hyperemic pharynx, retropharyngeal granulation, rhinitis, asthmatic bronchitis, eosinophilic infiltration in the lungs, and exudative pleurisy), and cardiovascular changes (palpitation, cardiac pain, hypotonia, and diffuse dystrophic changes in the myocardium detectable by electrocardiography) are observable [72].

A severe form of the acute opisthorchiasis can be represented by typhoid, hepatocholangitic, and gastroenteritic clinical variants [73]. Severe toxic and allergic responses appear as toxic epidemic necrolysis (Lyell's syndrome), Stevens-Johnson syndrome, acute myocarditis, Quincke's edema, or hives [60].

In the absence of treatment, the acute phase transforms into a chronic one [63], which can continue for 20 years [61] and proceed either latently or with clinical manifestations [62]. A latent course is more frequent characteristic of the aboriginal population in the opisthorchiasis foci and in young people [60]. Patients have no complaints, and laboratory tests are normal. Opisthorchiasis is diagnosed in these cases only by chance during a periodic health examination or examination for other diseases [62]. In practice, this is the situation for 8% of several thousands of patients [63].

Characteristics of a latent opisthorchiasis are periods of remission and exacerbation [62]. In an endemic focus, opisthorchiasis initially follows a chronic course without any acute manifestations. Clinical symptoms may appear 10–20 years after infection. Patients frequently develop the symptoms of cholangitis and cholecystitis (80–87% of the cases) [74, 75], including right subcostal pain, heaviness in the stomach, nausea, fat intolerance, dryness and bitter taste in the mouth [58], abdominal distention, frequent liquid stool [63], vomiting, eructation, hepatomegaly, and jaundice during exacerbation [73]. Part of the opisthorchiasis patients develops pancreatitis with a wave-like course (frequent alternation of remission and exacerbation periods); 45–50% of the patients experience gastritis, duodenitis, and gastric and duodenal ulcers [73, 76]. In case of gastric involvement, patients frequently develop intestinal dyspepsia and dysbacteriosis, with the absence of bifidobacteria or their decrease and an increased content of facultative opportunistic pathogenic microflora, such as *Staphylococcus epidermidis* and *Staphylococcus aureus* [74]. Patients complain of undue fatigability, petulance, sleep loss, headache, hyperhidrosis (frequently local, for example, sweaty hands), excessive salivation, pronounced dermographism, tremor (eyelids, tongue, and/or fingers), vasomotor vascular response, and subfebrile temperature [76, 77].

The immunological response to antigens clinically manifests itself as an allergic syndrome, with skin itching, hives, recurrent Quincke's edema, arthralgia, alimentary allergy, moderate eosinophilia, and specific IgE in the blood [61]. A constant presence of the liver fluke antigen wears off the immune system and decreases its ability to suppress infection [69, 78, 79].

Chronic opisthorchiasis is a factor that is able to induce liver cancer development [63]. The early manifestations of liver cancer are an increase in the right subcostal pain and epigastria; their constant unceasing character, especially during nighttime; sensation of discomfort and heaviness; and pronounced dyspeptic disorders (anorexia, idiopathic weight loss, early satiety, abdominal distension, alternation of constipation and diarrhea, and so on). Weakness, general uneasiness, and sleep disorders rapidly worsen. The prescribed treatment of chronic opisthorchiasis fails to bring relief [80]. Hepatomegaly is characteristic of the liver cancer (the liver is dense, nodular, and painful); typical manifestations are hypochromic anemia, eosinophilia, accelerated ESR, and, in the case, of cancer, lymphopenia [80].

In pancreatic cancer, patients more frequently experience weakness, vomiting, and progressive weight loss. In part of patients, vomiting is caused by impaired gastric emptying because of the tumor compression or its invasion to the duodenum. Patients lose 5–32 kg over 2–3 months [80].

The main sign of pancreatic cancer is jaundice; it is persistent, increasing in its intensity, and accompanied by a high body temperature and chill. The fever and itching exhaust patients so that they lose sleep and experience growing adynamia and apathy. The liver may be increased; it has smooth surface and is less dense [80]. Characteristic of jaundice is a high concentration of bilirubin in the blood as well as increased alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase activities. Amylase activity is also increased in the liver and pancreatic cancers; thymol and sublimate tests are changed, which suggest an advanced cancer process [80].

Pathogenesis is determined by the combined impact of parasites on the host body (mechanical, toxic, and neuroreflectory) and host body responses (immunopathological) [60, 61, 64].

In the early phase, the immunopathological mechanisms with development of the immediate type allergic response are more pronounced [61, 64]. The liver fluke antigens enter the blood through mucosa and sensitize the organism (gastrointestinal tract, lungs, kidneys, liver, etc.) [60, 61]. The liver fluke metabolites induce toxic and allergic syndrome [58, 64], which are accompanied by edema, proliferation, desquamation of bile duct epithelium, and metaplasia of bile ducts with formation of goblet cells and small gland-like structures [58].

In the late phase, the liver fluke metabolites induce an immune inflammation in many organs and systems [81, 82]. The immunopathological effect appears as a secondary immunodeficiency with prevalence of a delayed type allergic response; characteristics of this response are vascular involvement and regeneration of cell elements in the connective tissue with development of extensive fibroplasia [73, 83].

Mechanical and toxic factors in the late stage become the most important [61, 64]. Young liver fluke individuals damage the bile duct walls by their spinules and the sexually mature individuals and by their oral and ventral suckers. Liver flukes consume the mucosal secretions and bile duct epithelium [45]. A mechanical stimulation of the walls of bile and pancreatic ducts interferes with the motor and secretory functions of the gastrointestinal tract [60].

Inflammatory and proliferative processes are induced and developed in the mucosal lesions, as well as peroxidation is activated and antioxidant defense is damaged [60, 84].

Clusters of liver flukes, their eggs, and crusts of desquamated epithelium in the ducts create a mechanical barrier for the outflow of bile and secretion, thereby enhancing the development of proliferative cholangitis and canaliculitis accompanied by different degrees of fibrosis in these organs [60].

Frequently, the pancreas responds to the presence of liver flukes and their metabolites by certain pathological changes. Both the exocrine and endocrine functions of the pancreas are damaged during pancreatitis [67, 85, 86].

Persistent hypertension develops in the duodenum, stomach, esophagus, and biliary system on the background of chronic duodenal stasis [61], creating the favorable conditions for secondary infections (*Escherichia coli*, staphylococci, yeast-like fungi, and others) [60].

