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ABSTRACT BOOK

Welcome to Baku!

Dear Colleagues,

On behalf of the Organizing Committee, it is an honor for me to invite you to the crossroads of Europe and Asia, amazing Azerbaijan!

As Delta problem moved from the shadow up on the stage, becoming one of the most crucial disease in Hepatology area, our STC 2019 is dedicated to hepatitis D, for the first time in the history of APASL STC topics. As hepatitis Delta occurs only with HBV infection, we will discuss hepatitis B, its epidemiology, work-up, current treatment and new horizons in the developing pharmaceutical agents. The scientific program will include the topics presented by the best speakers and the experts in Delta and B hepatitis.

This conference is a good chance to meet and interact with leading clinical professionals and researches and to obtain latest information for hepatologists.

Along with the informative and productive scientific program, we are delighted to introduce you the cultural heritage of ancient and modern Azerbaijan, its fusion of the past and the future. Our region is located on the way of Ancient Silk Way and is a homeland of the fire-worshipers, thus it might be interesting for the guests from India, near and Far East.

Be sure that Azerbaijan will amaze you with its beautiful nature, tasty cuisine and hospitable people.

PhD. Dr. Gulnara Aghayeva

President of Azerbaijan Gastroenterology and Hepatology Association

APASL Member since 2004

APASL STC HEPATITIS DELTA

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Content

Hepatocellular carcinoma in HDV infected patients from Republic of Moldova: from risk factors to survival

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Objectives: Moldova is the European country with the highest incidence of hepatocellular carcinoma (HCC) in both sexes. The problem of viral hepatitis burden in Moldova is known for a long time as it has been reported as early as Soviet Union period There is, however, no data comprehensively describing the presentation and the risk factors of HCC in the country. We decided to analyze cases of HCC recently received in a tertiary healthcare Institution from Chisinau, Republic of Moldova. Methods: A series of 154 of HCC were retrospectively analyzed for demographic features, serological and biochemical data, and clinical presentation. Results: The mean age of patients was 57±9.12 years (range: 19-67) with a M:F sex ratio of 1.7. 18.5% of patients was infected with the HDV, a situation that concerned therefore almost one-half of HBsAg(+) patients (47.2%). Overall, at least one of the viruses responsible for persistent liver infectious (HBV, HCV or HDV) was present in more than 81% of cases. Moreover, HBV-HCV coinfections were found in 13.6% and 7.2% of the whole series were, indeed, affected by a triple HBV-HCV-HDV infection. In total, one patient every four was infected with at least two viruses. Patients infected with Delta virus were characterized by a variety of salient features. HCC was diagnosed six years younger than other patients (54.0±8.3 vs 60.5±10.1 years, P=0.0041). They were also affected with larger tumors (75.7±9.6 vs 56.0±3.2, 0.0184). Liver cirrhosis tended to be almost universally present in these patients (95.8 vs 79.2%, OR= 5.96, 95%CI: 0.87-256.95, P= 0.074, ns). CLIP score was slightly higher in HDV than in HCV, HBV. Regarding risk factors of super-infection with Delta viroid, intravenous drug use was more frequent among seropositive patients than others (23.8 vs 6.5%, OR=4.34, 95%CI: 0.93-19.52, P=0.0312. Conclusions: A striking feature of the present series was the frequent presence of HDV as this agent used to be usually marginally present in HCC cases from European patients. As a risk factor, it represents undoubtedly the hallmark of Moldova in Europe. A pro-active policy of screening for persistent liver infection targeting population at risk of HCC (>50 years) and coupled with the distribution of antivirals in positive cases should be rapidly implemented in Moldova to reduce incidence or primary liver cancer.

Comparison of three HDV-RNA quantitative commercially available tests in untreated and in myrcludex-B treated patients with hdv related chronic hepatitis in a real-life setting

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Background and Aim. As new anti-hepatitis delta (HDV) therapies are being developed, highly sensitive and reliable quantitative tests are needed. Aim of the study was to compare

three commercially available HDV-RNA kits. Methods. 92 serum samples from 4 categories of patients were tested for HDV-RNA by 3 assays: RoboGene (HDV-RNA quantification 2.0, Aj-Roboscreen, Germany, LLQ 6 IU/mL), EurobioPlex (HDV qRT-PCR, Eurobio, France, 100 IU/mL) and Dia.Pro (HDV-RNA Quantitation, Dia.Pro Diagnostic Bioprobes, Italy, 50 IU/mL). Total RNA was extracted by EZ1 DSP Virus Kit (Qiagen, Hilden, Germany). Results. Group 1: 48 Caucasians with known active HDV-hepatitis [50 years, 56% males, 73% cirrhotics, 64% on tenofovir/entecavir, 80% undetectable HBV-DNA, 50% previously interferon-exposed, ALT 66 (24-304) U/L] had a median HDV-RNA of 5.5 (1.1-7.1), 5.9 (0-8.4), 3.9 (0-6.6) log IU/mL by RoboGene, EurobioPlex and Dia.Pro; viremia tested undetectable in 0 (0%), 3 (6%) and 5 (10%) patients, respectively. Group 2: 15 HBsAg-positive patients [age 42, 27% cirrhotics, 7% HBeAg-positive, 40% on tenofovir/entecavir, 73% undetectable HBV-DNA, 3 with abnormal ALT] had HDV-RNA undetectable with all 3 assays except for one subject who had HDV-RNA 697 IU/mL with Dia.Pro. Group 3 included 9 international quality control sera. The only true-negative sample tested negative by all the 3 assays, while the 8 positive controls were correctly identified in 100%, 87.5% and 25% of the cases by different assays. Group 4: 21 sera collected during Myrcludex B-treatment. First patient: baseline HDV-RNA was 23,600, 640,006, 12,283 IU/mL; during therapy, RNA progressively declined with both RoboGene and EurobioPlex, till undetectability at week 36; Dia.Pro gave 5 false-negative results. Second patient: baseline HDV-RNA 392,000, 4,248,001, 1,140 IU/mL; RNA declined with the first two assays but not with the last one (2 false-negative results). Overall, the HDV-RNA sensitivity was 100%, 92%, 80%, respectively. Conclusions. RoboGene is the most sensitive and reliable test for HDV-RNA quantification.

Safety, effectiveness and t-cell activation profiles of long-term myrcludex-B treatment in two patients with hdv related compensated cirrhosis

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Background and Aim. Mycludex B (MYR) is a new promising anti-HDV therapy, but the effectiveness and safety of long-term administration in compensated cirrhotics treated in a real-life setting are presently unknown. Aim of this study was therefore to describe the effectiveness, safety and impact on HDV/HBV-specific T cell profiles in the first two European patients treated with MYR outside clinical trials. Methods. A 69-year-old female and 51-year-old male Caucasian HBeAg-negative patients with HDV related compensated cirrhosis on long-term term TDF treatment, started MYR 10 mg/day on January and May 2018 in a compassionate use program. Liver function tests, bile acids and virological markers were monitored every 4 weeks. HDV RNA was tested by RoboGene®. HDV and HBV specific T cell quantity were analyzed monthly in blood by direct ex-vivo IFN-γ ELISPOT methods using overlapping peptides covering the HDV and

HBV proteome. Results. Both patients had active compensated HDV related cirrhosis at baseline: ALT 150 and 250 U/L, GGT 23 and 250 U/L, platelets 95 and 74 x109/L, bilirubin 0.7 and 0.4 mg/dL, total bile acids 7 and 15 µmol/L, AFP 7 and 21 ng/mL, albumin 4.3 and 3.6 g/dL, HDV RNA 23,600 and 392,000 IU/mL, HBsAg 9 and 11,111 IU/mL, undetectable HBV DNA. Liver stiffness were 17 and 18 kPa, spleen length 12 and 14 cm, small esophageal varices were present in the second patient. During 48 and 36 weeks of MYR treatment, ALT levels rapidly normalized (16 and 8 weeks), as well as AFP levels (to 3 ng/mL in 28 weeks and 24 weeks); platelets progressively increased up to 154 and 112 x109/L, as well as albumin (4.5 and 4.4 g/dL). HDV RNA levels progressively declined in both patients to became undetectable after 36 weeks and 28 weeks, respectively. Liver stiffness at week 24 were 17 and 14 kPa; last HBsAg levels were 26 and 7,995 IU/mL. These clinical and virological improvements were not associated with changes of circulating HDV/HBV-specific T cells that remained at a very low frequency during the first 6 months of the study. As far as safety is concerned, total bile acids rapidly increased up to 53 and 124 µmol/L, but this was not associated to any symptom, neither to bilirubin nor GGT alteration. Conclusions. Myrcludex-B 10 mg/day, in combination with TDF, is a safe and effective treatment option for HDV compensated cirrhotics, yet without any recovery of T cell function.

Epidemiology aspects of the chronic HBV with HDV infection in Kazakhstan

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Epidemiology aspects of the chronic HBV with HDV infection in Qazaqhstan INTRODUCTION The Scope of the Problem The prevalence of HBV and HBV-HDV has been unknown in Kazakhstan for a long time. According to the current statistics, 30 to 50 thousand people become infected every year in Kazakhstan. Kazakhstan is being considered as a high endemic country within the context of hepatitis B (more than 8%). With regard to the HDV prevalence, Kazakhstan has been referred as a medium endemic country. However, within the country the prevalence of the viral hepatitis is not homogenous and the statistical data are not completely reliable to the full extent. Implementation of the vaccination programs against hepatitis B for the prevention of the disease has resulted in the positive results. However, currently Hepatitis D is diagnosed in the late stages, which is therefore characterized by a rapidly progressive course of the disease, and low efficacy of the antiviral therapy. The epidemiology data regarding the prevalence of the hepatitis B and hepatitis D infection in Kazakhstan is still limited. Aim of the study: To determine prevalence and clinical characteristics of chronic hepatitis B virus with hepatitis D virus in different regions of Kazakhstan Materials and Methods: The study utilizes epidemiological methods of descriptive statistics of the output data of the SPC

"Sanitary-epidemiological expertise and monitoring" of the KZPP MNE RK. The current study analyzes the epidemiological data within the period of 5 years from 2012 to 2016. RESULTS AND DISCUSSION: The incidence of chronic viral hepatitis B with the hepatitis D infection in various regions of Kazakhstan throughout the period of 2012-2016. Taking into account the fact that infection with Hepatitis D can only occur in the presence of hepatitis B virus, the prevalence of the chronic form of the hepatitis B virus has been investigated. It was found that in the five-year period from 2012 to 2016 there has been a decrease in the incidence of HBV infection from 35.4 to 29.6 cases per 100,000 people. However, with regard to the HBV infection with HDV, a substantial increase in the disease prevalence has been determined. In particular, the HDV infection disease incidence has increased by 40% reaching a value of 0.39 cases per 100,000 people in 2016.The following endemic regions of the country with the highest disease prevalence has been determined: South Kazakhstan, West Kazakhstan, Zhambyl, Aktobe regions and the city of Astana. The highest disease prevalence of HBV infection has found to be the capital of the country with the value of 1.7 cases per 100,000 people. What's more, the disease prevalence in Astana has been consistently substantial in comparison to the other parts and regions of Kazakhstan. Figure 1 The incidence of the chronic form of hepatitis B with hepatitis delta (HDV) per 100,000 people within the period of 2012-2016 Figure 2 The median values of the prevalence of the chronic form of hepatitis B with HDV per 100,000 people in different regions of Kazakhstan 2016 Figure 3 The region-specific prevalence of the chronic form of hepatitis B and hepatitis D (HDV) per 100,000 people in 2012 and 2016.

Natural history and predictors of poor outcomes in acute liver injury patients in a setting without liver transplant facility

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Introduction Hepatitis is one of the leading causes of mortality globally and Pakistan, too, has a very high burden of liver disease and associated morbidity and mortality. Significant burden combined with lack of adequate transplant facilities make it crucial to understand predictors and natural history of more severe stages of liver damage or inflammation, such as acute liver injury, as is the aim of this study. Even though it is known that Acute Liver Injury (ALI) is defined as INR ≥ 2.0, ALT ≥ 10X ULN, and Total Bilirubin ≥ 3 mg/dl, there is a dearth of literature on factors and prognosis associated with ALI. Methods This was a retrospective cohort study of patients older than age 18 years and meeting ALI criteria admitted at the Aga Khan University Hospital from January 2014 to December 2017. Patients with chronic liver disease or hepatic encephalopathy at presentation were excluded. We categorized patients into 2 subgroups: 1.5 < INR < 1.9 and INR > 2 to compare outcomes based on INR derangement. Linear regression was used to determine predictors of poor outcomes

including mortality. Results 110 patients out of the 1500 reviewed patients met ALI criteria, with 70 patients in INR > 2 group. The most common etiology was hepatitis E infection followed by Hepatitis A, Dengue, Drug-induced, ischemic, Hepatitis B and D. A total of 27 patients developed at least one of the poor outcomes i.e. ALF, death, or liver transplantation. AST (p=0.03), creatinine (p=0.02), and length of hospital stay (p=0.04) were found to be the predictors of death. INR > 2 was associated with more derangement in GGT, lower WBC, development of a poor outcome in more patients (24 vs. 3; p=0.002), and higher mortality rate (13 vs. 1 p=0.01). Conclusion ALI patients with severely raised AST, acute renal deterioration, and longer hospital stay are more likely to develop poor outcomes.

