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PARENTERAL VIRAL HEPATITIS IN CHILDREN IN RUSSIA, PARTICULARLY IN THE NORTHWESTERN FEDERAL DISTRICT

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Among acute viral hepatitis in children aged 0 to 14 years nosological entities with enteric transmission prevail over the parenteral ones which account for not more than 3–5%. Thus, in 2017 out of 1851 cases of acute viral hepatitis reported in the Russian Federation among the children under 15 years of age 10 cases were of acute hepatitis B and 40 cases — of acute hepatitis C. 417 Cases of chronic viral hepatitis in children aged 0–14 years were reported in Russia in 2017. As well as in adult population, chronic hepatitis C predominates, accounting for 83.7% of all reported cases. Relative share of chronic hepatitis B is 14.9% and that of an unspecified chronic hepatitis — 1.4%. Preventive measures against infection with hepatitis B and hepatitis C contributed to significant decrease in the parenteral hepatitis incidence rate. Timely implementation of a wide hepatitis B immunization program for 1-year old children in the Northwestern federal district resulted in the fact that since 2013 the number of cases of acute hepatitis B has not exceeded 1–2 and in some years, there were no such cases at all. Within the Northwestern federal district in 2009–2010 acute hepatitis C was reported both in infants and older children. Decrease in incidence rate in infants from 5.1 per 100 000 people in 2009 down to 1.78 per 100 000 people in 2017, as well as lack of reported cases in older age groups, shows the improvement of epidemiological situation. The incidence rate of chronic hepatitis B and hepatitis C in children is more than 40 times lower than the incidence rate in adults. In 2017 in the Northwestern federal district the incidence rate of chronic hepatitis C in children was 6.5 times higher than that of chronic hepatitis B (1.5 and 0.2 per 100 000 people, respectively). Despite of positive dynamics in the parenteral hepatitis incidence rate, the total number of pediatric patients in the Northwestern federal district over the last years has remained constant (250–300 children), and the attack rate in 2017 was 3.7 per 100 000 people in case of chronic hepatitis B and 11.7 per 100 000 people in case of chronic hepatitis C. Thus, in spite of decrease in its incidence rate in children, the problem of post-transfusion hepatitis infection remains of high concern.

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MONITORING OF LONG-TERM ANTIVIRAL TREATMENT OF CHRONIC HEPATITIS B

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Rapidly progressing and hard to treat HBeAg-negative chronic hepatitis B is for the prevalent type of the disease in the world, including Russia. Antiviral therapy by nucleot(z)ide analogues is aimed at the permanent suppression of hepatitis B virus replication. Undefined duration of the nucleot(z)ide analogues treatment in HBeAg-negative patients is a serious problem taking into account absence of adequate predictors of the disease course after treatment discontinuation. Thus, our task is to analyze the results of the long-term antiviral therapy of HBeAg-negative chronic hepatitis B patients. Analysis was performed in 79 HBeAg-negative patients with confirmed chronic hepatitis B who had not previously treated. The administration medicine was telbivudine in a daily dose of 600 mg (n = 49) or entecavir in a daily dose of 0.5 mg (n = 30). The therapy course, which lasted from 5 months to 7 years, also included patients with a viral load less than 2.0×10^4 IU/ml in presence of severe hepatic fibrosis (F3 or F4 stages by METAVIR). Efficacy of the treatment was evaluated based on the activity of ALT and the level of HBV DNA, monitoring also included the biochemical and serological parameter measurements. The study had shown that viral load reached undetectable levels in 92.3% of cases after 52 weeks of therapy ($p < 0.05$). Five patients out of six non-responders, received telbivudine. A significant decrease in the proportion of patients with ALT levels above upper line normal (16.8% vs. 44.3% at the beginning of the treatment), as well as severity of cytolytic activity (ALT levels 109.8±102.4 IU/L vs. 68.8±39.2 IU/l at the beginning of the treatment) ($p < 0.05$) were noted. The remarkable fact was the decrease in the proportion of patients responding to treatment at 104–156 weeks of antiviral therapy. In most cases, failure of the therapy was associated with the telbivudine administration, and telbivudine replacement with entecavir was associated with increase of the virological response rates. Thus, it can be concluded that treatment with telbivudine is currently impractical due to the high level of virological breakthroughs. Entecavir has demonstrated higher efficacy during the treatment, lasting for up five or more years. However, there is a number of issues related to the prediction of the relapse risks after discontinuation of the nucleot(z)ide analogues therapy, which remains unsolved and requires further studying.

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DEVELOPMENT AND APPROBATION METHOD OF IDENTIFICATION MUTATIONS THE RESISTANCE OF THE HEPATITIS C VIRUS TO DIRECT-ACTING ANTIVIRAL AGENTS (DAAs)

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Hepatitis C Virus (HCV) treatment has been improved dramatically thanks to the introduction of direct-acting antiviral agents (DAAs). These antivirals have significantly increased response rates (up to 98%) and greatly reduced treatment duration. Currently available DAAs are classified into four categories given their molecular targets in the HCV replication cycle: NS3/4A protease inhibitors bind to the active site of the NS3/4A protease; NS5A inhibitors interact with domain 1 of the NS5A dimer; nucleotide analog NS5B polymerase inhibitors are incorporated into the nascent RNA chain resulting in chain termination by compromising the binding of the incoming nucleotide; nonnucleoside NS5B polymerase inhibitors. However, the high replication rates of HCV, can lead to the extreme mutations in the virus.

The objectives were development and approbation the method of identification mutations the resistance of the hepatitis C virus to direct-acting antiviral agents (DAAs).