The liver fluke invasion has a negative effect in the mother-placenta-fetus system [87], increasing the probability of gestoses and miscarriage [88].

The involvement of gastrointestinal tract affects digestion and absorption, leading to dysmetabolic sensitization. As a consequence, allergic skin lesions are developed, including urticarial rash in the early phase and chronic hives with exacerbation periods and remissions in the late phase [85, 86]. The urticarial rash rather frequently transforms into papular and vesicular rash. In some cases, hives can follow a hemorrhagic pattern owing to release of erythrocytes, which fall apart and form pigment spots [61, 79, 89].

The host immunopathological response is the cause underlying the dystrophy and necrosis of the epithelium of biliary tract and pancreatic ducts [79, 89, 90].

The sclerotic processes leading to the development of chronic hepatitis are prevalent in the late phase. Superinvasion and reinvasion lead to development of an active hepatitis as a result of an immune inflammation in the liver [61, 68, 91].

Complications of opisthorchiasis most frequently develop in the chronic stage. This disease belongs to the group of carcinogenic helminthiases [55, 59, 92, 93]. Liver tumors [55, 57, 94] as well as stomach, pancreas, and breast tumors most frequently develop on the background of liver fluke superinvasion [95, 96].

The carcinogenesis on the background of opisthorchiasis involves multifactorial mechanisms comprising inflammatory, mechanical, and secretory-excretory processes [84, 97].

In case of superinvasion, maritae provide a sustainable basis of the food substrate—permanent proliferation and differentiation of liver and pancreatic stem cells as well as the stem cells in the organs beyond their ecological niche [55].

An overt inflammation determines a constant response as the regenerative cell proliferation [55, 98].

Activated macrophages and polymorphonuclear leukocytes produce reactive oxygen species, proteolytic enzymes, proinflammatory cytokines, and growth factors. Reactive oxygen and nitrogen species and oxysterol production play the decisive role in the disturbance of the function of proto-oncogenes, the DNA regions the abnormalities in which induce cancer transformation of liver cells [45, 66]. As a result, adjacent cells are altered, and an active regeneration of injured tissues is triggered [97, 99].

Maritae interfere with the bile outflow in a purely mechanical manner. The stagnant bile in the ducts interacts with free radicals to form endogenous carcinogens, which has a mutagenic effect on the DNA of cholangiocytes [100, 101]. Eggs can penetrate to the periductal tissues via the ulcerations at the sites of liver fluke sucking and cause there a granulomatous inflammation [93]. The liver fluke excretory and secretory antigens (by themselves or via the interaction with free radicals) initiate cell proliferation during a liver fluke superinvasion [57] and display direct cytotoxic and mutagenic effects [96, 98, 102–104].

Hemozoin, a liver fluke pigment, is able to induce a carbonyl (extracellular) stress [105, 106]. A long-term injury of cholangiocytes and a mitogenic effect of growth factors are the cause underlying the complications, such as epithelial hyperplasia, periductal fibrosis, and strictures, and cysts of bile ducts followed by cholestasis, as well as lead to development of cholangiocarcinoma [80, 84, 105, 107, 108].

Morphologically, up to 80% of all tumors in opisthorchiasis cases are cholangiocarcinomas [109]. The risk of cholangiocarcinoma development correlates with the duration and intensity of liver fluke invasion [109–111]. The external factors enhancing cholangiocarcinoma development in opisthorchiasis cases are alcohol (demonstrated for *Opisthorchis viverrini*) and food nitrosamines (independent risk factor), especially in the endemic regions [98, 112, 113].

In 1970–2005, 1170 patients underwent surgery because of the complications of opisthorchiasis, which accounts for 24.6% of the total opisthorchiasis cases (4756). The patients with cholangiocholecystitis (70.3%), cholecystopancreatitis (18.4%), and hepatocholecystitis (11.3%) received a conservative treatment. A repeated invasion was observable in the overwhelming majority of patients; most of the opisthorchiasis cases (75%) were of the working age with the overall age range of 21–87 years [114].

Opisthorchiasis is complicated by liver abscesses, ascending cholangitis, hepatitis, and gastric and duodenal ulcers [115]. Frequently met surgical complications of opisthorchiasis are opisthorchiasis pancreatitis, observed in 16% cases [115]. A dangerous complication of opisthorchiasis cysts in the liver is abscesses and their rupture followed by bile peritonitis [114].

6. Prevention of opisthorchiasis

The prevention measures against opisthorchiasis comprise in the following:

- detection and treatment of opisthorchiasis cases in the disease focus;

- dehelminthization of domestic carnivores; and

- protection of water bodies from feces, proper keeping of the areas of settlements, use of sewage containers in river vessels, decontamination of sewage, and prohibition of using the content of outhouse latrines for fertilization of vegetable gardens [63].

The degree of human protection is determined by the level of their knowledge about the measures ensuring the invasion prevention and their sanitary culture [64].

The personal precautions mainly reduce to good cooking practices in fish processing, which ensures fish disinfection [63]. A special attention must be paid to teaching the population to properly process fish at home [64].

The disinfection is attained by thermal treatment, freezing, smoking, and salting [58].

The fishes with a weight of up to 1 kg must be frozen at a temperature of −28°C for 41 h or at −35°C for 10 h. In a household refrigerator, metacercariae retain viability for over 1 month [64].

Fish (in the case of a large individual, cut into pieces of no more than 2 cm) should be stewed for at least 20 min from the moment of boiling or fried as small flattened pieces (or minced) for 20 min in a large volume of oil. Fish pies must be kept in the oven (200°C) for at least 60 min [63].

Fish salting requires at least 2 weeks (2 kg salt per 10 kg fish; [64]). Before cold smoking, fish is disinfected by either salting or freezing [63].

Hot smoking requires a temperature of 70–80°C for 2–2.5 h [64].

The preservation meeting the Codex Alimentarius rules also guarantees safety from the liver fluke metacercariae [58].

It is always necessary to carefully wash your hands and kitchen utensils after processing raw fish [64].

It is strongly recommended to avoid consumption of raw fish, weakly or shortly salted fish, or raw minced fish as well as the frozen fish as stroganina (cut into thin slices), and other local variants of raw frozen fish as well as freshly caught fish in any home-made slightly salted, smoked, or dried variants prepared without observing the described technologies and by unknown persons [63].