Phylodynamic analysis of hepatitis delta virus genotypes 1 and 2 in the Russian Federation

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Background: Hepatitis delta virus (HDV) infection has an uneven prevalence in the Russian Federation, with low infection rates in European part. But, there are several endemic regions in the country, such as Republic Saha (Yakutia), Republic Tuva and Republic Dagestan. The aim of this study was to elucidate the transmission history of HDV in the Russian Federation Materials and methods: Total 161 sequences coding HDV R0 region (321 nt) were amplified and sequenced from samples obtained from patients with chronic hepatitis delta from Tuva (n=127), Yakutia (n=7), and Dagestan (n=27). HDV genotype was assigned according to ICTV 2018 classification. Resulting database of HDV sequences of genotype 1 (n=157) and 2 (n=4) was supplemented with 454 sequences from GenBank with known the year and the country of isolation, which had divergence at least 2%. Bayesian analysis was performed by using the software package BEAST v1.8.3, ESS was > 200. Results: The phylodynamic analysis demonstrated that HDV genotype 1 was introduced to the Russian Federation in the 1960s (95% HPD interval: 1958 - 1978). The introduction has occurred in parallel from two directions. The first direction was from the islands in the Pacific Ocean, through Yakutia, further spreading through the territory of Russia. Sequences from Pakistan, Israel, Poland, Georgia and Mongolia also belonged to this cluster. The second direction of HDV introduction was from Europe. As a result of this event, two closely related strains have formed on the territory of Russia with estimated time of divergence in the early 1980s (95% HPD interval: 1966 -1990). The first strain is endemic in Dagestan, Tuva and Samara. The second strain formed the monophiletic group of sequences from Tuva, with common ancestors in Romania, Mongolia and Pakistan. In addition to the above-mentioned large clusters, there are also small clusters or even single sequences isolated resulted from the continuous migration between Russia and Central Asia. HDV genotype 2 originates from the eastern part of the Asian continent, and was introduced in Yakutia around 1940s (95% HPD interval:

1912-1949). Since then this genotype had a stable circulation in Yakutia, but it did not extend beyond the region, being absent in other parts of Russia. Conclusion: The evolution history of current HDV strains in the Russian Federation spans about 80 years. Our data suggest multiple introductions of viral strains in 20th century.

The study of the functional state of endothelium in patients with chronic viral Hepatitis C

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Keywords: nitric oxide, endothelin-1, chronic viral hepatitis, lipid peroxidation

Introduction Hepatitis C is the leader among hepatotropic infections in developed countries, where 1- 24% of the population is infected. Currently, the pathological mechanisms controlling the rapid progression of the disease are being actively studied and increased sensitivity to oxidative stress may play a role in this. As a result violation of lipid peroxidation (LPO) processes occur. Increased levels of lipid peroxidation contribute to the development of endothelial function, which aggravates liver damage and contributes to the progression of liver fibrosis. Nitric oxide (NO) and endothelin-1 (Et-1) are markers of endothelial dysfunction. The aim of the study. The aim of the study was to determine the level of nitric oxide (NO) and endothelin-1 (Et-1) in the blood plasma of patients with chronic viral hepatitis C (CVHC). Blood was examined in 87 patients aged 17-38 years old, which were divided into 2 groups: The I Group - 45 patients with chronic viral hepatitis C and the II Group - 42 patients with chronic hepatitis C, complicated by bacterial infection (pneumonia). The control group composed of 20 healthy donors. Materials and Methods. The biochemical assessment was carried out by studying markers such as total, direct and indirect bilirubin according to the method of Endrashik; AlAT, AsAT - according to the method of Reitman-Fraenkel, the activity of the enzyme γ-glutamyltransferase - using commercial kits of the company "Diasys" (Germany). The concentrations of nitric oxide and endothelin-1 were determined by the R & D system and Cloud Clone Corp. China, respectively. Results and discussion All biochemical parameters (bilirubin, its fractions and ALT activity) increased compared with the norm, and the degree of these changes corresponded to the activity and clinical manifestations of hepatitis. In the II group, the AsAT concentration increased significantly ($p < 0.01$), and in the I group it was within the normal range. A typical criterion of deterioration and unfavorable prognosis is an increase in the levels of AsAT and AlAT, as well as the enzyme γ-glutamyltransferase (in the II group, this index increased by 1.9 times), indicating severe hepatocyte necrobiosis. Markers of the endothelium damage were analyzed in the groups of patients with chronic hepatitis C and chronic hepatitis C complicated by pneumonia. Thus, a significant decrease in the level of NO was revealed, which indicates an insufficient basic

production of NO in the endothelium of the patients with chronic viral hepatitits C. In patients of the I group, the content of NO was 18.4 ± 3.01 μmol / l at a control of 28.32 ± 3.3323 μmol / l, whereas in the group of patients with pneumonia, this index decreased to 17.3 ± 2.98 μmol / l ($p < 0.01$). The concentration of Et-1 in patients increased significantly, indicating an increase in its production in patients with chronic viral hepatitits and confirmed the endothelial dysfunction in these patients. In both groups, the concentration of endothelin-1 increased to 5.29 ± 0.36 pg / ml and 7.17 ± 1.16 pg / ml, respectively, at a control of 3.97 ± 0.28 pg / ml. Conclusion It was revealed that in patients with chronic viral hepatitis C, along with changes in liver function samples and biochemical markers, endothelium dysfunction occurred, which was manifested in the decrease of the nitric oxide production and increase in endothelin-1 synthesis. Increased production of Et-1 and a decrease in NO contribute to the progression of chronic liver damage in patients with chronic viral hepatitis C due to the activation of fibrosis.

Treatment options for iatrogenic bile duct injuries with the loss of confluence

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Introduction. Iatrogenic bile duct injuries (IBDI) with the loss of confluence are the most feared types of biliary injury and represent 4% of all IBDI. The loss of confluence understood as when the right and the left hepatic ducts lose continuity with the common bile duct tree and to restore this continuity is a serious surgical challenge. Aim. The aim of this study is to share our results concerning the surgical treatment options of IBDI with the loss of confluence. Material and methods. During in a 10 years period (2008-2018) 105 patients with IBDI were admitted to our centers for surgical treatment. Among these patients there were only 13 patients with the loss of confluence (Strasberg E4 type). The diagnosis was confirmed by magnetic resonance cholangiopancreatography (MRCP) and contrast-enhanced computed tomography (CT) and classified according Strasberg classification as a Strasberg E4 type. Medical records of these patients were retrospectively analyzed and the general data were collected including the type of surgical procedures and postoperative outcomes. Results. Totally six males (46%) and seven females (54%) enrolled to our study (age ranged 23 to 66). The treatment options for these patients were following: nine patient (70%) treated with double-barrel hepaticojejunustomy (HYS) and five of them were placed transhepatic transanastomotic drains. In two patient (15%) were constructed neo-confluence. Finally in two patients(15%) were performed portoenterostomy (Kasai procedure). In all patients Roux-en Y HYS was used. The postoperative complications were seen only in two patients. One patient experienced intraabdominal abcess and in one patient has been noted wound infection. Both cases were successfully managed with drainage and antibiotics. The postoperative mortality was

nil. Conclusion. The treatment of Strasberg E4 type bilary injuries represents great technical difficulties. There are several surgical options (neo-confluence, double-barrel anastomosis, portoenterostomy) but, it is considered that double-barrel Roux-en Y HYS is the best choice for this patients. Key words. Biliary injuries, loss of confluence, neo-confluence, double-barrel anastomosis, portoenterostomy.

Management strategy for patients with chronic viral hepatitis b and chronic viral hepatitis D, taking into account progression factors in liver cirrhosis

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Background: The invasiveness of the liver biopsy technique for determining the stage of liver disease was the reason for the development and introduction into clinical practice of non-invasive diagnostic methods which will significantly reduce the time and material costs of the examination. An alternative histological, non-invasive method should provide quantitative measures of fibrosis progression, a method that is accurate, cost-effective and relatively simple. Japanese researchers (Kuno A., Ikehara Y. et al., 2013) found that serum levels of glycated Wisteria floribunda agglutinin positive Mac-2 binding protein (WFA + –M2BP) can reflect the severity of liver fibrosis in patients with chronic hepatitis B and should be very useful for screening the stage of fibrosis and assessing disease progression in untreated individuals or patients on or after treatment. Methods: To evaluate the diagnostic significance of determining WFA+–M2BP to determine the degree of liver fibrosis in clinical practice and the possibility of using this serum marker for predicting the risk of developing LC and identifying the functional reserves of the liver. For the severity of liver fibrosis and the ability to predict the outcomes of hepatitis B and hepatitis D, M2BP immunoprecipitation from serum samples was used, for which an automated protein purification system was used (BioSciences Ltd., Yokohama, Japan). The degree of fibrosis was also assessed using the apparatus FibroScan 502 S01462 made in France. The serum values of WFA + –M2BP were evaluated in 41 naive patients with CHB and CHD and viral LC. The diagnostic accuracy of WFA + –M2BP was compared with various markers of fibrosis, such as needle biopsy and liver elastography. Results: From the data we obtained, there was no significant difference between the average WFA +–M2BP in patients with CHB and CHD. In chronic hepatitis B, histological data did not coincide with those of liver elastography of 33.3%, but corresponded to clinical diagnoses and M2BP values. Only one patient with a histological diagnosis of chronic hepatitis with minimal M2BP activity was high. With further observation, this patient showed signs of LC. High WFA + –M2BP with CHB of low activity can serve as a prognostic marker of the progression of the process. In CHD, it is difficult to assess the true condition of the patient, since the clinical picture can be pronounced even with minor changes in the liver. Elastography indicators did not determine the true state of the disease in

27.2% of cases. The WFA + –M2BP indicators could help in a certain patient's condition, since the M2BP results did not match the histological diagnosis in only 13.3% of patients, which is significantly less than the errors of clinical diagnoses (46.7%) and liver elastography (40.0%). When CHB with the transition to the LC did not coincide M2BP indicators with the results of the study of liver biopsy specimens in 18.2% of cases. The histological diagnosis did not coincide with the clinical one in 5 and with the elastography indices in 3 (27.2%) patients. High rates from 3.22 to 12.05 were in 9 out of 11 (81.8%) patients examined in this group. Only two patients (18.2%) had low M2BP values of 0.35 and 1.55 and did not correspond to the severity of the process. In the group of patients with formed LC, high levels of liver elastography were observed, which amounted to 20.8 ± 7.0 kPa. Clinical diagnoses in 5 of 6 patients coincided with histological and WFA+ –M2BP values. Only one patient had low M2BP values - 1.41; in the rest, serum markers ranged from 3.33 to 14.73, which averaged 6.62 ± 0.5. This indicates that in the group of patients with LC it is not advisable to use WFA+ –M2BP since the clinical diagnosis in almost all cases corresponded to the histological one. Thus, WFA+ –M2BP should be considered an important serum marker of chronic viral hepatitis B and D, reflecting the degree of liver fibrosis. Prognostic outcomes should be associated with low WFA+ –M2BP. Conclusion: An important serum marker of chronic viral hepatitis B and D, reflecting the degree of fibrosis should be considered as WFA + –M2BP. In CHB, histological diagnoses coincided with M2BP values. Prognostically favorable outcome of the disease in some patients should be associated with low WFA + –M2BP. Patients with a picture of low or moderate chronic hepatitis, but with high WFA + –M2BP, require close and longer observation, since normal ALT, lack of complaints and objective changes do not exclude the possibility of transition to the LC. Serum WFA + –M2BP levels can be used to interpret disease prognosis.