The subtype-specific oligonucleotides were designed based on HCV sequence alignments from NCBI HCV database. The sequences were retrieved with the inclusion criteria of belonging to full genome sequences (confirmed non-recombinant genomes), being devoid of large insertions/deletions, and corresponding to 1a, 1b, 2a. It is these subtypes that are most common in Russia. Specific oligonucleotides were designed to therapeutically relevant regions: NS3/4A, NS5A, NS5B.

The methodological pipeline described here is adequate to characterize in-depth mutant spectra of HCV populations, and it provides a tool to understand HCV diversification and treatment failures. The pipeline can be periodically extended in the event of HCV diversification into new genotypes or subtypes, and provides a framework applicable to other RNA viral pathogens, with potential to couple detection of drug-resistant mutations with treatment planning.

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THE SIGNIFICANCE OF THE HIV RESISTANCE ANALYSIS IN ANTIRETROVIRAL THERAPY

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The widespread use of antiretroviral therapy, the development of new drugs and treatment regimens are inherently associated with the emergence of HIV resistance. Systematic laboratory monitoring of patients with ineffectiveness of antiretroviral therapy is necessary.

Objective was to assess the significance of the resistance analysis in the current algorithms for control HIV infection in individuals.

Blood plasma samples of 66 patients from different regions of the North West Federal District were used in the work. All patients were referred for testing the drug resistance of the virus due to the virological ineffectiveness of antiretroviral therapy. The nucleotide sequences obtained with the use of a set of reagents for the detection of mutations of drug resistance to antiretroviral drugs AmpliSens® HIV-Resist-Seq.

For this group of patients two main scheme of therapies were used: the first one included two drugs from the Nucleoside Reverse Transcriptase Inhibitors group in combination with one drug from the Non-Nucleoside Reverse Transcriptase Inhibitors group and the second one from the Protease Inhibitors group in combination with two drugs from the Nucleoside Reverse Transcriptase Inhibitors group. The analysis of nucleotide sequences in the protease gene showed that most commonly there are mutations that cause drug resistance to groups of nucleoside and non-nucleoside reverse transcriptase inhibitors. In 45 patients (60%) a mutation in the position of M184V was detected, which is responsible for the presence of a high level of resistance to lamivudine. In 34 (52%) cases, a mutation was found in the K65R position, responsible for the cause of resistance to abacavir and didanosine. In 12 (18%) patients, a combination of mutations M184V + L74V, also resulting in resistance to didanosine and abacavir, was detected. This indicates that when the therapy is changed, the percentage of the most frequent mutations increases, along with the appearance of new ones, which indicates the need for an analysis of the resistance of HIV to antiretroviral therapy not only in cases of virological inefficiency of therapy, but also during the change of therapy and similarly, naive patients should be analyzed for existing mutations to optimize treatment.

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FORECASTING OF INCIDENCE OF HAV WITH USE OF THE SCHEDULED PLAN OF WALD

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The incidence of viral hepatitis A (HAV) has high epidemiological significance. According to The Federal service for supervision of consumer rights protection and human welfare in Russian Federation during 2010–2016. 44 666 cases of HAV among adult population, and the children's population 21 308 respectively are registered.

For the purpose of assessment of an epidemiological situation on HAV the analysis of official statistical data on incidence of HAV is carried out to the Moscow in 2016 and forecasting of an epidemic situation for 2017. The forecast of number of cases was carried out with use of linear approximation and the developed method of forecasting of incidence of HAV with use the plan — Wald's graphics.

It is established by the results of the analysis of the dynamics of the incidence of HAV in Moscow, using the method of linear approximation in 2017, the incidence of HAV in adults and children was 240 and 115 cases These statistical indicators characterize the epidemiological situation as unfavorable.

According to the results of the statistical analysis, the threshold level of the incidence of HAV in Moscow among children for the period 2010–2016 analyzed. 11 cases were made, which is defined as an incremental total, with a minimum monthly prognostic level of 7 cases, a maximum of 17. The monthly increase in the number of diseases in the dynamics of the analyzed year was 0.9 cases. The forecast of the maximum number of diseases of the HAV in 2017 exceeds the threshold level of morbidity and indicates a possible worsening of the epidemiological situation in Moscow. The forecast of the total minimum and maximum incidence rate in 2017 will be 84 and 204 cases respectively.

Based on the results of the analysis of the incidence of HAV for the period from 2010 to 2016, using the Wald schedule it was shown that the epidemic situation in Moscow among the adult population and among the children under 17 is estimated as unstable. The method of analysis and forecasting using the Wald schedule allows to predict the total minimum and maximum levels of the incidence of HAV, which is of great importance for practical public health and makes it possible to adjust planned preventive and antiepidemic measures.

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RISK FACTORS OF PERINATAL TRANSMISSION OF HEPATITIS C VIRUS

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Worldwide, the virus of hepatitis C (HCV) infected 2–3% of the population (more than 185 million people). The proportion of pregnant women with hepatitis C (HC) is 1–2.4%. In previous studies, it was reported that perinatal transmission of HCV is due to the level of viral load of HCV, HIV co-infection, increased activity of alanine aminotransferase, duration of anhydrous period. The use of amniocentesis and internal monitoring of the fetus may increase the risk of perinatal transmission of HCV. There is no evidence of a reduction in the risk of HCV transmission from the mother to the baby in cesarean section and the rejection of breastfeeding.

The aim of the study was to determine the risk factors for perinatal transmission of the hepatitis C virus.

To diagnose perinatal transmission of HCV, 140 children born to women with HS were examined. The diagnosis of congenital HS was established when HCV RNA was detected in the blood plasma of a child older than 2 months twice with an interval of at least 3 months or anti-HCV in a child over 18 months old using commercial reagent kits. The ELISA method was used to detect antibodies to HCV ("ELISA-HCV-Ab", The Republican Scientific and Practical Center for Epidemiology and Microbiology, Belarus, Monolisa HCV