Unfortunately, insufficient attention has been recently paid to education of population, which naturally resulted in an increase in the number of opisthorchiasis cases [116].

7. Natural, climatic, and social factors enhancing preservation of the opisthorchiasis focus

The activity of epizootic process in Western Siberia depends on the parameters of water regime in this territory. The vastness of the Western Siberian floodplains increases from south northward as well as the regular pattern, volume, and duration of spring floods; duration of summer-fall floods in the floodplains; and good water heating [57, 64]. The Western Siberian rivers are rather slow, with a long freeze-up period, preventing aeration, and winter deficiency in oxygen. Poor soil draining and excessive moistening enhance an abundance of water in the region and an increased number of floodplain water bodies, favorable for the development of Bithyniidae mollusk population [57].

In addition, large-scale hydrotechnical engineering activities (construction of channels, cascade artificial water reservoirs, dead dams without byways, and littering of water bodies with household and construction waste) create favorable conditions for mollusk development [57, 64].

Water and soil contamination with the liver fluke eggs significantly contribute to sustainable circulation of the opisthorchiasis agent in natural biocenoses; the liver fluke eggs have been detected in 1.13 ± 0.1% of the soil samples, 15.4 ± 0.9% of wastewater and silt samples, and 1.34 ± 0.2% of water from water bodies. The intensity of wastewater and sediment seeding with liver fluke eggs was maximal and varied from 2000 to 4000 eggs/m^3; this value for the soil specimens was significantly lower, 0–40 eggs/kg soil. Because of poor disinvasion efficiency, the wastewater discharged into water bodies remains uncontaminated, thereby maintaining the circulation of this pathogen in nature [57, 117].

A high level of population infection with opisthorchiasis is aggravated by social factors, namely, a decrease in population living standards and an increase in the share of fish and home-made fish products in the diet of the inhabitants of the cities and villages adjacent to rivers. Population buys fish in shops or unofficial markets or harvests it by themselves. In particular, 52% of opisthorchiasis cases bought the fish in unofficial markets; 34% of them were infected as a result of amateur fishing; and 14.0% received the fish shipped from a northern part of the region [57].

The main risk factors of opisthorchiasis are a high infection rate of the cyprinid fish species and the eating behavior pattern, i.e., prevalence in insufficiently disinfected fish in the common diet; in addition, the cyprinid fish is typically accessible to population, as is demonstrated by all-year-round fishing. In particular,

over half (58.36 ± 2.81%) of the questioned subjects were amateur fishermen, and 41.44 ± 3.33% of them have their own fishing gear (nets, dragnets, etc.). This explains why the cohort of fishermen, water transportation workers, amateur fishermen, and their family members form the risk group with the maximum infection rate in the epicenter of the Ob-Irtysh opisthorchiasis focus. In the Khanty-Mansiysk Autonomous Okrug, the opisthorchiasis rate in the most important risk groups—buoy keepers and motor fishing fleet workers with their families—amounts to 75.6 ± 2.7 and 67.8 ± 3.8%, respectively [57]. In the southern part of the focus, the infection rate of the Tobolsk fish processing plant workers was 78 ± 0.3%; of the amateur fishermen in the Tobolsk raion, 36.6 ± 3.2%; and of the persons constantly involved in fishing in the Tyumen raion, 30.8 ± 3.8 and 50.0 ± 8.1% [57].

A high risk of opisthorchiasis is characteristic of the socially vulnerable cohorts, which eat the fish products conditionally approved as fit for human consumption, processed and prepared without taking into account the good cooking practice [57, 118–120]. In many households, weakly salted (in particular, large batches of ungutted fish salted in barrels), undercooked, freshly frozen, and freshly harvested cyprinid fish are the common all-year-round component of their diet. Infection can take place when testing minced fish "for salt" and accidental ingestion of liver fluke larvae from hands or kitchen utensils during fish processing. Children can be infected when cooking fish broth by themselves, making a kind of barbecue, or eating fresh fish [64, 85]. A high invasion rate of the indigenous northern population in Siberia is determined by the local tradition of eating stroganina, sliced frozen raw fish [64].

Population has little knowledge about the prevention measures. Only 27.93 ± 4.25% of the adult population is aware of the thermal processing practice, and 7.74 ± 1.31% knows the proper rules for fish salting and drying [57]. As has been shown, 89.0% of the opisthorchiasis cases either neglected the good fish cooking and salting practice or do not know them at all, and 1% of the infected subjects consume raw fish (stroganina) [57].

The effect of urbanization on the epidemic process is rather ambiguous [57]. One of the factors of an autogenic impact on the function of parasitic liver fluke system is the migration of population. Migration "supplies" the cohorts with a high risk of infection and poorly or completely unaware of how to prevent the invasion (who eat the improperly cooked fish) to the territories with a high risk of opisthorchiasis. An increase in population enhances the decrease in its morbidity owing to "dilution" of the aboriginal population by a large influx of uninfected newcomers, involved in shift work or expeditions [57].

Improvement of the sanitary knowledge owing to development of the medical network and sanitary education activities at the locations of newcomer cohorts decreases the risk for opisthorchiasis [57].

Low rates of dehelminthization result in an increase in the number of infection sources. Human pollution of the habitat increases the risk of infection of the population. In particular, 90% of the opisthorchiasis subjects listed for regular medical check-up in the Khanty-Mansiysk Autonomous Okrug ignored the prescribed treatment [31]. In the city of Langepas (Khanty-Mansiysk Autonomous Okrug), the incidence of opisthorchiasis increased 1.2-fold because of the problems with providing the necessary drugs, refuse of the treatment, and ignore the therapy without any particular reason [121].

8. Discussion

Opisthorchiasis is an anthropozoonous natural focal biohelminthosis caused by trematodes of *O. felineus*. Invasion has been recorded mainly in the Ob-Irtysh basin since 1891.

The main source of opisthorchiasis caused by *O. felineus* is a person infected with opisthorchiasis, all fish-eating mammals (dogs, cats, foxes, muskrats, etc.) can also be the final hosts. In addition to human distributing up to 56.6% of invasive material, cats (15.8%), dogs (3.6%), and pigs (up to 0.9%) are assumed to be another source of infection [26]. Intermediate and additional hosts of *O. felineus* inhabit water bodies, and foci of opisthorchiasis are concentrated near rivers.