Clinical aspects of HDV liver cirrhosis etiology

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Background: Clinical manifestations of liver cirrhosis (LC) are quite varied from minimal to severe signs of the disease. The emergence of new methods of diagnosis have led to a revision of certain provisions of the natural history of HBV and HDV -infection. Aim: To identify the clinical aspects of the initial stages of HDV etiology LC. Material and methods. A comprehensive clinical and laboratory examination of 67 patients with HBV LC etiology, 140 HDV etiology LC was conducted. The mean age was 46.9±5.6%; 34.2±3.8 years, respectively. It was used the following research methods: clinical, biochemical, serological, molecular biological, instrumental. Results: The complexity of early diagnosis of LC is due to the diversity of the first clinical manifestations. The period of developed clinical manifestations is characterized by a variety of clinical symptoms, involving many organs and

systems in the pathological process. The initial stages of LC formation can be asymptomatic or with minimal symptoms, which makes them difficult to diagnose. As a result, there is a discrepancy between clinical, histological diagnoses and indicators of instrumental methods of research. Unlike HBV Etiology LC, more severe symptoms are observed with HDV infection. In most patients with LC associated with viral hepatitis B, the disease was latent with scanty symptomatology, doctors misjudged the patient's condition. Another group of patients, mainly with chronic HDV infection, had pronounced clinical symptoms with the appearance of external signs of liver failure. The HDV etiology LC was diagnosed; the diagnosis was not confirmed during a liver biopsy. To clarify the diagnosis, 41 patients underwent liver biopsy, followed by histological analysis, and a comparison was made with the result of liver elastography. Of the 12 patients with HBV LC, the clinical diagnoses did not coincide with the histological diagnosis in 2 (16.7%). Of the total number of patients with HDV infection, there was a discrepancy between clinical and histological diagnoses in 7 (24.1%) patients. Among patients with LC, an increase in alpha-fetoprotein (AFP) concentration was observed in 31 (46.3%) with HBV infection and 86 (61.4%) with HDV infection. Their level ranged from 28 to 120 ng / ml, averaging 32.5 ± 8.9 and 53.0 ± 9.3 ng / ml, respectively. The level of AFP depended on the severity of the pathological process and reliably reflected the functional state of the liver. Enzyme activity and the degree of dysproteinemia were not directly dependent on the severity of the process. Individual fluctuations and unreliable differences in the activity of AlAT in LC of different severity of the disease indicate that the indicators of AlAT did not characterize the severity of the course. The rise of AsAT in the dynamics of the disease was an indicator of the systemic nature of the disease with damage to other organs and systems. Quantitative indicators of protein fractions were characterized by a decrease in the level of albumin. A significant decrease in albumin was observed with class B LC ($P < 0.05$) and C ($P < 0.005$). The revealed changes in the protein spectrum of blood testified to a persistent violation of protein metabolism as a result of inhibition of the protein-synthetic function of the liver. The prothrombin index was reduced to 63.6% with HBV LC and to 54.1% with HDV LC and 62.5% of Child-Pugh class C. Significant changes in peripheral blood were detected depending on the severity of the disease. Conclusion: 1. The severity of clinical manifestations, not in all cases combined with morphological changes. 2. It was observed a direct correlation between the severity of the clinical manifestations of HBV LC and HDV LC and the duration of the disease. 3. The results of the study of indicators of bilirubin metabolism and ALT activity indicate that when the LC, these criteria are very conditional. A significant decrease in albumin was observed with class B LC ($P<0.05$) and C ($P<0.005$). The revealed changes in the blood protein spectrum testified to the persistence of a violation of protein metabolism as a result of the inhibition of the protein-synthetic function of the liver.

Electron microscopy of new phenomenon in hepatology: Shedding of the lymphocyte's cell membrane in chronic delta hepatitis liver

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Backround and aims: Cell-mediated cytotoxicity is one of the major mechanisms of liver damage in chronic viral hepatitis. In the present work we studied the ultrastructural aspects (mechanisms) of immune-mediated cell injury in the liver of the patients with chronic delta hepatitis (CHD). Methods: Ultrathin sections of liver biopsies from 20 patients with CHD after staining were examined in a JEM-100S Electron Microscope (JEOL, Japan). Results: Electron microscopic study revealed cooperation of macrophage with lymphocyte (L) in the lumen of the sinusoids and penetration of L through the sinusoidal wall between hepatocytes. Under high magnification these lymphocytes had similar ultrastructure of the secretory cells with well developed Golgi apparatus (Ga) and probably were cytotoxic T cells. In the liver of one patient we observed (fig. 1) shedding of the lymphocyte cell membrane (CM). This phenomenon has not been reported elsewhere. The two plasma membranes fuse, forming three-layered membrane structures. In the process of shedding of the L CM the integrity of the CM is unimpaired. Fig. 1. Ultrastructure of Shedding of lymphocyte cell membrane. Liver biopsy, CHD, 7500x. Discussion: As it is described assembly of the main components of the CM occurs in the Ga. The Golgi vesicles secrete their content into the intercellular space and their membranes fuse with the CM. Directly after the release of the product of secretion the extent of the CM is substantially increased. Up to present time the question of the removal of the excess membranes remains open. It can be assumed that shedding of the CM of the L is a compensatory mechanism freeing it of the excess of this membrane. Conclusions: Our results demonstrated that cooperation of immune competent cells with killer effect of Ls and shedding of the L CM is one of the mechanisms of liver damage in CHD. It is important to take into account described above shedding of L CM in pathogenetic therapy of CHD, including purification of the patients serum from these membranes. (For more information: abahrom@mail.ru)

Assessment of prognostic factors affecting disease-free and overall survival of patients with liver resection for colorectal metastases

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AIM: More than 50-60% of patients with colorectal cancer will eventually develop hepatic metastases during the course of their disease. Hepatic resection is a safe and effective therapy for metastatic colorectal cancer and has become a routine part of the treatment and is the only therapy to date to be potentially curative. The aim of this study is to evaluate the prognostic factors affecting the disease-free and overall survival in

patients undergoing hepatic resection for colorectal cancer metastasis.
MATERIALS-METHODS: Between January 2006 and December 2017;105 patients underwent hepatic resection for colorectal metastasis at Okmeydani Research and Training Hospital, were retrospectively reviewed using the hospital's medical records. Overall and disease-free survival rates were calculated using the method of Kaplan-Meier,Log-Rank (Mantel-cox) test was used to compare survival in the univariate analysis and multivariate analysis was calculated using a Cox regression risk model.Patients were evaluated for age,site of primary tumor,time between two surgeries (colorectal and hepatic resection),primary tumor histological type,differentiation grade and lymph node status,timing of hepatic metastasis (metachronous/synchronous), preoperative CEA level, distribution of liver metastasis,size and number of metastatic liver lesions,surgical margin status and extent of liver resection to define prognostic factors affecting overall and disease-free survival.
RESULTS:In our study, age, primary tumor histological type,differentiation grade,primary tumor lymph node status,preoperative CEA level,size of metastatic lesions,surgical margin and extent of liver resection ($p<0.0001$ for all) were significantly associated with overall survival.Similarly,the patient's age, differentiation grade,primary tumor lymph node status, preoperative CEA level,size of metastatic lesions and extent of liver resection ($p<0.0001$ for all), timing of hepatic metastasis ($p=0.011$) and surgical margin ($p=0.011$) were significantly associated with disease-free survival.Primary tumor localization,time between two operations,distribution and number of metastatic lesions were found to not associated with overall survival,primary tumor localization,histological type, distribution and number of metastatic lesions were found to not associated on disease-free survival.
CONCLUSION:In patients undergoing hepatic resection for colorectal metastases,overall survival and disease-free survival are affected by many factors.It is necessary that this factors must consider while planning surgery. Our results suggest that the prognostic factors which are significant in our study should be taken into consideration in the preoperative planning and postoperative follow-up of the patient. KEYWORDS: Colorectal cancer, liver metastases, hepatic resection, survival.

Baseline hypertension associated with treatment failure in interferon based anti-HCV therapy

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AIM: Not many studies were investigated the association between baseline hypertension and the benefit of PegInterferon and Ribavirin therapy in chronic hepatitis C (CHC) patients. We aimed to investigate the sustained virological response (SVR) rate in hypertensive or non-hypertensive CHC patients. METHODS: The 440 treatment naïve CHC patients enrolled in this study. We have assessed hypertension by measuring blood pressure at the initiation of the therapy and also checked the patients who received

antihypertensive drugs. Demographic and laboratory parameters were assessed and appropriate statistical methods were performed for the analysis. RESULTS: One hundred and eighteen (26.8%) patients had high blood pressure or detected active use of antihypertensive drugs were enrolled in this retrospective analysis. Multivariate logistic regression analysis revealed that age (OR-1.06; 95% CI – 1.03-1.09; p<0.001), body mass index (OR-1.13; 95% CI – 1.05-1.20; p<0.001) and hyperlipidemia (OR-4.48; 95% CI – 2.05-9.80; p<0.001) were significantly associated with hypertension in CHC patients and HCV RNA log (OR-0.67; 95% CI – 0.57-0.79; p<0.001), total cholesterol (OR-0.99; 95% CI – 0.98-0.99; p=0.030) level, HCV genotype non 1 (OR-0.67; 95% CI – 0.57-0.79; p<0.001), hypertension (OR-0.56; 95% CI – 0.33-0.94; p=0.030) and diabetes (OR-0.45; 95% CI – 0.24-0.82; p=0.009) were significantly associated with SVR. The HCV RNA log (OR-0.71; 95% CI – 0.53-0.95; p=0.025) was associated with SVR in hypertensive CHC patients by multivariate analysis. CONCLUSION: Baseline hypertension at the initiation of antiviral therapy was associated with treatment failure and hypertensive patients who did not achieved SVR were associated with high viral load.

The prevalence of genotypes and subgenotypes of HBV and HDV viruses according to a study of 8 regions of Kazakhstan

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Currently, there are 240 million people positive for HBsAg worldwide [Ott et al. 2012], making the prevalence of HDV infection about 15 million carriers. The 6-year experience of the transplant Centre in Almaty has shown that the causes of terminal liver disease were viral hepatitis D in 35.7%, primary biliary cirrhosis in 21.4%, hepatitis B virus in 17.85%, hepatitis C virus in 14.2%, and autoimmune hepatitis in 10.7%. Cirrhosis in the outcome of CHD is the most common cause of liver transplantation in Kazakhstan. CHD is associated with the most severe form of hepatotropic-induced viral hepatitis [Rizzetto M, et al, 1983]. Chronic hepatitis D is associated with the most severe form of hepatotropic-induced viral hepatitis. Cirrhosis caused by CHD develops 10 years earlier than with monoinfection of HBV [Moatter T, Abbas Z, Shabir S, 2007]. The factors of liver disease progression in HDV include HDV genotypes and HBV genotypes, HBV-HDV replications and patient's profile Multivariate analysis identified age, HBV genotype C, and HDV genotype I as independent factors for poor outcomes [Su CW, Huang YH, Huo TI, et al., 2006]. The aims. The A.Syzganov's National Scientific Center of Surgery in 2017 has started the scientific project to study the factors of progression of liver cirrhosis in the Kazakh population. One of the factors of

progression of liver cirrhosis in Kazakhstan are genotypes of HBV and HDV. Method: Blood samples of patients were examined for the determination of genotypes of HBV and genotypes of HBV by the PCR method. Isolation of HDV RNA and HBV DNA was performed using the GeneJETViral DNA and RNA Purification Kit, ThermoScientific, according to the manufacturer's instructions. PCR was performed using specific primers. Purified PCR products were sequenced in two directions, using a forward and reverse primer (BigDye ™ Terminator v3.1 CycleSequencingKit). Results: 413 patients in chronic hepatitis B and D were examined, including 189 men, 224 women. The average age was 43.6±6,5 years. In 152 patients diagnosed with chronic viral hepatitis D, 261 patients with CHB. Among patients with CHD, 70 patients (46,1%) had a positive PCR result of HDV RNA in the absence of HBV DNA in the blood. 53,9% (82) patients with CHD were HBV DNA-positive and HDV RNA-positive at the same time. In patients with CHD the stage of liver fibrosis F0 (Metavir) had 28 (18,4 %) patients, F1- 14 (9,2%), F2 – 13 (8,6%), F3 – 30 patients (19.7 %), F4 had 67 (44,1%) patients. In patients with CHB, 257 patients were HBeAg-negative, i.e. mutant strain of the virus and only 4 patient (1,5 %) was HbeAg-positive. In patients with CHB 15 patients had a viral load of less than 2000 IU . The stage of liver fibrosis F0 (Metavir) had 52 (19,9%) patients with CHB, F1 -47 (18.0%) , F2 – 44 (16.9%), F3 – 53 patients (20.3%), F4 had 65 (24.9%) patients. The PCR analysis has showed that in all patients (100%) with CHD have 1 genotype of HDV. From 261 HBV DNA-positive patients in 95,7 % genotype D was found. Only 4.2 % of cases was identified genotype A of the hepatitis B virus, 1,5% - genotype C of HBV. The 82 patients with positive PCR of HBV DNA and HDV RNA has genotype D of HBV. In the study of subgenotypes of the hepatitis B virus, it was found that the A1, C1, C2 subgenotype was found in 0.38% each. The A2 subgenotype ws found in 3.83% of cases. Patients in whom only the D1 genotype was determined accounted for 64.3%, D2 in 9.6% and D3 in 9.6% of cases. The combination of subgenotypes 1 and 2 of genotype D was found in 2.7%, the combination of subgenotypes 1 and 3 in 3.43% of cases, subgenotypes 1, 2 and 3 of genotype D in 0.7%. The combination of four subgenotypes 1, 3, 4 and 6 of genotype D of HBV have 0.7% of patients. Conclusion: The severe course of chronic viral hepatitis D is due to the prevalence of the 1 genotype of HDV. For chronic hepatitis B, the most common genotype is D1.

HDV co-infection modifies the immunoproteasome profile of HBV infected hepatocytes leading to increased CD8 T-cell recognition: Implication for immunotherapy

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Background and Aims: Patients with HBV/HDV co-infection are at risks to develop liver cirrhosis and cancer. Immunological therapy utilizing engineered virus-specific T cells might eradicate HBV/HDV infected hepatocytes. However, the impact that HDV

might exert on the T cell recognition of HBV infected hepatocytes is unknown. Here we first analyzed in vitro how HDV modifies HBV antigen presentation to CD8 T cells. We then tested the antiviral efficacy of engineered T cells in HBV/HDV co-infected humanized chimeric mice. Method: Quantity of HBV CD8 T cell epitopes were measured on primary human hepatocytes (PHH) infected with HBV alone or co-infected with HBV/HDV using antibodies and CD8 T cells specific for either core or envelope HLA-A0201 restricted HBV epitopes. HDV infection was concomitantly stained with a Primeflow RNA assay and expression of innate immunity genes were analyzed using Nanostring technology. HBV-specific TCR T cells were engineered using TCR mRNA electroporation on T cells of healthy and HDV chronically infected subjects. HBV/HDV co-infected uPASCID/beige/IL2rg-/-(USG) mice repopulated with HLA-A02 matched primary human hepatocytes were used for in vivo adoptive T cell transfer experiments. Results: HBV/HDV co-infected hepatocytes displayed a selected increase presentation of HBV envelope (~100times) but not of core CD8 T epitopes. The increased epitope presentation was linked with activation of type I IFN genes and modification of immunoproteasome profile, leading to an enhanced target recognition by HBV-envelope specific CD8 T cells. Adoptive transfer of T cells engineered with TCR specific for envelope/A0201 complexes into HBV/HDV co-infected human liver chimeric mice triggered a rapid decrease of both HDV (>0.5log) and HBV viremia (>1log) in only 12 days. Intrahepatic analysis indicated that the amplitude of anti-HDV effects correlated to the amount of HBV/HDV co-infected cells present at baseline. Of note, TCR-redirected T cells engineered utilizing T cells of HBV/HDV co-infected patients display identical functional profiles with TCR-T cells of healthy controls. Conclusion: The ability of HDV to activate immunoproteasome activity in HBV infected hepatocytes and boost the presentation of envelope derived HBV epitope support the therapeutic use of HBV envelope specific TCR engineered T cells in HBV/HDV co-infection.

Long-term results of the use of Bulevirtide (Myrcludex B) for the treatment of chronic hepatitis D

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Liver cirrhosis with rapid decompensation and high risk of hepatocellular carcinoma develops within 5–10 years in 50-70% of patients with chronic hepatitis D (HDV). The severity of the prognosis for chronic hepatitis D, low efficiency and limitations for the use of peginterferon-α determine the relevance of the search for new effective antiviral drugs. The sodium-taurocholate blocker of the cotransporting peptide – bulevirtide (Myrcludex B) is one of them. AIM: To assess the long-term results of the first trial of using bulevirtide for patients with HDV. MATERIAL AND METHODS: 24 patients were enrolled in a study conducted in 2014-2016, they were divided into three groups. In group A, patients received bulevirtide 2 mg/day for the first 24 weeks, then peginterferon α2a 180 mcg/week for 48 weeks; in group B, in the

first 24 weeks, combination therapy with bulevirtide and peginterferon α2a was performed, then 24 weeks of monotherapy with peginterferon α2a; in group C (control), monotherapy with peginterferon α2a was performed. The term for evaluating long-term results of treatment ranged from 2.5 to 3.5 years. RESULTS: Among 24 patients, the certain results were evaluated in 15 of them. An undetectable level of HDV RNA was recorded in 4 patients (2 patients from group A, 2 patients from group B), while 1 patient from group B achieved HBsAgseroconversion with the formation of anti-HBs; HBsAg is not detected in 1 patient, but anti-HBs have not been detected; 2 people retain HBsAg in the absence of HDV RNA in repeated studies. In all these 4 patients, ALT activity is normal, the stage of fibrosis does not exceed F1 according to liver elastography. Among 11 patients without a virological response, negative dynamics was registered in 1 case (group B): liver cirrhosis was diagnosed 3 years after the end of antiviral therapy (class AChild-Pugh). Disease course of 10 remaining patients without response to therapy is stable without negative dynamics: ALT levels fluctuate to 3 upper limits of the norm (average 67.16 +/- 30.7 U / ml), the stage of fibrosis according to elastography 1 –2 points. CONCLUSION: The virological response achieved with the use of Bulevirtide in patients with HDV is persistent and is accompanied by normalization of biochemical parameters, as well as stabilization or reduction of fibrosis.

Successful treatment of an HDV patient with severe fibrosis (clinical case)

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Background: HDV infection is characterized by the most severe and unfavorable course compared to other viral hepatitis, therefore treatment is required for the most patients, despite the fact that it is associated with considerable difficulties. Clinical case: In 2002, a male 29 y.o. patient was admitted to the hepatology department of Vasilenko Clinic Sechenov University due to changes in laboratory tests: ALT – 10ULN, AST- 7 ULN; all other tests were normal. He had an acute HBV infection in 1999 and was discharged from the hospital with normal biochemistry, however data of virologic markers was absent He didn't smoke and his alcohol intake was not above 21 standard drinks per week. Virological examination revealed markers of HBV and HDV infection (HBsAg, anti-HBe, HBcoreIgG, anti-HDV IgG, HDV RNA). HBV RNA, HCV infection markers and autoantibodies (antinuclear, anti-smooth muscle, to liver and kidney microsomes) were not detected.Liver histology (baseline):chronic high activity hepatitis with severe fibrosis (histological activity score (Knodell) 13 points, F3 Metavir). A clinical diagnosis was established: chronic hepatitis D (HBsAg +, HBeAg-, anti-HBcoreIgG +, HBV DNA-, anti-HDV IgG +, HDV RNA +) with high histological activity and severe fibrosis. Antiviral therapy was initiated: interferon α2b 10 ME three times a week. Side effects during

the therapy: leukopenia (Grade 1-2) and local reactions. During antiviral therapy ALT and AST level decreased 30-40 units per month. End of treatment (12 months): ALT, AST within normal range , HDV RNA undetectable Liver biopsy (end of treatment): histological activity score (Knodell) 10 points, F3 Metavir).In order to obtain sustained virological and biochemical response, as well as suppress the processes of fibrogenesis, a maintenance course of interferon α2b was prescribed at a dose of 1 ME daily for 6 months. After a 6-month follow-up period, a third liver biopsy was performed: F1 Metavir, histological activity score (Knodell) 8 points. During the next 12-month follow-up period, the patient remained HBV DNA and HDV RNA -negative (HBsAg +, HBeAg-). Conclusion: This clinical case demonstrates the need for active detection of HDV infection in patients with anamnestic indications of acute hepatitis B. The course of interferon α2b therapy led not only to the persistent elimination of HDV RNA transaminase normalization and to decrease in inflammatory infiltration of the liver tissue, but also to significant (2 points) fibrosis reduction. However, it should be noted that the patient retains markers of persistence of HBV infection (HBsAg, anti-HBcoreIgG), which dictates the need to monitor him with periodic research of biochemical parameters and viral markers.

Protective effect of bioengineered silver nanoparticles against diethylnitrosamine induced hepatocarcinogenesis via knockdown of oxidative stress and inflammation by regulating nf-κb pathway

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Over the recent years, nanoparticle approach for targeted drug delivery is considered as a promising therapeutic method to improve the potential of antitumor agents. Trianthemaportulacastrum (TP) leaves has been utilized as a strong hepatoprotective in Indian traditional medicinal system. Current study was designed to biofabricate, characterize and evaluate protective effect of TP extract mediated silver nanoparticles (AgTPNPs) against diethylnitrosamine (DEN) induced hepatocarcinoma in rat model. Liver damage in rats was induced with a single dose of DEN (200 mg/kg) as well as double dose of phenobarbital. Simultaneously, animals were administered with AgTPNPs at two dose levels (10 and 20 mg/kg p.o.) for 16 weeks. At the end of study, serum biomarkers, hematological status, antioxidants enzymes, proinflammatory cytokines, i.e., tumor necrosis factor-α, interlukin-6, interlukin-1β, and nuclear factor kappa beta (NF-kB), were examined to assess the protective effect of AgTPNPs. Additionally, gene expression (Akr1b10, Foxp1 and ING3) concerned with hepatocarcinoma as well as was as histological studies were also undertaken to assess the outcomes of current

study. AgTPNPs were synthesized by co-precipitation method and different characterization techniques confirmed the formation of spherical crystalline nanoparticles with size range of 50-80 nm. FTIR results showed the existence of possible bioactive functional groups of phytoconstituents in the synthesized AgTPNPs. Results demonstrated that DEN significantly induced the hepatocellular carcinoma in each group, which was significantly reversed ($p < 0.001$) by AgTPNPs in a concentration dependent manner. A significant reduction in level of serum hepatic and non-hepatic marker enzymes, oxidative stress and different inflammatory markers via direct and indirect inhibition of NF-kB expression were observed in rats administered with AgTPNPs. Regarding gene expression, AgTPNPs treated group exhibited significant elevation in Akr1b10 and ING3 expression whereas reduction in Foxp1 gene expression level as compared to control group. Histopathological study further favored the restructuring effect on destructed hepatic tissue. Collectively, results demonstrated that AgTPNPs potentially ameliorated the damaging effects of DEN induced hepatocellular carcinoma and it can be utilized as an effective nano technology based anticancer approach.

Plasma microRNA-199a-5p as biomarker of liver injury in patients with chronic viral hepatitis

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Background. MicroRNAs are small non-coding molecules that negatively regulate gene expression. miRNAs are stable in frozen samples that make them attractive as a potential biomarker. Micro-RNA-199a-5p was chosen for our study as it is expressed in different levels depending on the type of virus in hepatocytes and has been reported to have an association with viral replication and hepatic fibrosis in chronic hepatitis B virus and hepatic C virus infection. The aim of this study was to evaluate and to compare the plasma levels of miR-199a-5p in group of patients with chronic hepatitis B, C and D as potential biomarker. Methods. Plasma samples were collected from a total number 106, included 30 healthy individuals as control group. 76 patients were divided into three groups: 32 with chronic HCV-, 25 with HBV- and 19 with HDV-infection. Total RNA was isolated and analyzed for miR-199a-5p expression with miScript PCR system (Qiagen, Germany) using C. elegans miR-39 as normalization control according to manufacturer recommendation. Results. We found increased level of miR-199a-5p in all three groups of interest to some extent compared to the control group. In the group with chronic HDV infection, there was significant increase in plasma levels compared to the group with chronic HBV mono-infection and chronic HCV infection. Moreover, in this group of patients, we observe direct correlation of miR-199a-5p level with ALT suggesting that serum miR-199a-5p might be a biomarker of severe liver injury. At the same time, there was no significant up-regulation of miR-199a-5p in the group with chronic HCV infection compared to patients

with chronic hepatitis B and chronic HDV infection. Conclusion. Results of the study show that plasma miR-199a-5p up-regulation correlates with serum ALT, thus, this microRNA could be a useful biomarker in acute liver injury. We report that serum miR-199a-5p is increased in viral hepatitis in various degrees and could depend on the severity of the viral infection.