The first intermediate host in the focus is freshwater mollusks, subclass Prosobranchiata, family Bithyniidae, genera *Codiella* and *Opisthorchophorus*. The mollusk invasion prevalence is very low, whereas the invasion intensity is very high. One mollusk lays up to 8000 cercariae [4–7].

The second intermediate host is fish of the family Cyprinidae. The prevalence of invasion of fish population ranges from 20 to 100%, while the invasion intensity varies from one to several hundred metacercariae (original data).

Russia has the highest incidence of this helminth. Natural foci of opisthorchiasis are located near the rivers Ob, Irtysh, Urals, Volga, Kama, Don, Dnieper, Severnaya Dvina, and Biryusa [32–42]. The world's largest focus of opisthorchiasis is located in the Ob-Irtysh basin.

The transmission mechanism of the infection fecal-oral route, and the transmission route is food. Infection occurs when a person eats raw or insufficiently thermally processed and freshly salted cyprinid fish, containing live larvae (metacercaria).

Natural susceptibility of people to opisthorchiasis is high. The population does not show durable immunity after curing. These helminths have adverse effects on human health, mainly affecting the hepatobiliary system and pancreas. Clinical manifestations of the acute phase of opisthorchiasis last from several days to 4–8 weeks or more, and the phase of chronic opisthorchiasis lasts 15–25 years or more. The duration of the incubation period (in the early phase of the disease) is 2–4 weeks (up to 6 weeks). Allergic reactions, mechanical, and neuroreflex effects of helminths play the main role in the pathogenesis of opisthorchiasis and cause biliary dyskinesia, temporary and complete cessation of bile flow, glandular proliferation in the epithelium of the biliary, and pancreatic ducts and other glandular organs. Pathological processes affect the liver (impaired secretion of enzymes and protein, reduced cholesterol synthesis, and antioxidant function of the liver), pancreas (impaired secretion of enzymes, including insulin), stomach and intestines (erosive gastritis and colitis), and skin (itching, cracks, and psoriasis). Severe complications of opisthorchiasis include biliary peritonitis, liver abscesses, liver cirrhosis, primary liver cancer (less commonly pancreas cancer), acute destructive pancreatitis, bronchial asthma, and diabetes mellitus. Due to the character of infection and a high degree of mutual adaptation of the host and the parasite, opisthorchiasis often proceeds latently (without clinical symptoms).

Among people of various professions, fishermen, river fleet personnel, agricultural workers, and forest industry workers are primarily infected. In endemic areas, opisthorchiasis can be recorded at the age of 1–3 years. The infection rate attains its highest level by 25 years and keeps stable up to 50–60 years. The prevalence among the local population can reach 100% (original data).

The most important prerequisites for an intensive epidemic process in these territories are natural and social factors:

- abundance of rivers and lakes rich in fish and mollusks (the highest infection rate among population is recorded in territories with numerous flood meadows and former riverbeds and places where the floodplain is more developed);

- hydrotechnical transformations;

- intensive contamination of rivers and floodplain lakes by helminths' eggs from permanent and temporary settlements, cities, etc. located on their banks;

- prevalence of insufficiently disinfected fish in the diet and cyprinid fish consumed by the population;

- specific ethnic or traditional behavior associated with food and nutrition that determines the nature of distribution and the infection rate among the population in endemic foci;

- poor knowledge of preventive measures; and

- infection is possible beyond these foci when exporting fish.

Simple personal preventive measures will contribute to prevention of opisthorchiasis.

9. Conclusions

The optimal natural and climatic conditions together with social and economic factors create the favorable conditions for preservation of the world largest Ob-Irtysh focus of the opisthorchiasis caused by the trematode *O. felineus*.

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References

[1] Report of United Nations. Department of Economic and Social Affairs Population Division; 2015. p. 149

[2] Beer SA. The Biology of Opisthorchiasis Agent. Moscow: KMK; 2005. p. 336 [in Russian]

[3] Zavoikin VD, Beer SA, Bocharova TA. Comparative opisthorchiasis situation in the largest Ob river tributaries. In: Human Opisthorchiasis: Proceedings of the Scientific Conference, Tomsk. 1979. pp. 60-62 [in Russian]

[4] Drozdov VN. Infection of Bithynia by liver fluke cercariae in the water bodies of the Irtysh River basin. In: Proceedings of the Scientific Conference on Medical Parasitology, Tyumen. 1964. pp. 76-78 [in Russian]

[5] Fedorov VG. The infection of Bithynia leachi mollusk by liver fluke cercariae in the water bodies of the Ob River upper reaches. In: The Problems in Natural Focality of Human Helminthiases, Tyumen. 1969. p. 71 [in Russian]

[6] Zavoikin VD, Zelya OP, Sokerina OA. Current state of the issue of opisthorchiasis in Western Siberia. In: Relevant Problems in Infectology and Parasitology: Proceedings of the First International Anniversary Conference, Tomsk. 2001. p. 99 [in Russian]

[7] Potseluev AN. The effect of hydrological regime and anthropogenic factors on the ecology of the first intermediate host of opisthorchiasis agent: A case study of the Ob-Irtysh Basin. [Candidate of Sciences (Med.) thesis]. Moscow; 1991. p. 21 [in Russian]

[8] Fattakhov RG. The distribution of opisthorchiid metacercariae in cyprinid fish in Western Siberia. In: Parasites and Diseases of Hydrobionts in the Ice Sea Province. Novosibirsk: Nauka; 1990. pp. 128-131 [in Russian]

[9] Krivenko VV, Filatov VG. Cyprinid fish are intermediate hosts of trematodes in the Tura–Pyshma interfluve. In: Parasites and Diseases of Hydrobionts in the Ice Sea Province. Novosibirsk: Nauka; 1990. pp. 131-135 [in Russian]

[10] Fattakhov RG. The distribution of *Opisthorchis felineus* (Riv., 1884) and *Metorchis bilis* (Braun., 1790) larvae in populations of the roach Rutilus rutilus (L.) and sunbleak Leucaspius delineates (Heck). In: The Tasks and Problems in Fish Management in Siberian Inner Water Bodies. Tomsk: Izd. Tomsk. Univ.; 1996. pp. 109-110 [in Russian]

[11] Fattakhov RG. Invasion of fish by opisthorchiasis agent in Russia and several adjacent countries. Meditsinskaya Parazitologiya i Parazitarnye Bolezni. 2002;**1**:62