Occurence of hepatites B and D markers among young people in two provinces of Vietnam

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The parenteral viral hepatites B (HB) and D (HD) is a major public health thread in South-East Asia. In various South-East Asia countries, high incidence rates are noted. Among the continental countries of the Western Pacific WHO region, Vietnam has the highest prevalence of HBV. So far, natural transmission routes continue to play an important role in the epidemic process in Vietnam. Since 2003, vaccination of newborns for hepatitis B is included in the National Expanded Program on Immunization (NEPI) of Vietnam. However, currently the Vietnamese population is insufficiently covered by the universal HBV vaccine which effectively protects against both HBV and HDV. The aim of this study was to estimate the prevalence of serological markers of HBV and HDV among university students aged 18-30 years in the North part of Vietnam. A total of 1259 blood serum samples obtained from university students of 18 to 30 years old from Thai Nguyen (n = 675, mean age 20.60 ± 2.07) and Da Nang (n = 584, mean age 20.28 ± 1.39). The serological markers HBsAg, anti-HBcor, anti-HBs, anti-HDV were detected by ELISA using commercial kits "DS-ELISA-ANTI-HBsAg", "DS-ELISA-ANTI-HBc", "DS-ELISA-HBsAg-0.01", "ELISA-ANTI-HDV" ("Diagnostic Systems", Russia). The titer of specific antibodies in serum above 10 mIU/ml was considered as seroprotective. The prevalence of HBsAg was 3.57% (95% CI, 2.68-4.75); anti-HBc – 20.17% (95% CI, 18.05-22.48), anti-HBs – 29.63% (95% CI, 27.17-32.21). The mono-anti-HBs antibodies indicating a post-vaccination immunity were found in 15.89% (95% CI, 13.97-18.01) of the investigated persons, the mono-anti-HBc antibodies indicating a possibly latent infection were detected in 2.86% (95% CI, 2.07-3.93) cases. The simultaneous presence of anti-HBs and anti-HBc indicating a post-infection immunity were revealed in 13.74% (95% CI, 11.95-15.75) cases. No serological HBV markers were detected in 63.94% (95% CI, 61.25-66.55) of the investigated persons. No anti-HDV markers were found in all the investigated cases. The obtained results indicate a low level of collective immunity among young people aged 18–30 years living in the Northern part of Vietnam. It is necessary to expand the vaccination program for this group of people in order to successfully implement the WHO strategy to eliminate the burden of viral hepatitis by 2030.

Molecular - genetic characteristics of occult hepatitis B in Uzbekistan

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Background. We have previously studied the occult form of hepatitis B among patients with viral hepatitis C and cryptogenic liver cirrhosis by identifying ccc DNA of HBV in samples. The aim of the study was to evaluate the characteristics of isolates causing the occult form of hepatitis B; Materials & Methods. 51 liver biopsies and blood plasma was collected from patients admitted to the intensive care unit in a serious condition, including 6 patients with hepatitis B + C (control group), 20 biopsies from patients with hepatitis C, 25 biopsies from patients with cryptogenic cirrhosis were investigated. All patients were from different regions of the country. The nucleotide sequences of Pre-S1 / Pre-S2 / S regions for 32 isolates were obtained (6 from patients with hepatitis B + C, 26 from patients with occult form of hepatitis B). The primary analysis of the obtained fragment were performed using the NCBI Blast program in comparison with the nucleotide sequences presented to the GenBank. To align the nucleotide sequences and phylogenetic analysis used the program Mega 6. Results. Based on the phylogenetic analysis of all 32 isolates, the D genotype was determined, which is the most common in Central Asia. At the same time, the D1 subtype prevailed - 84.38% compared with the D2 subtype - 3.12% and the D3 subtype - 12.5%. When analyzing the sequence of the fragment, the nucleotide identity in the group was 97.65%. There was no connection between the virus genotype and the geographic region. Thus, patients with the D3 subtype, whose intragroup percent nucleotide identity was more than 99%, came from different regions of the country. That confirms the connection of the prevalence of certain genotypes and subtypes in different groups with the paths of transmission, and not with geographic proximity. Conclusions. Identifying only the D genotype in the study group, in contrast to the distribution not only of D genotype, but also A and C, previously shown in Uzbekistan, has probably several reasons. The study included only patients in serious condition. Hepatitis B virus genotype D can cause a more severe course of the disease, including correlated with more severe liver diseases and a higher level of drug resistance than other genotypes of this virus. It is also known, that subtype D1 is characterized by low viral load and early HBeAgseroconversion, which can create problems for the timely detection of the virus in patients and lead to the development of a more serious condition in patients.

The pharmacological activity of the total extract phytocomposition in toxic liver injury

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Background: Liver diseases remain a serious public health problem throughout the world. Currently, liver diseases occupy one of the

main places among the causes of disability of the population. Worldwide, there are approximately 200 million patients with chronic liver diseases. Liver diseases are among the ten most common causes of death. The mortality rate remains high with the development of liver failure. In recent years, the popularity of herbal medicine, despite great progress in the creation of chemical drugs, is increasing. Interest in natural healing substances and drugs created on their basis is increasing due to the unique properties of phytopreparations and cost-effective production.

The aim: In connection with the above, this experimental work carried out to identify the pharmacological possibilities of the total extract of Phytocomposition №I+PhytoF (PhN№I+PhytoF) from plants of the flora of Azerbaijan.

Methods. ThePhN№I+PhytoF was administered to experimental animals with toxic liver damage, which developed with intramuscular injection of carbon tetrachloride in a dose of 0,1ml/kg in equal parts with peach oil for 10 days.

Results. Under the conditions of pathology, a significant increase in the activity of transaminases activity, which indicates necrotic changes in the liver, accompanied by the release of enzymes into the bloodstream. Under the action of PhN№I+PhytoF, anexpressed neutralizing ability of hepatoprotectors. In a comparative aspect with Essentiale Forte N (EGF), PhN№I+PhytoF has a similar pharmacotherapeutic effect. However, PhN№I+PhytoFis worse in some indicators than EGF, and in some better. A comprehensive analysis of disorders of protein metabolism was performed, the protein coefficient was determined, the coefficient of hepatoprotective activity of the main enzyme systems of the liver, occurring in experimental animals when modeling toxic liver damage by carbon tetrachloride, was established. Positive results changed in accordance with the duration of PhN№I+PhytoFtreatment; in particular, protein metabolism in hepatocytes normalized. Thus, the metabolism of ceruloplasmin, one of the main components of antioxidant protection and adaptation of the organism to stress factors, which is part of the ·2-globulin fraction, increased.

Conclusion.For the first time based on medicinal plants Azerbaijan developed and pharmacologically confirmed the biological activity of the newly created total extract PhN№I+PhytoF with antioxidant, antiradical, hepatoprotective, immunomodulating, adaptogenic, and antihypoxic activity.

Features of the course of chronic viral hepatitis D (according to the register of the Stavropol region)

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Chronic viral hepatitis D is currently one of the unresolved problems of modern hepatology. The disease is progressive in character, and existing therapies are not effective enough. Aim - to study the clinical features, course and outcomes of chronic viral hepatitis D in the Stavropol region. Material and methods. 72 patients were included in the register of patients with chronic viral

hepatitis D, during the period from 2010 to 2019 living in the Stavropol region and neighboring territories. Women were 25 and 47 men. Mean age of the patients constituted 38.8 ± 1.4 years. Standard clinical, laboratory and virological methods were adapted for examining the patients. Stage of liver fibrosis was studied by the method of elastometry or through puncture biopsy of liver. Results. All the patients had signs of HDV replication (presence of anti-HDV and HDV-RNA), in 25 of them (37.7%), parallel replication of HBV-DNA was observed. Overall, moderate biochemical activity prevailed (51.4% of the patients). At the moment of approaching of patient to the clinic, prevalence of advanced stage of fibrosis – F3 (26.4%) and 4 (38.9%) was observed. In 27 patients with liver cirrhosis: 11 had stage of decompensated cirrhosis, 23 patients had expressed thrombocytopenia, and 14 had esophageal varices. 29 patients (40.3%) had received treatment with TNF- α preparations (5-received repeated courses). Only in 4 of the patients, normal levels of transaminases, and in 3 –stable absence of HDV-RNA with persisting anti-HDV were observed. During the period of observation, 10 patients were dead (13.8%). Transplantation of liver (from family members) was done in 4 patients, 2 of the patients had retention of aviremia, and 2 with recurrent hepatitis D of transplant and formation of cirrhosis of transplant (during 4 and 5 year). Conclusion. Chronic viral hepatitis D frequently diagnosed late – in the stage of advanced fibrosis, 15.2% patients had decompensated cirrhosis. Treatment with TNF- α preparations had minimal effectiveness, had necessity of search in new methods of treatment. High lethality in chronic viral hepatitis was observed.

Single agent directly acting agent in hcvpcr positive liver transplant patients, experience from a developing country

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Introduction and Aims: Chronic hepatitis C (CHC) is the leading cause of decompensated liver disease and liver transplant indication in Pakistan, which is the second most prevalent country with a prevalence of 3.5% to 5.2%. Being the seventh most populous country in the world, lacking significantly on medical grounds reflected by only one liver transplant centre for more than 10 million chronically affected liver disease patients. Before the era of directly acting antiviral agents (DAAs) most common problem faced in the post liver transplant period was recurrence of HCV and most of the patients were non responders to interferon therapy well before transplantation of liver graft. Aim of this study is to see the outcomes of single agent DAA in HCV PCR positive liver transplant patients. Methods: This cross sectional analysis was carried out in CHC infected post liver transplant patients with high viremia. The effect of DAAs were noted in the form of eradication of virus and achievement of sustained virological response (SVR). DAAs used, were also recored. Also to note the interaction with immunosuppresants and development of side effects notably derangement of liver function test or failure of graft and anemia. And to note the

development of acute kidney injury or any other untoward effect. Results: During study period of 24 months, from January 2015 to December 2016, 51 HCV positive liver transplant patients were enrolled in the study. 26 (52%) out of 51 found to have active viral replication with positive PCR. All 26 received combination of Sofosbuvir (only DAA avaialbe till December 2016 in Pakistan) and Ribavirin. Achievement of viral eradication was 100% so was for SVR. There was no interaction with immunosuppressants. Most commonly reported side effect was fatigue and a feeling of nausea. Kidney and liver function tests remained normal. Contrary to recent data, there was no recurrence of hepatocellular carcinoma (HCC) in patients who recieved liver graft for HCC on background of CHC cirrhosis. Conclusions: Directly acting antiviral therapy has revolutionized outcomes of HCV infected post liver transplant patients in a country lacking modern and advanced health care system. Even the single agent therapy has done wonders for the economically less privileged. Keywords : Single agent DAA, HCV PCR positive, Liver transplant patient.

Treatment of haemodynamic disorders of patients with chronic liver disease in the practice of family doctor

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Since last period of time in the practice of family doctor, hemodynamic disorders in the patients who have liver disease has been seen quite often. From this point of view we were studied structural and functional changes of cardiovascular system. We analysed ECG and echocardiography of 20 patients with chronic hepatitis and cirrosis of the liver. In majority of patients (70%) with liver cirrosis were determined the sings of hypertrophy of the right part of heart, impaired diastolic function of right ventricule. Also has determined hypertrophy of the left ventricule, transverse and longitudinal dilatation of the left atrium, an increase in stroke and minute volume, decreased ejection fraction, increase of thickness of back wall of left venticule. This disorders of the blood-circulatory system and related to it metabolic and distrophic changes in myocard has been resulted to the development of heart failure. Given datas testifies that in chronic liver disease detected the structural functional and dystrophic changes of the right and left parts of the heart. Identified changes require mandatory correction of protein, electrolyte, vitamine metabolism with drugs, such as, potassium, magnium (panangin, Mg B6), antioxidants (vit A, E, quercetin) and cytoprotectors (preductal, carnitin L, omega 3).

Clinical evaluation of a new liver fibrosis biomarker, WFA+-M2BP (M2BPGi)

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WFA+-M2BP (M2BPGi) is a new biomarker reflecting liver fibrosis status in hepatitis patients. This biomarker focuses on the presence of glycosylation isomer of a serum

protein, M2BP, which has altered glycan structure due to the liver fibrosis progression. M2BPGi is detected by sandwich assay between an anti-M2BP antibody and WFA lectin and that value is relating to HCC development and survival in HCV, HBV and non-viral hepatitis patients. However, there is no report for the clinical usefulness of this biomarker in co-infection (HBV and HDV) patients, therefore we clarify the basic performance of this biomarker in co-infection patients comparing with that of other hepatitis patients. The M2BPGi values were measured using HISCL M2BPGi kit (Sysmex, Kobe, Japan) on fully-automated immunoanalyzer, HISCL-800 (Sysmex). The relationship between M2BPGi value distribution and the status of liver fibrosis was evaluated in 41 of HCV, 33 of HBV, 49 of Co-infection and 52 of non-viral hepatitis patients. The relationship between clinical findings of each patient and M2BPGi value also analyzed in 62 of HCV patients, 74 of HBV patients, 53 of co-infection patients and 54 of non-viral patients. The M2BPGi value in each criterion was statistically analyzed by Wilcoxon test. The M2BPGi value was increased according to the progression of the liver fibrosis stage in each disease. M2BPGi value (median) in mild fibrosis stage (F0 and F1), moderate fibrosis stage (F2 and F3) and severe fibrosis stage (F4) were 0.87, 2.00 and 6.56 in HCV patients, respectively. In the case of HBV and non-viral patients were 0.67 and 0.77 in mild fibrosis stage, 0.92 and 1.07 in moderate fibrosis stage and 0.69 and 3.16 in severe fibrosis stage patients, respectively. Our data also showed a similar result as other researchers reported. In the case of co-infection patients, the M2BPGi values in mild, moderate and severe fibrosis stage were 1.11, 1.73 and 2.68, respectively, then these values are statistically higher than those of HBV patients. The median values of M2BPGi between chronic hepatitis and cirrhosis patients were significantly different. As we expected, the M2BPGi values in co-infection patients were almost the same as that of HCV patients. Therefore, M2BPGi value shows the prognosis in hepatitis patients, this is well concord with the clinical knowledge that the prognosis in co-infection patients are worth than HBV patients.

HBsAg Level in Patients with Chronic Hepatitis Delta

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Background and aims. Chronic hepatitis Delta (CHD) is one of most severe form of chronic viral hepatites. Worldwide, about 15-20 million patients are chronically infected by the hepatitis D virus (HDV). Patients with CHD have a high risk of a liver cirrhosis and a hepatocellular carcinoma development. The aim of this study was to investigate the relationship between the HBsAg level, the HBV viral load, the HDV viral load and the fibrosis stage in patients with CHD. Patients and methods. A total of 22 patients were included in this study (11 males and 11 females). The mean age of patients was 43.91 ± 5.68 years (from 24 to 70 year). In patients included in this study, the CHD diagnosis has been detected for 4.81±2.82 years, while the CHB diagnosis has been

detected for 11.19±4.09 years. Three patients were HBeAg positive. The HBV DNA level was quantified with COBAS TaqMan HBV test (Roche Diagnostics). The HDV RNA was measured by AmpliSens® HDV (InterLabService, Russia). The lower detection limits for the HBV DNA and HDV RNA assays were 150 IU/ml and 200 IU/ml, respectively. The HBsAg level was measured by the fully automated Architect HBsAg QT (Abbott Laboratories) assay. The fibrosis stage was measured by transient elastography method (FibroScan). The statistical relationship were estimated by the Pearson correlation coefficient. Results. In the investigated group the median value of the HBsAg level was 23540.28 IU/ml (Q1 4510.94 — Q3 40407.34), the median value of the HBV DNA level was 1595.50 IU/ml (Q1 150 — Q3 5280000), the median value of the HDV RNA level was 3010000 IU/ml (Q1 623500 — Q3 9412500). The correlation between HBsAg and HBV DNA levels was not significant ($r = 0.13321$, $p = 0.61028$), while the correlation between the HBsAg level and the HDV viral load was significant ($r=0.663$, $p=0.002$). The correlation between the HDV RNA level and the fibrosis stage was also significant ($r=0.50$, $p<0.05$). The correlation between the HBsAg level and the fibrosis stage was less significant ($r=0.42$, $p=0.07$). Conclusions. In patients with CHD, the HBsAg level did not correlate with the HBV DNA level. A severe fibrosis was mostly associated with a high HDV RNA level and, to a lesser degree, with a high level of HBsAg. In our study a high level of HBsAg was predominantly associated with a high HDV RNA level. Therefore, our results indicate that the HBsAg level can be used for estimation of the HDV viral load.

Update on HDV infection in southern Taiwan

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Background: Hepatitis D caused by the hepatitis delta virus (HDV), one of the most complex viral infections of liver that along with hepatitis B virus (HBV) is a health problem, which could lead to progressive chronic hepatitis, liver cirrhosis (LC), and hepatocellular carcinoma (HCC). Aims: This cross-sectional study aimed to investigate the prevalence of HDV in southern Taiwan. Methods: A total of 1185 HBV-infected patients were enrolled from Kaohsiung Chang Memorial Hospital, Taiwan from June 2018 to Dec. 2018. The patients were screened for HDV using newly established HDV-specific antibody (Ab) ELISA techniques (GBC). Results: From 1185 patients included, 27 had positive HDV Ab, which makes HDV seroprevalence 2.3%. The baseline characteristics were comparable between patients with and without HDV Ab, except for anti-HCV, LC and HCC. Of them, the highest HDV prevalence was found in the triple infection (HBV + HDV + HCV) group (9.1%, 9/99, $p <0.001$), followed by the LC group (3.6%, 18/496, $p = 0.008$) and the HCC group (3.6%, 17/471, $p = 0.013$). There was no incident HDV infections in hepatitis B carriers who born after July 1984 in which HBV vaccination program was launched in Taiwan. Multivariate analysis showed HDV Ab

seropositivity was associated with development of LC (OR: 3.346, p = 0.011). Conclusion: Although it seems to be a very low prevalence of HDV infection in southern Taiwan, HDV and HBV dual infections are still risk factors for liver cirrhosis development. We suggest that anti-HDV should be monitored in hepatitis B patients.

Biglycan as a Non-Invasive Marker for the Assessment of Liver Fibrosis in Chronic Hepatitis B and C Patients

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Background/Aims: Liver biopsy represents the gold standard for the assessment and quantification of liver fibrosis in CLD. However, non-invasive methods allow safe and simple monitoring. The aim of this study is to evaluate the role of serum BGN in the assessment of the degree of liver fibrosis in CHB and CHC infections. Methods: Included 50 CHB, 50 HCV patients and 50 normal controls. BGN, HBs Ag, HCV Ab, AFP by ELISA and HBV DNA and HCV RNA by PCR and Fib-4 Score (for patients only). This research has been approved by an ethical committee. Results: the mean levels of BGN were increased in CHB patients than control but not in CHC patients (p= <0.001 & 0.960 respectively). The mean level of serum BGN in CHB patients was higher with fibrosis stages F3-4 (1541.37 ± 64.76) than F0-1 (560.59 ± 282) (P < 0.001). In cirrhotic CHC patients, serum BGN levels (133.0 ± 20.9) were higher than non-cirrhotic CHC patients (112.0 ± 35.7) (p=0.015). In both CHB and CHC patients serum BGN levels were positively correlated with AFP (p=0.033& 0.008 respectively), FIB-4 score (p<0.001&0.005 respectively), INR (p < 0.001& 0.017 respectively) and APRI (p < 0.001& 0.032 respectively). No correlations were found between BGN levels and viral load in both CHB and CHC patients. The cutoff value of BGN to differentiate between CHB patients and controls was >200 pg/ ml with 100% sensitivity & specificity (AUC= 1.0) while in CHC patients the cutoff point of serum BGN was >121.1 pg/ml differentiating cirrhotic from non-cirrhotic CHC patients with 72% sensitivity, 76% specificity (AUC=0.750). Conclusion: In CHB patients, BGN was found to be a good prognostic marker for the detection of fibrosis while in CHC patients it was found to be of considerable sensitivity and specificity. Key words: biglycan, CHC, CHB, fibrosis.

Salivary cortisol in the diagnosis of adrenal insufficiency in CHC patients with cirrhosis

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Background: The prevalence of AI in cirrhotic patients varies widely according to the stage of the liver disease, the diagnostic criteria defining AI and the methodology used. Aim of the work: Evaluation of salivary cortisol (SC) and serum total (STC) and calculated free cortisol (CFC) levels in diagnosis of AI in CHC patients with cirrhosis. Patients and Methods: 50 patients with liver cirrhosis and 34 healthy controls were enrolled in the study. All

subjects underwent complete clinical examination and laboratory investigations (CBC, LFTs (INR, albumin, bilirubin and transaminases), fasting serum total cortisol, salivary cortisol and corticosteroid binding globulin levels from which free cortisol level is calculated. Results: SC, STC, cortisol binding globulin (CBG) and CFC were significantly lower in patients than control (p=0.0001 for each). In patients group, SC, CFC, & CBG were significantly decreased with the severity of liver cirrhosis according to child-Pough classification (p=0.000 for each) while STC no significant difference was found between patients with child-Pough class B &C (p=0.069). SC together with STC, CBG and CFC correlated well with child score, HDL, albumin and platelets count. On ROC analysis SC had sensitivity of 76% and specificity of 87.5% compared to 38% and 97.3% respectively for STC at a cut off value 5.65 for SC and 12.6 ng/ml for STC. Conclusion: Salivary cortisol is a direct measurement of the free cortisol so it can be used to diagnose AI in patients with hypoalbuminemia as it can detect AI more than STC.

Microrna-122 expession in chronic HDV-induced liver fibrosis

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Background. Non-invasive assessment of liver fibrosis is a promising direction of hepatology and is of particular interest for the early diagnosis, prevention and treatment of patients with chronic viral hepatitis of various etiologies. Circulating microRNAs can serve as major regulators of gene expression and are involved in the pathogenesis of chronic viral hepatitis of various etiologies, including liver fibrosis. There are few data on the diagnostic and prognostic role of various microRNAs in HDV-infection. In this regard, we studied the value of microRNA-122 in patients with chronic hepatitis D. Methods. Plasma specimens were collected from 29 patients with chronic hepatitis D with various stages of liver fibrosis and 30 healthy individuals. Patients were divided according to severity of fibrosis into no/mild fibrosis (F0-F1), moderate fibrosis (F2), and severe fibrosis (F3/F4). Total RNA was isolated using the MiRNeasy Serum/Plasma Kit (QIAGEN, Germany). Reverse transcription followed by Real-time PCR was performed using the MiScript II RT Kit and the MiScript SYBR® Green PCR Kit (QIAGEN, Germany). For the analysis of the relative expression of microRNA-122 was used the 2^-ΔΔCt method proposed by Livak K.J. Results. The microRNA-122 values in the patients with chronic hepatitis D and control group (healthy individuals) were significantly different. The average 2^-ΔΔCt values of microRNA-122 in these groups were - 412.9 and 3.5, respectively. The plasma microRNA-122 expression of chronic HDV-infected patients had higher levels than those of healthy individuals (fold change - 116, 5). We found that the level of microRNA-122 in patients with chronic hepatitis D differs depending on the stage of liver fibrosis showing negative correlation in the group of patients with advanced stages of fibrosis. Conclusions. Circulating microRNA-122 could serve as a non-invasive biomarker for the detection of

early stages of liver fibrosis in patients with chronic hepatitis D. A comparative study of the levels of microRNA-122 at different stages of liver fibrosis of chronic HDV-infection is of practical interest for early diagnostics of liver fibrosis and requires further study at a larger scale, which will allow evaluating their prognostic significance and potential as a differential biomarker.

Features of the course of chronic viral hepatitis D (according to the register of the Stavropol region)

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Chronic viral hepatitis D is currently one of the unresolved problems of modern hepatology. The disease is progressive in character, and existing therapies are not effective enough. Aim - to study the clinical features, course and outcomes of chronic viral hepatitis D in the Stavropol region. Material and methods. 72 patients were included in the register of patients with chronic viral hepatitis D, during the period from 2010 to 2019 living in the Stavropol region and neighboring territories. Women were 25 and 47 men. Mean age of the patients constituted 38.8 ± 1.4 years. Standard clinical, laboratory and virological methods were adapted for examining the patients. Stage of liver fibrosis was studied by the method of elastometry or through puncture biopsy of liver. Results. All the patients had signs of HDV replication (presence of anti-HDV and HDV-RNA), in 25 of them (37.7%), parallel replication of HBV-DNA was observed. Overall, moderate biochemical activity prevailed (51.4% of the patients). At the moment of approaching of patient to the clinic, prevalence of advanced stage of fibrosis – F3 (26.4%) and 4 (38.9%) was observed. In 27 patients with liver cirrhosis: 11 had stage of decompensated cirrhosis, 23 patients had expressed thrombocytopenia, and 14 had esophageal varices. 29 patients (40.3%) had received treatment with TNF- α preparations (5- received repeated courses). Only in 4 of the patients, normal levels of transaminases, and in 3 –stable absence of HDV-RNA with persisting anti-HDV were observed. During the period of observation, 10 patients were dead (13.8%). Transplantation of liver (from family members) was done in 4 patients, 2 of the patients had retention of aviremia, and 2 with recurrent hepatitis D of transplant and formation of cirrhosis of transplant (during 4 and 5 year). Conclusion. Chronic viral hepatitis D frequently diagnosed late – in the stage of advanced fibrosis, 15.2% patients had decompensated cirrhosis. Treatment with TNF- α preparations had minimal effectiveness, had necessity of search in new methods of treatment. High

lethality in chronic viral hepatitis was observed.