[12] Gafina TE. On the current state of the helminth fauna of the main commercial; fish species in the Ob Reservoir tail pond. In: The Tasks and Problems in Fish Management in Siberian Inner Water Bodies, Tomsk. 1996. pp. 105-106 [in Russian]

[13] Fedorov VG, Belov GF, Naumov VA. The problem of human trematodiases in Western Siberia. In: Topical Problems in Infectology and Parasitology, Proc. of the First International Conference devoted to 110th Anniversary of Prof. K.N. Vinogradov's Discovery of Liver Fluke in Humans, Tomsk. 2001. p. 34 [in Russian]

[14] Sous' SM. Analysis of the specific morphoecological features of opisthorchiasis and metorchiasis in the Novosibirsk oblast. Sibirskiy Ekologicheskiy Zhurnal. 2006;**4**:399-407

[15] Sous' SM, Bocharova TA. The dynamics of cyprinid infection by liver

fluke metacercariae in water bodies of the Tomsk and Novosibirsk oblasts. In: Current Problems in Hydrobiology of Siberia. Tomsk: Izd. Tomsk. Univ.; 2001. pp. 149-150 [in Russian]

[16] Sous' SM, Rostovtsev AA. Opisthorchiasis, metorchiasis, and fish tapeworm disease. Prevention. In: Parasites of Fish in the Novosibirsk Oblast. Tyumen: Gosrybtsentr; 2006 [in Russian]

[17] Karpenko SV, Chechulin AI, Yurlova NI, et al. Characteristics of Opisthorchosis Nidus in the South of Western Siberia. Sibirskiy Ekologicheskiy Zhurnal. 2008;**5**:675-680

[18] Bocharova TA. The role of some cyprinid species in the opisthorchiasis epidemiology in the Tomsk oblast. In: Topical Problems in Infectology and Parasitology, Proc. of the First International Conference devoted to 110th Anniversary of Prof. K.N. Vinogradov's Discovery of Liver Fluke in Humans, Tomsk. 2001. p. 141 [in Russian]

[19] Bocharova TA. The muscle parasitic fauna of the cyprinid fish in the lower Tom River basin. In: Parasitological studies in Siberia and the Far East. Proc of Interregional Conference. Novosibirsk. 2002. pp. 29-32 [in Russian]

[20] Bocharova TA. An epidemiological state of the opisthorchiasis foci in the Tomsk oblast. In: Topical Problems in Medical Biology, Tomsk. 2002. pp. 67-69 [in Russian]

[21] Bocharova TA. The dynamics of muscle infection in some cyprinid species in the lower Tom River basin. Vestnik Tomskogo Gosudarstvennogo Universiteta. 2003;**8**:22-24

[22] Bocharova TA. The role of small water flows in the opisthorchiasis focus of the lower Tom River basin. In: Topical Problems in Biology, Medicine, and

Ecology, Tomsk. 2004. pp. 404-405 [in Russian]

[23] Bocharova TA. The effect of microwave beams on the survivability of trematode larvae in the muscles of the common dace in the Tom River lower reaches. In: Parasitological Studies in Siberia and the Far East. Proc. of the 11th Interregional Conference, Novosibirsk. 2005. pp. 29-31 [in Russian]

[24] Bocharova TA. Opisthorchiasis Agent and Other Muscle Parasites of the Cyprinid Fish in the Lover Tom River Basin. Tomsk: Izd. Tomsk. Univ.; 2007. 66 p [in Russian]

[25] Simakova AV, Babkina IB, Babkin AM, Interesova EA. Infestation of alien cyprinid fishes with trematode Opisthorhis felineus Rivolta, 1884 in the middle Ob River basin. Russian Journal of Biological Invasions. 2019;**10**(2):178-180. DOI: 10.1134/s2075111719020115

[26] Krivenko VV. Biological Properties of liver fluke eggs and the role of some definitive host species as sources of invasion material during opisthorchiasis in Western Siberia. [Candidate of Science (Biol.) thesis]. Moscow; 1984 [in Russian]

[27] Shibitov SK. Opisthorchiasis of carnivorous animals in Western Siberia: Prevalence, pathogenesis, diagnostics, and control measures. [Candidate of Sciences (Vet.) thesis]. Moscow; 2013 [in Russian]

[28] Zubareva IM. Main helminthiases of domestic carnivorous animals in large cities (a case study of Novosibirsk). [Candidate of Sciences (Vet.) thesis]. Novosibirsk; 2004 [in Russian]

[29] Fedorov KP, Pashkevich VY, Konyukhov EN. Helmithofauna of the muskrat in Western Siberia. Problems in Ecology. 1976;**4**:113-120

[30] Resolution no. 179 of the Federal Service for Supervision of Consumer Rights Protection and Human Well-being of December 12, 2016 "On Prevention of Distribution of the Parasitic Diseases Transmitted via Fish and Fish Products in the Russian Federation" [in Russian]

[31] Letter no. 1/12315-2018-27 of the Federal Service for Supervision of Consumer Rights Protection and Human Well-being of September 24, 2018 "On implementation of the Resolution of the Chief State Sanitary Inspector of the Russian Federation of December 12, 2016 "On Prevention of Distribution of the Parasitic Diseases Transmitted via Fish and Fish Products in the Russian Federation"" [in Russian]

[32] Beer SA. Parasitological monitoring in Russia (basics of the concept). Medical Parasitology and Parasitic Diseases. 1997;**1**:3-8

[33] Mordvinov VA, Yurlova NI, Ogorodova LM, Katokhin AV. *Opisthorchis felineus* and *Metorchis bilis* are the main agents of liver fluke infection of humans in Russia. Parasitology International. 2012;**61**: 25-31. DOI: 10.1016/j.parint.2011.07.021

[34] Fedorova OS, Kovshirina YV, Kovshirina AE, Fedotova MM, Deev IA, Petrovskii FI, et al. Analysis of the prevalence of *Opisthorchis felineus* invasion and malignant neoplasms of the hepatobiliary system in the Russian Federation. Bulletin of Siberian Medicine. 2016;**15**(5):147-158

[35] State Report "On the Sanitary and Epidemiological Well-being of the Population of the Yamalo-Nenets Autonomous Okrug in 2014-2018" [Internet]. [in Russian]. Available from: http://89.rospotrebnadzor.ru [Accessed: 25 September 2019]

[36] State Report "On the Sanitary and Epidemiological Well-being of the

Population of the Khanty-Mansiisk Autonomous Okrug–Yugra in 2014-2018" [Internet] [in Russian]. Available from: http://86.rospotrebnadzor.ru [Accessed: 30 September 2019]