Current epidemiology of hepatitis delta in the Russian Federation

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Background: Data on the epidemiology of hepatitis delta virus (HDV) infection in the Russian Federation are limited. The aim of this study was to assess the current trends in epidemiology of hepatitis delta, and to determine the genetic diversity of HDV in the endemic regions of the Russian Federation. Material and methods: Sera from 1154 healthy volunteers (age 0 to over 60 years) from Tuva Republic were tested for markers of HBV (HBsAg, anti-HBc, HBV DNA) and HDV (anti-HDV, HDV RNA). HDV genomic sequences coding R0 region (400 nt) were obtained from 213 patients with chronic hepatitis delta from Tuva (n=130), Yakutia (n=56) and Dagestan (n=27). Complete genome sequences (1690 nt) were obtained for 48 most divergent strains. Time-scaled phylogenetic analysis was performed using Bayesian analysis implemented in the BEASTv1.8.4 program. Results: HBsAg positivity rates in general population in Tuva was 8.2% (95/1154), peaking in age group 15-19 (17.6%), and lowest in children under 1 year (2.3%). The prevalence of anti-HDV among HBsAg-positive individuals in Tuva was 28.4% (27/95), peaking in the age group 40–49 years (75%). No anti-HDV positive case was detected in children under 7 years old, who were born after the introduction of mass vaccination of newborns against hepatitis B. All HDV isolates from Tuva and Dagestan belonged to genotype 1 and formed several clusters, grouped with sequences from the Russian Federation, Turkey, China and Mongolia. HDV genotypes 1 and 2 are both prevalent in Yakutia (48% and 52%, respectively). The phylogenetic analysis with the time scale demonstrated that HDV strains from Tuva diverged from a common ancestor 52.5 years ago (95% HPD interval: 40-66 years), while HBV strains circulating in Tuva have evolution history over several hundred years. Total 8 family clusters of HDV infection were observed among patients with chronic hepatitis delta, including 4 clusters in Tuva (8 patients) and 4 in Dagestan (12 patients). Bayesian analysis confirmed the intrafamilial transmission in all 4 clusters from Dagestan. But, the level of heterogeneity of HDV sequences within each of 4 family clusters from Tuva did not support the possible intrafamilial transmission. Conclusion: Vaccination of newborns against hepatitis B is effective for prevention of HDV infection in endemic region. All HDV infections in endemic regions in the Russian Federation are associated with viral genotype 1, except Yakutia, where both genotypes 1 and 2 circulate.

Novel Self Nano Emulsifying Formulation of Furosemide: A Drug Used in Portal Hypertension

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Poor water solubility is one of the reasons for erratic absorption after oral administration of furosemide (FSM), an antihypertensive loop diuretic. Aim of this study was to utilize Self nano emulsifying drug delivery system (SNEDDS), a novel drug delivery system, for improvement of water solubility, permeability and ultimately bioavailability of FSM. Solubility of FSM was determined in various vehicles oils, surfactants and co surfactants. Self emulsification region for the rational design of SNEDDS formulations was identified by pseudoternary diagrams. Developed formulations were characterized by zeta potential determination, droplet size analysis, dilution test, viscosity determination, in vitro dissolution studies and in vivo pharmacodynamic evaluation. A remarkable increase in dissolution was observed for the optimized SNEDDS when compared with the plain FSM and marketed formulation by in vitro dissolution studies. The pharmacological effect of FSM was improved by SNEDDS formulation as compared to plain FSM. The study confirmed that SNEDDS formulation can be used as a possible alternative to traditional oral formulations of FSM to improve its bioavailability.

Screening and surveillance of hepatitis B virus infection in a new dialysis facility of a tertiary care hospital, what is cost effective?

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Introduction: Pakistan is 6th most populous country in the world with highest prevalence of chronic viral hepatitis, evident from the recent polaris observatory keeping Pakistan at the second place for highest burden of chronic viral hepatitis C. Pakistan is also endemic for chronic hepatitis B viral infection as well. With the huge burden of viral liver diseases in Pakistan the most vulnerable population is one who is immune-incompetent i.e. patients on hemodialysis. So screening and surveillance protocols for identifying dialysis dependent patients contracting hepatitis B and C virus infection is the mainstay for the early identification. Aim of the study: Aim of this study is to know the cost effective screening and surveillance program for identifying hepatitis B virus infection in a new dialysis facility of a tertiary care centre from a developing country. Methods: This cross sectional study included 31 patients which were enrolled in the new dialysis facility of our hospital. Few of the patients were on maintenance hemodialysis at another centre and were shifted in this facility due to various reasons and remainder were new cases of end stage renal disease requiring renal replacement therapy. The protocol was to check all the patients for hepatitis B and C serology and Hepatitis B antibody titre for effective immunization boosters. All the new patients were also tested at the time of shifting in the new facility and at the 6 month interval. Results: Out of 31 patients enrolled, One patient was found positive for hepatitis B surface antigen and was completely evaluated and started on antiviral therapy. Remaining patients were on regular surveillance of 6 months and among them 2 were found to be surface antigen positive over next 6 months, their further record entails that these were new ESRD cases with positive family history of hepatitis B in the siblings. This outbreak was reported with the infectious control department and a shift in policy was advised for all patients, to be checked for occult HBV infection.

Conclusion: CHB is prevalent in Pakistan and all the dialysis centre are following routine strict policies of checking for surface antigen positivity. It is advisable to check for the occult HBV infection to prevent outbreaks in such vulnerable populations.

The incidence of chronic hepatitis B with a D-agent in the Republic of Dagestan

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In the Republic of Dagestan, the proportion of HBV patients infected with the hepatitis Delta virus was about 6%, which makes it possible to attribute it to areas of low endemicity. But in some regions of the republic the percentage of B and D co-infection reaches 10-15%, which makes it possible to attribute them to areas with moderate endemicity. An analysis of 145 case histories of patients with chronic hepatitis B with a delta infection showed that hepatitis is recorded mainly in men and women in people of working age. The largest percentage is between 25 and 45 years old. Patients are detected in the later stages. So, according to our data, the stage of fibrosis 4 on the METAVIR scale was established in 25% of patients, the stage of cirrhosis is also in 25%, which in total amounts to 50%. The high incidence of hepatitis B with a delta agent cannot but cause anxiety, since in the long term already 50% of patients may need a liver transplant. Currently, 10 patients need liver transplantation immediately. Only in 3 three months of the year 2019, liver transplantation was performed for two patients already, 8 patients are on the waiting list. They died in 2018-2019 7 patients.

Influence of genetic factors on the formation of HDV liver cirrhosis etiology

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Background: HDV infection occurs worldwide, but the prevalence varies widely in different countries. Approximately 10 million people worldwide have dual infections with hepatitis B and D viruses. It often occurs in individuals at risk for hepatitis B virus infection in countries where hepatitis B is endemic, including in Central Asia. Many published evidences establish a correlation between clinical manifestations and HDV transmission, which may occur simultaneously with a new hepatitis B infection ("co-infection") and as superinfection with chronic hepatitis B. Not all cases with different clinical manifestations can be explained only by the mode of transmission and the light of increasing reports about the role of host factors for many infections can be assumed that these factors can influence the clinical manifestations and outcomes. We didn't find any research on the effects of gene polymorphism IL28V to forecast the outcome of hepatitis D. This prompted us to analyze the relationship of polymorphisms IL28B gene from the CPU in the outcome of hepatitis D. The aim of the study was to study the effect of genetic variations of the human gene IL28B on the risk of developing cirrhosis and the possibility of predicting the outcome of

the disease in HDV infected patients. Methods. To assess the effect of IL28B rs8099917 SNP among the studied groups, the genotype rs8099917 in the IL28B locus TaqMan SNP was determined by genotyping in 94 individuals, including 72 patients with LC associated with HDV infection. For comparison, a group of 22 patients with HBV LC etiology was taken. Results: From the 72 patients with LC associated with HDV infection, men were 40 (55.6%), women 32 (44.4%). The age of patients ranged from 17 to 56 years old, averaged 31.2 ± 1.6 years. The degree of liver damage was assessed by the Child-Pugh scale. Class A was determined in 20 (27.8%), B –22 (30.6%), class C in 30 (41.6%) patients. An SN28 rs8099917 analysis of the IL28B gene showed that in patients with Cp, the outcome of hepatitis D and the T allele was major, and the G - minor. In 45 people (62.5%), the TT genotype was detected, the TG heterozygous genotype was determined in 24 (33.3%), the GG genotype in 3 (4.2%) patients. With LC in the outcome of viral hepatitis B there were 12 men (54.5%), women 10 (45.5%) people, the average age was 45.3±2.5 years. Assigned to class A 12 (54.5%), to class B-7 (31.8%) and to class C-3 (13.7%) of patients. In HBV Etiology LC, the genotypes were distributed as follows: TT genotype in 4 (18.2%), heterozygous TG genotype was determined in 18 (81.8%) cases and no GG genotype was detected in any patient. The SNP rs8099917 of the IL28B gene differed significantly in the HBV LC of etiology and HDV of the LC both in the TT allele (P <0.001) and in the TG allele (P <0.001). Conclusion: The results of the studies showed that the distribution of genotypes in CPV induced by HDV infection was significantly different from the HBV CPU etiology, both in TT genotype and TG genotype. Genetic analysis is a promising method for non-invasive diagnosis of the risk of developing CPU. The advantage of genetic markers is that they carry information about susceptibility to the disease and its outcome, regardless of other factors, both the environment and the individual characteristics of the organism. Genomic screening of SNPs will make it possible to develop a standard approach to predicting susceptibility to various diseases.

The pharmacological activity of the total extract phytocomposition in toxic liver injury

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Background: Liver diseases remain a serious public health problem throughout the world. Currently, liver diseases occupy one of the main places among the causes of disability of the population. Worldwide, there are approximately 200 million patients with chronic liver diseases. Liver diseases are among the ten most common causes of death. The mortality rate remains high with the development of liver failure. In recent years, the popularity of herbal medicine, despite great progress in the creation of chemical drugs, is increasing. Interest in natural healing substances and drugs created on their basis is increasing due to the unique

properties of phytopreparations and cost-effective production.

The aim: In connection with the above, this experimental work carried out to identify the pharmacological possibilities of the total extract of Phytocomposition №I+PhytoF (PhN№I+PhytoF) from plants of the flora of Azerbaijan.

Methods. The PhN№I+PhytoF was administered to experimental animals with toxic liver damage, which developed with intramuscular injection of carbon tetrachloride in a dose of 0,1ml/kg in equal parts with peach oil for 10 days.

Results. Under the conditions of pathology, a significant increase in the activity of transaminases activity, which indicates necrotic changes in the liver, accompanied by the release of enzymes into the bloodstream. Under the action of PhN№I+PhytoF, an expressed neutralizing ability of hepatoprotectors. In a comparative aspect with Essentiale Forte N (EGF), PhN№I+PhytoF has a similar pharmacotherapeutic effect. However, PhN№I+PhytoF is worse in some indicators than EGF, and in some better. A comprehensive analysis of disorders of protein metabolism was performed, the protein coefficient was determined, the coefficient of hepatoprotective activity of the main enzyme systems of the liver, occurring in experimental animals when modeling toxic liver damage by carbon tetrachloride, was established. Positive results changed in accordance with the duration of PhN№I+PhytoF treatment; in particular, protein metabolism in hepatocytes normalized. Thus, the metabolism of ceruloplasmin, one of the main components of antioxidant protection and adaptation of the organism to stress factors, which is part of the ·2-globulin fraction, increased.

Conclusion. For the first time based on medicinal plants Azerbaijan developed and pharmacologically confirmed the biological activity of the newly created total extract PhN№I+PhytoF with antioxidant, antiradical, hepatoprotective, immunomodulating, adaptogenic, and antihypoxic activity.