[37] State Report "On the Sanitary and Epidemiological Well-being of the Population of the Tyumen Oblast in 2014-2018" [Internet]. [in Russian]. Available from: http://72. rospotrebnadzor.ru [Accessed: 30 September 2019]

[38] State Report "On the Sanitary and Epidemiological Well-being of the Population of the Tomsk Oblast in 2014-2018" [Internet]. [in Russian]. Available from: http://70.rospotrebnadzor.ru [Accessed: 30 September 2019]

[39] State Report "On the Sanitary and Epidemiological Well-being of the Population of the Novosibirsk Oblast in 2014-2018" [Internet] [in Russian]. Available from: http://54. rospotrebnadzor.ru

[40] State Report "On the Sanitary and Epidemiological Well-being of the Population of the Kemerovo Oblast in 2014-2018" [in Russian]. Available from: 42.rospotrebnadzor.ru [Accessed: 30 September 2019]

[41] State Report "On the Sanitary and Epidemiological Well-being of the Population of the Altai Krai in 2014-2018" [Internet] [in Russian]. Available from: http://55. rospotrebnadzor.ru [Accessed: 30 September 2019]

[42] State Report "On the Sanitary and Epidemiological Well-being of the Population of the Tomsk Oblast in 2014-2018" [Internet] [in Russian]. Available from: http://22.rospotrebnadzor.ru [Accessed: 30 September 2019]

[43] Beer SA. Stages in the evolution of distribution ranges of some opisthorchiids and opisthorchiasis

paleo foci. In: Relevant Problems in Opisthorchiasis. Tomsk: Izd. Tomsk. Univ.; 1986. pp. 12-15 [in Russian]

[44] Bronshtein AM. Communication 3. Incidence of opisthorchiasis and diphyllobothriasis among the population of the village of Vanzetur, Khanty-Mansiisk Autonomous Okrug. Medical Parasitology. 1986;**5**:10-14

[45] Il'inskikh EN. Relevant topics in the study of opisthorchiasis in Siberia. Bulletin of Siberian Medicine. 2002;**1**:63-70

[46] Osipova LP, Ofitserov VI, Tkachenko TN, Zhadanov SI, Rugin VP. Enzyme immunoassay of liver fluke invasions among the population of the Shuryshkarskii raion of Yamalo-Nenets Autonomous Okrug. Medical Parasitology and Parasitic Diseases. 2004;**1**:14-17

[47] On the Sanitary and Epidemiological Well-being of Population of the Russian Federation in 2014: State Report. Moscow: Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor); 2015 [in Russian]

[48] On the Sanitary and Epidemiological Well-being of Population of the Russian Federation in 2015: State Report. Moscow: Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor); 2016 [in Russian]

[49] On the Sanitary and Epidemiological Well-being of Population of the Russian Federation in 2016: State Report. Moscow: Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor); 2017 [in Russian]

[50] On the Sanitary and Epidemiological Well-being of Population of the Russian Federation in 2017: State Report. Moscow: Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor); 2018 [in Russian]

[51] On the Sanitary and Epidemiological Well-being of Population of the Russian Federation in 2018: State Report. Moscow: Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor); 2019 [in Russian]

[52] Khodzhayan AB, Kozlova SS, Golubeva MV. Medical Parasitology and Parasitic Diseases: Textbook. GEOTAR-Media: Moscow; 2014. p. 448 [in Russian]

[53] Abdelgantsev RF. Specific epidemiological features of opisthorchiasis in the city of Urai. In: Proceedings of the Regional Workshop on the Relevant Problems in Epidemiological Surveillance of Parasitic Diseases in Siberian and Ural Federal Regions, Surgut. 2018. pp. 67-69 [in Russian]

[54] Fedotova MM. The role of *Opisthorchis felineus* invasion in the development of food sensitization in children. [Candidate of Sciences (Med.) thesis]. Tomsk; 2014 [in Russian]

[55] Bychkov VG, Molokova OA, Kalenova LF, Kulikova SV, Kurchatova AN, Bazhin AS, et al. The results of antihelminthic effect of cynaropicrin on opisthorchiasis (preclinical studies). Health and Education Millennium. 2016;**18**(1):260-266 [in Russian]

[56] Uskov PA, Nikitin AA, Letyushev AN. Opisthorchiasis in the Omsk oblast: Epidemiological aspects. Relevant problems in epidemiology and microbiology. National Priorities of Russia. 2013;**9**(2):136-138 [in Russian]

[57] Belyaeva MI. Specific ecological and biological features in formation of

opisthorchiasis endemic foci in Western Siberia. [Doctor of Sciences (Biol.) thesis]. Moscow; 2017 [in Russian]

[58] Bronshtein AM, Tokmalaev AK. Human Parasitic Diseases: Protozoiases and Helminthiases. Textbook. Izd. RUDN: Moscow; 2002 [in Russian]

[59] Grigor'eva IN. Opisthorchiasis: Traditions and innovations. Experimental and Clinical Gastroenterology. 2012;**4**:54-59

[60] Kuznetsova VG, Krasnova EI, Paturina NG. Opisthorchiasis in clinical practice of an infectious disease physician. In: Attending Physician. Moscow: Otkrytye sistemy; 2013. p. 74 [in Russian]

[61] Filimonova LA, Borisenko NA. Opisthorchiasis: Clinical manifestations. Siberian Medical Review. 2006;**2**(39):812 [in Russian]

[62] Diunov AG, Zharikov GP, Tikhomirova SV. Medical Parasitology for the First Year Students. Yaroslavl: Avers Plus; 2011 [in Russian]

[63] Mamonov YP, Mamonova EY, Kalinina MY. Opisthorchiasis Is a Natural Danger in the Khanty-Mansiisk Autonomous Okrug–Yugra. Nizhnevartovsk: NGGU; 2008 [in Russian]

[64] Moiseenko AV. Opisthorchiasis (Textbook for Students). Izd. TGMA: Tyumen; 1999 [in Russian]

[65] Sergiev VP. Human Parasitic Diseases (Protozoiases and Helminthiases): Manual for Physicians. Foliant: St. Petersburg; 2006 [in Russian]

[66] Bogdanov AO, Prokudina DV, Baikov AN, Saltykova IV. Molecular mechanisms that mediate cholangiocarcinoma development during chronic liver fluke invasion. Siberian Oncological Journal. 2015;**6**:83-90

[67] Pal'tsev AI. The pathology of digestive organs in chronic opisthorchiasis: Pathomorphosis, diagnostics, therapy, and prevention. [Doctor of Sciences (Med.) thesis]. Novosibirsk; 1995 [in Russian]

[68] Trukhmanov AS. Gastroesophageal reflux disease: Clinic, diagnosis, treatment. Diseases of Digestive Organs. Russian Medical Journal. 2001;**3**(1):19-25

[69] Khardinova SA, Beloborodova EI, Pesterev PI. Morphofunctional changes in the gastrointestinal tract in combined therapy of psoriasis and chronic opisthorchiasis. Medical Parasitology and Parasitic Diseases. 2005;**4**:48-51

[70] Parfenov SB, Ozeretskovskaya NN, Shuikina EE. Comparative characterization of clinical and immunological parameters in different cohorts of opisthorchiasis patients in its focus. Communication 2. Indigenous population. Medical Parasitology and Parasitic Diseases. 1989;**2**:42-45

[71] Parfenov SB, Ozeretskovskaya NN, Shuikina EE. Comparative characterization of clinical and immunological parameters in different cohorts of opisthorchiasis patients in its hyperendemic focus. Communication 4. Transplacental transmission of *Opisthorchis felineus* antigens. Medical Parasitology and Parasitic Diseases. 1991;**3**:42-44

[72] Nikolaeva NI, Nikolaeva VP, Gigileva AV. Opisthorchiasis: Etiology, clinics, diagnostics, and therapy. Russian Journal of Parasitology. 2005;**5**:23-26

[73] Kalyuzhina MI. The state of digestive organs in the patients during residual period of chronic opisthorchiasis. [Doctor of Sciences (Med.) thesis]. Tomsk; 2000 [in Russian]

[74] Kuznetsova VG. Pathogenetic mechanisms and the specific clinical

features of the opisthorchiasis consequences. [Doctor of Sciences (Med.) thesis]. Novosibirsk; 2000 [in Russian]

[75] Pal'tsev AI. Chronic opisthorchiasis from the standpoint of a systemic approach: Clinics, diagnostics, Pathomorphosis, and therapy. Russian Journal of Medicine. 2005;**2**:96-101 [in Russian]

[76] Svyatenko IA, Beloborodova EI. Specific features of the clinical and endoscopic pattern in gastroesophageal reflux disease during chronic opisthorchiasis. Siberian Medical Journal. 2010;**1**:41-44

[77] Yablokov DD. Human Opisthorchiasis. Tomsk: Izd. Tomsk. Univ.; 1979 [in Russian]

[78] Leutskaya ZK. Some Aspects of Immunity in Helminthiases. Moscow: Nauka; 1990 [in Russian]

[79] Kulaga VV, Romanenko IM. Allergic Skin Diseases. Zdorov'e: Kiev; 1997 [in Russian]

[80] Brazhnikova NA, Tolkaeva MV. Cancer of liver, biliary tract, and pancreas in chronic opisthorchiasis. Bulletin of Siberian Medicine. 2002;**2**:71-77

[81] Migdalovich MG. The clinical significance of immunoregulatory function of the blood neutrophils in opisthorchiasis patients before and in dynamics after biltricide therapy. [Candidate of Sciences (Med.) thesis]. Chelyabinsk; 1995 [in Russian]

[82] Sutarung S, Haswell-Elkins MR, et al. Relationships between the synthesis of N-nitrosodimethylamine and immune responses to chronic infection with carcinogenic parasite, *Opisthorchis viverrini*, in men. Carcinogenesis. 1998;**19**(3):485-491

[83] Zubov NA. To pathomorphosis in opisthorchiasis. Medical Parasitology and Parasitic Diseases. 1996;**2**:23-26

[84] Baikova OA, Nikolaeva NN, Grishchenko EG, Nikolaeva LV. The cholangiocarcinoma associated with chronic opisthorchiasis and clonorchiasis. Health and Education Millennium. 2018;**20**(4):27-32 [in Russian]

[85] Lepekhin AV, Mefodiev VV, Filatov VG, Buzhak NS. Epidemiology, Clinics, and Prevention of Opisthorchiasis. Tomsk: Izd. Tomsk. Univ.; 1992 [in Russian]

[86] Suvorov AI, Krylov GG, Bychkov VG. Duodenogastroesophageal reflux disease as a complication of opisthorchiasis superinvasion. Medical Parasitology and Parasitic Diseases. 2004;**4**:17-19

[87] Bekarova AM, Binbasova TA, Buslaeva GN. Pediatrics. Selected Lections. GEOTAR-Media: Moscow; 2009 [in Russian]

[88] Solov'eva AV. Chronic Opisthorchiasis and Pregnancy: Manual for Physicians. GEOTAR-Media: Moscow; 2007 [in Russian]

[89] Pytskii VI, Andrianova NV, Artomasova AV. Allergic Diseases. Meditsinskaya nauka i obrazovanie: Moscow; 1991 [in Russian]

[90] Parfenov SB. Specific features in the course of opisthorchiasis and immune status of the patients of different population cohorts as the basis for development of differential approach to its therapy. [Candidate of Sciences (Med.) thesis]. Moscow; 1990 [in Russian]

[91] Glumov VY. Morphology, morphogenesis, and pathogenesis of chronic hepatitis and liver cirrhosis during opisthorchiasis. [Doctor of Sciences (Med.) thesis]. Moscow; 1981 [in Russian]

[92] Watanapa P, Watanapa WB. Liver fluke-associated cholangiocarcinoma.