Diagnosis of liver fibrosis changes in family doctor practice

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Background. Early diagnosis of liver fibrosis because of progression of chronic diffuse diseases of the liver, evaluation of the effectiveness of fibrosis treatment and reverse of fibrosis are the most common problems that family doctors and hepatologists are facing. The methods such as invasive (puncture), minimally invasive(Fibro Test, Acti-Test) and non-invasive elastography (FibroScan) are used to determine liver fibrosis. FibroTest (FT) is a patented test algorithm developed by "BioPredictive" (an independent bio-pharmaceutical company). This test uses quantitative results of 5 serum biochemical markers analyses (α2-macroglobulin, haptoglobulin, γ-glutamyltranspeptidase, total bilirubin, apolipoprotein A1).

Aim. The purpose of the study is to investigate fibrosis changes in the liver with FT.
Methods. FT had been carried out to determine fibrosis changes in liver among 5 practically healthy patients and 18 diseased patients based on clinical, instrumental and laboratory results in the "Family Doctor Clinic". The results of 5 biomarker in venous blood taken from patients were analyzed using special software, considering the gender and age of the patients. The results of the FT were evaluated by METAVIR scoring system showing the development stages of liver fibrosis and colored diagram image of fibrosis was presented(0,00- 0,19 F0; 0,2-0,39 F1; 0,4-0,59 F2; 0,60- 0,79 F3; 0,80-1,0 F4). As a result of the FT, the stages of fibrosis were determined with the following results: 5 healthy patients-F0; 3 people with fatty liver disease-F0; 3 patients-F2; 3 patients with virus hepatitis-F1; 4 patients-F3; 2 patients-F4; 2 people with alcoholic hepatitis-F2; 1 patient-F3
Result. FT is an effective alternative to biopsy in patients with chronic hepatitis C or B, alcoholic liver disease and non-alcoholic fatty liver disease. The test have been used in several countries to estimate hepatic fibrosis of the chronic hepatitis C patients, diagnose fibrosis in carriers of chronic hepatitis B virus, evaluate hepatic fibrosis in co-infected HIV carriers, evaluate fibrosis in patients suffering from metabolic conditions(nonalcoholic fatty liver disease) and patients with excessive alcohol consumption. This examination method with high sensitivity and specificity, accurate biochemical analyses, perfect risk/benefit ratio comparable to the diagnostic and prognostic value of 25mm, covering all age groups, without any risk that can be frequently repetitive allows early diagnosis of liver fibrosis changes, monitoring of fibrosis development, dispensary observation, and evaluation of anti-inflammatory therapy. It should be noted that not only liver disease patients, but also healthy individuals can calculate the results of the FT online, get information on the condition of the liver, and control their health.

Diagnosis of vascularization changes in liver parenchyma in patients with chronic hepatitis C virus(HCV) in family doctor practice

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Background. HCV remains a serious threat to humanity as a medical, social and economic problem, leading to temporary loss of ability to work, disability, and lethargy. HCV is dubbed 'the silent killer' as it typically progresses without symptoms, often leaving patients unaware they are infected until their condition is very serious. HCV damages the liver slowly over many years and if left untreated, it can cause life-threatening damage to the liver. HCV is the leading cause of liver cirrhosis and cancer.
Aim. The purpose is to investigate the effect of fibrotic changes in the liver during chronic HCV on its vascularization through Ultrasonography(US) Examination.

Methods. US examinations were performed in the "Family Doctor Clinic" to 11 individuals with HCV RNA and anti-HCV diagnosis, aged 35-54 years (7 male; 4 female) with 10 ± 2 years average duration of the disease. It should be noted that the results of the FibroTest and FibroScan examination, used to study fibrotic changes in the liver, are overlapping in all patients. The results were evaluated with the METAVIR scoring scale and the stages of fibrosis were determined as below: 2 patients with F0 fibrosis; 2 patients with F1 fibrosis; 3 patients with F2 fibrosis; 3 patients with F3 fibrosis; 1 patient with F4 fibrosis. The diagnosis of vascularization changes of liver parenchyma in HCV-infected patients was performed with VOLUSON 8T Ultrasound Machine.

Result. All patients underwent 2D and grayscale standard US, and visualization of liver size, parenchymal structure, density, homology, the diameter of the portal and splenic veins were determined. Later, the condition of the fibrotic changes in the liver and the condition of the perivascular area were evaluated by the 3D US. Moreover, the Energy Doppler(Power Doppler-PD) mode was used to assess blood flow in the small vessels of the liver, vascularity of tissues and the intensity of blood supply in different parts of the parenchyma. So, through the VOCALTM computer program by using the 3D+PD mode, the one-dimensional image of liver parenchyma was obtained in some parts of periportal space, moreover, the 3D model of the veins was created and the histogram of the vascular component was established. Through the VOCALTM program' the indications such as vascularization Index(VI), blood flow index(BFI), vascularization flow index(VFI) for assessing the intensity of peripheral blood circulation and blood supply status were determined.

Conclusion.As the stage of fibrosis increases in HCV patients, vascular shape of liver changes, blood flow and blood supply are being violated, and peripheral blood circulation indicators(VI, BFI, VFI) are gradually decreased. Non-invasive, risk-free, affordable 3D+PD US vizualization method allows for the evaluation of blood circulation in HCV-infected patients, monitoring the development of fibrosis, and the effectiveness of antiviral and anti-fibrotic therapies.

Comparison of the efficacy of Ursodeoxycholic acid (UDCA) versus vitamin E plus vitamin C in non-diabetic patients with nonalcoholic Steatohepatitis (NASH)

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Background and aim: Nonalcoholic steatohepatitis (NASH) is a frequent liver disease that can progress to cirrhosis and for which effective therapy is still lacking. Despite an important role of oxidative stress in the pathogenesis of NASH, antioxidant approaches have not been investigated sufficiently. The aim of the study was to compare ursodeoxycholic acid (UDCA) versus vitamin E plus vitamin C in non-diabetic patients with nonalcoholic steatohepatitis. Methods: Patients with elevated aminotransferase levels and drinking, less than 40g alcohol/week with NASH diagnose

were randomly assigned to receive either UDCA 15 mg/per kg/day (group A) or vitamin E 800 mg/day plus vitamin C 500 mg/day (group B) for 12 months and control group, which did not receive any medical treatment. Lifestyle modification was advised to all groups. The primary study end point was improvement in alanine transaminase (ALT) levels, secondary end points were improvement in steatosis score and improvement in fibrosis score. Results: 107 patients were included 35 in the group A, 52 in the group B and 20 in control group, 11 patients dropped out, non because of side effects. Baseline characteristics were not significantly different between groups. After 12 months treatment with vitamin E plus C, as compared with UDCA, was associated with a significant reduction of mean alanine aminotransferase (ALT) levels. Similarly, there was significant reduction of both mean steatosis score and fibrosis score. Conclusion: Vitamin E plus C combination is an effective, safe and inexpensive treatment option in patients with NASH and may be useful to reduce damage from oxidative stress and slow the process leading to cirrhosis.

Changes in theSynthesis of Cortisol and Transcortinin Severe Courses of Viral Hepatitises

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Introduction: Prescribing of hormones forpatients with infectious diseases began almost immediately after discovery of the anti-inflammatory effect of glucocorticosteroids (GCS). GCS have been used in the treatment of viral hepatitis (VH) since 1950th. However, administration of GCS is not always jugulating inflammatory process in the liver with hepatic pathologies. Addressing the need for the administration of glucocorticoid therapy in patients with severe and complicated viral hepatitis requires the study of the specific features of the manifestation mechanisms of the GCS effect in patients with severe viral hepatitis. Goal: Study changes in the content of cortisol binding protein – transcortin the blood, cortisol in the blood and saliva in patients with severe course of viral hepatitis and liver cirrhoses. Materials and Methods: We studied 51 patients with severe course of viral hepatitis B and C.We used ELISA method to detect the levels of transcortin and total cortisole in the blood serum and cortisole levels in saliva. Blood serum and saliva of the patients served as the material for the study. Results and Discussion: According to the clinical examination of patients, a severe course of chronic viral hepatitis exacerbation was noted in all the patients. The liver-synthesized transcortin content in the serum blood of patients with severe viral hepatitis composed 32.0±4.26 μg/ml, which was ↓3.20 times as lower as in healthy individuals (105.22±2.01 μg/ml). This provesa significant decrease in the protein-synthesizing function, in particular, the synthesis of transcortin in the liver against the background of pronounced activity of the pathological process. The total cortisol content in the blood of patients with severe viral hepatitis and liver cirrhosis was increased to an average of 1284.3±89.50 nm/l, which was

↑2.04 times as higher as allowable parameters of the healthy individuals -140-630 nm/l (Table 1). The free cortisol content in saliva was also increased by ↑1.85 times and composing 12.8±1.03 ng/ml against the upper allowable norm equalingto 6.9ng/ml (Table 1). So, in case of the active pathological process in the liver with the hepatocytes protein synthesizing function dispragia, the hepatocytes synthesis and release into the blood of the glucocorticoid binding protein of transcortin is interrupted– its content in the blood decreases. At the same time glucocorticoid hormones are losing the ability to bind to the transport protein and not acquiring bioavailability, which makes GCS unable to reach the target organs or decreases such ability , hence, the cascade of reactions that should have started will be decreased or completely absent. Consequently, the glucocorticoid hormones content in the blood and saliva increases, that is, there is no glucocorticoid insufficiency. Further on, we raised the question, how to jugulate the shortage of transcortin? In order to find substitution therapy aiming to increase the transcortin in the blood, we studied the transcortin content in FFP and 20% albumin solution in 27 healthy donors blood. A study of the transcortin content in FFP and albumin showed105.22±2.01μg|ml of transcortin FFP and 5.22±0.15 μg|ml of transcortin 20% albumin solution. Therefore, transfusion of FFP is the optimum for replenishment of transcortin deficiency in case of severe viral hepatitis.

HDV reactivation patterns after liver transplantation and attempts to treat

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Since the introduction of immunoglobulin against HBV (HB-Ig) into the routine practice, the reactivation of HBV has ceased to be a real problem in the management of liver transplant recipients for end-stage HBsAg-positive hepatitis. Rare cases of HBV and HDV reactivation are observed in recipients, who stop taking antiviral drugs and HB-Ig. The purpose of our study was to determine the causes and patterns of reactivation of HBV and HDV, and the effectiveness of antiviral therapy of HDV relapse after liver transplantation (LT). Eighty patients undergoing LT from 2001 to 2018 for the terminal stages of HBV/HDV were analyzed. Combined prophylaxis (CP) with nucleos(t)ide analogs (NA) and HB-Ig throughout life was recommended for all of them. In a few months after surgery all pts lost HBsAg and anti-HBs appeared in the blood. The HBV relapse occurred in 5 pts after self-terminating HB-Ig and NA, and in 1 patient on lamivudine (2008). This patient died in one year due to HCC progression. In the other 5 cases HBsAg re-appearance was observed in 26-68 months after LT and 2-48 months after the CP cessation. In two patients with recurrent HBV (without HDV) after entecavir (ECV) renewal, HBV DNA and HBsAg lost, and HB-Ig was resumed. Patient #3, 18 mo. after CP cessation, developed an acute hepatitis, with ALT up to 3000 IU/ml, and serum HDV

RNA, HBV DNA (106 IU/ml). After exclusion of rejection, PEG-IFN and ECV led to complete clinical and virological response. After the disappearance of HBsAg, HB-Ig was resumed. The patient alive 9 years after HBV/HDV recurrence without any signs of transplant dysfunction. In patient #4, the recurrence HBV (HBeAg pos., DNA>108 IU/ml) and HDV occurred 6 mo. after the CP cessation. There was a rapid hepatitis progression with the decompensated graft cirrhosis development. Treatment with tenofovir (TDF) reduced HBV DNA to 385 IU/ml, and seroconversion to anti-HBe achieved, but PEG-IFN for 7 weeks led to a worsening of the graft dysfunction. The patient died in 21 mo. In the latter case, the return of HBV (DNA 108 IU/ml, HBeAg pos.) and HDV occurred 48 mo. after the CP cessation. Treatment with PEG-IFN for 24 and 36 weeks did not lead to success. Treatment with TDF and ECV led to HBV DNA disappearance, but HBeAg and HDV RNA persists. The patient is followed-up for 39 mo. after the recurrence. The liver density is 14.4 kPa, ALT activity 150- 250 IU/ml. Conclusion. The HBV or HBV/HDV relapse after LT occurred in recipients who are non-complied to immune- and antiviral prophylaxis. The pattern of the disease can be any (latent hepatitis, acute hepatitis, chronic active hepatitis with different rates of progression). HBV viremia is usually high and does not interfere with HDV replication. The PEG-IFN administration may be effective in some patients.