British Journal of Surgery. 2002;**89**(8):962-970

[93] Kaewpitoon N, Kaewpitoon SJ, Pengsaa P, Sripa B. *Opisthorchis viverrini*: The carcinogenic human liver fluke. World Journal of Gastroenterology. 2008;**14**(5):666-674

[94] Khadieva ED, Lukmanov IR, Sabirov AK, Bychkov VG. Gastrointestinal stromal tumors (GISTs). Medical Science and Education in the Ural. 2010;**3**:165-167 [in Russian]

[95] Sabirov AK. Histological, immunohistological, and molecular genetic markers in breast cancer on the background of liver fluke invasion. Medical Science and Education in the Ural. 2010;**1**:82-83 [in Russian]

[96] Zuevskii VP, Bychkov VG, Tselishcheva PV, Khadieva ED. Opisthorchiasis as a promoter of gastro-carcinogenesis. Medical Parasitology and Parasitic Diseases. 2015;**4**:7-10

[97] Sripa B, Brindley PJ, Mulvenna J, Laha T, Smout MJ, Mairiang E, et al. The tumorigenic liver fluke *Opisthorchis viverrini* - multiple pathways to cancer. Trends Parasitol. 2012;**28**(10):395-407. DOI: 10.1016/j.pt.2012.07.006

[98] Smout JM, Sripa B, Laha T, et al. Infection with the carcinogenic human liver fluke, *Opisthorchis viverrini*. Molecular bioSystems. 2011;**7**(5):1367-1375

[99] Pal S, Bhattacharjee A, Ali A, Mandal NC, Mandal SC, Pal M. Chronic inflammation and cancer: potential chemoprevention through nuclear factor kappa B and p53 mutual antagonism. Journal of Inflammation (Lond). 2014;**11**:1-28. DOI: 10.1186/1476-9255-11-23 [eCollection 2014]

[100] Wonkchalee O, Boonmars T, Kaewkes S, Chamgramol Y,

Pairojkul C, Wu Z, et al. *Opisthorchis viverrini* infection causes liver and biliary cirrhosis in gerbils. Parasitology Research. 2011;**109**(3):545-551. DOI: 10.1007/s00436-011-2282-y

[101] Jusakul A, Loilome W, Namwat N, Haigh WG, Kuver R, Dechakhamphu S, et al. Liver fluke-induced hepatic oxysterols stimulate DNA damage and apoptosis in cultured human cholangiocytes. Mutation Research. 2012;**731**(1-2):48-57. DOI: 10.1016/j.mrfmmm.2011.10.009

[102] Tielens AG, van den Heuvel JM, van den Bergh SG. The energy metabolism of *Fasciola hepatica* during its development in the final host. Molecular and Biochemical Parasitology. 1984;**13**(3):301-307

[103] Ninlawan K, O'Hara SP, Splinter PL, Yongvanit P, Kaewkes S, Surapaitoon A, et al. *Opisthorchis viverrini* excretory/ secretory products induce toll-like receptor 4 upregulation and production of interleukin 6 and 8 in cholangiocyte. Parasitology International. 2010;**59**(4):616-621. DOI: 10.1016/j.parint.2010.09.008

[104] Daya M, Loilome W, Techasen A, et al. Progranulin modulates cholangiocarcinoma cell proliferation, apoptosis, and motility via the PI3K/ pAkt pathway. Onco Targets and Therapy. 2018;**11**:395-408

[105] Maksimova GA, Zhukova NA, Kashina EV, Lvova MN, Katokhin AV, Tolstikova TG, et al. Role of *Opisthorchis felineus* on induction of bile duct cancer. Parazitologiia. 2015;**49**(1):3-11

[106] Saltykova IV, Ogorodova LM, Ivanov VV, et al. Carbonyl stress phenomena during chronic infection with *Opisthorchis felineus*. Parasitology International. 2017;**66**(4):453-457

[107] Sripa B, Kaewkes S, Sithithaworn P, Mairiang E, Laha T,

Smout M, et al. Liver fluke induces cholangiocarcinoma. PLoS Medicine. 2007;**4**(7):1148-1155. DOI: 10.1371/journal.pmed.0040201

[108] Onishchenko SV, Darvin VV, Lysak MM. Acute cholangitis in the patients residing in an endemic opisthorchiasis focus. Annals of Surgical Hepatology. 2009;**2**:38-43

[109] Glumov VY, Kotrikov VV, Tret'yakova NA. Pathogenesis and morphology of the primary liver cancer developing of the background of opisthorchiasis. Problems in Oncology. 1974;**9**:46-49

[110] Sriamporn S. Epidemiologic study of liver cancer using a population-based cancer registry as a guide in Khon Kaen, Thailand. Health Reports. 1993;**5**(1):51-58

[111] Bouvard V, Baan R, Straif K, et al. A review of human carcinogens—Part B: Biological agents. Lancet Oncology. 2009;**10**(4):321-322

[112] Sriraj P, Aukkanimart R, Boonmars T, et al. Does a combination of opisthorchiasis and ethyl alcohol consumption enhance early cholangiofibrosis, the risk of cholangiocarcinoma? Parasitology Research. 2013;**112**(8):2971-2981

[113] Buisson Y. Control of *Opisthorchis viverrini* infection for cholangiocarcinoma prevention. Bulletin de la Société de pathologie exotique. 2017;**110**(1):61-67. DOI: 10.1007/s13149-017-0544-8

[114] Merzlikin NV, Brazhnikova NA, Al'perovich BI, Tskhaiyu VB. Surgical Diseases. GEOTAR-Media: Moscow; 2015 [in Russian]

[115] Aftaeva LN, Mel'nikov VL, Nikol'skaya MV. Opisthorchiasis in the perspective of severe complications. Proceedings of higher education institutions. Volga region. Medical Science. 2018;**4**(48):27-32 [in Russian]

[116] Arinzhanov AE, Lyadova AY. Opisthorchiasis: Epidemiology, prevention, treatment. Territory of Science. 2016;**6**:7-13 [in Russian]

[117] Nacheva LV, Bibik OI, Starchenkova TE, Dodonov MV. Helminthiases among Kuzbass population. Medicine in Kuzbass. 2007;**1**:22-29 [in Russian]

[118] Onishchenko GG. Incidence of parasitic diseases in the Russian Federation and the main directions in the activities on its stabilization. Medical Parasitology. 2002;**4**:3-10

[119] Onishchenko GG. On the measures for strengthening prevention of parasitic diseases in the Russian Federation. Medical Parasitology and Parasitic Diseases. 2003;**3**:35

[120] Guzeeva TM. The state of incidence of parasitic diseases in the Russian Federation and the goals for reorganization of the service. Medical Parasitology and Parasitic Diseases. 2008;**1**:3-11

[121] Tsareva TP, Grebneva VN. Epidemiological surveillance of acute and chronic opisthorchiasis in the City of Langepas. Analysis of the causes of infection and the conditions and factors of infection in the periods of increased incidence. In: Relevant Issues of Epidemiological Surveillance of Parasitic Diseases in the Siberian and Ural Federal Regions. Proceedings of Regional Conference, Surgut. 2018. pp. 69-72 [in Russian]