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Abstracts

ORAL PRESENTATIONS

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1st Plenary Session
Is the end of hepatitis C in Poland in sight?

Changes in characteristics of patients treated due to HCV infection in Poland

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Introduction: Interferon-free therapy for HCV infection became available just few years ago. Due to initial high costs access was limited in majority countries, but it droped down leading to possible changes in the number and profile of patients. The aim of the study was to analyze changes in characteristics of HCV infected patients treated at the beginning of the interferon free era and currently.

Methods: Analysis included patients registered in the EpiTer-2 database, who started therapy of chronic hepatitis C according to the treatment protocol of the National Health Fund in two periods: A – 2015-2016 and B – 2017. Details of period A were just published (J Viral Hepat 2018 doi: 10.1111/jvh.12861).

Results: A total of 2879 patients were included in period A and 3162 were included in period B. Gender and BMI distributions were similar in both periods. Patients treated in period B were significantly younger compared to A (52.8 ± 14.4 vs. 55.2 ± 13.3), more frequently treatment naïve (60% vs. 47%) and less frequently infected with genotype 1b (78% vs. 87%). They had also less advanced liver disease demonstrated with frequency of cirrhosis (23% vs. 44%), decompensation history (2.6% vs. 6.7%), Child-Pugh B or C (2.8% vs. 6.0%), MELD > 20 (0.7% vs. 0.9%) and history of liver transplantation (1.3% vs. 3.5%). On the other hand more patients coinfected with HIV were treated in period B (3.9%) than A (1.4%). Ombitasvir/paritaprevir/ritonavir±dasabuvir±ribavirin regimen was the most frequently administered in both periods, but rates decreased from 64% in A to 44% in B. Sofosbuvir based regimens were administered in 31% and 37% whereas grazoprevir/elbasvir in 0 and 12% respectively.

Conclusions: Data from the EpiTer-2 database demonstrated significant differences between characteristics of patients treated in 2015-2016 vs. 2017 in Poland, particularly regarding age, genotypes, coinfections, advancement of liver disease and history of previous therapy. These differences can be explained by priority given to patients recognized as "difficult to treat" at the begining of access to interferon-free regimens.

Effectiveness of different HCV screening strategies – Polish and international experience

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A major barrier to achieve HCV control or even elimination is the fact the substantial percentage of infected persons are unaware of their infection. Several organizations have issued hepatitis C testing recommendations in recent years. The choice of most useful strategy in particular country depends of local epidemiology. The example is clear HCV epidemiology in United States and Canada that cause to recommend and introduce routine HCV testing for persons born during the years 1945 to 1965. CDC recommends using both birth cohort and risk-based screening.

In countries like Poland it is not possible to define birth screening and most of strategies are based on risk-based one. However there is number of limitations of use risk-based screening alone. Despite the well-publicized recommendations for risk-based screening in Poland about 70% of persons with HCV infection remain unaware of their HCV infection status. Cooperation of primary care physicians is required to address testing to wide range of population, but many of them are not familiar with the recommendations. Further, many persons who only experimented with injection drugs or occasionally used intranasal cocaine do not report this information to their medical provider. On the other hand the recent testing of 90876 patients by GPs in Poland reveled that anti-HCV prevalence was 0.46% – much lower than previously reported. It may suggest that in Polish reality testing by primary care providers will not allowed to identify most of HCV-infected. Furthermore the linkage-to-care was poor and many of identified patients had problematic access to specialist diagnosis and therapy.

There is a number of well defined risk factor that should be consider in selecting the target population. A major seems to be the history of multiple invasive medical intervention. There are also some populations with confirmed risk factors but the prevalence is low, including health-care personnel, public safety workers or people with multiple sex partners.

Selecting the most effective HCV screening strategy in Poland is still a challenge. Maybe „new" groups of patients require extensive testing to identify remaining 70% of patients. With easy access to effective treatment proper diagnosis may help to save thousands of lives.

Durability of virologic response, risk of *de novo* hepatocellular carcinoma, liver function and stiffness two years after treatment with Ombitasvir/Paritaprevir/Ritonavir±Dasabuvir ±Ribavirin in the AMBER, real-world experience study

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Introduction: We followed for 2 years patients treated with Direct Acting Agents (DAA) to assess long-term durability of virologic response, improvement of liver function, reduction of liver stiffness (LS), and risk of hepatocellular carcinoma (HCC).

Methods: Study included patients from 16 hepatologic centers involved in years 2014-2015 in the AMBER, investigators initiated study on treatment of chronic hepatitis C patients infected with genotype 1 or 4 with Ombitasvir/Paritaprevir/ritonavir±Dasabuvir±Ribavirin.

Results: A total of 204 patients among 209 (98%) from the primary study were enrolled. All 200 patients with available testing reports at 2 years follow-up (2yFU) were undetectable for HCV RNA. During 2yFU 4 patients died, 17 had decompensation, 3 needed liver transplantation due to decompensation. *De novo* hepatocellular carcinoma was diagnosed in 4 and its recurrence in 3 patients; all except one developed in the second year of the follow-up. Statistically significant decrease in bilirubin concentration, MELD, and Child-Pugh scores as well as increase of albumin level were observed between the end of treatment and 2yFU. Paired results of liver stiffness examination demonstrated its significant reduction during 2yFU. The improvement was observed in 98 (82%) patients and 50 (42%) demonstrated stiffness reduction by at least 3 kPa.

Conclusions: Two-years follow-up confirmed durability of virologic response after treatment with Ombitasvir/Paritaprevir/ritonavir±Dasabuvir±Ribavirin. It was accompanied by improvement of major measures of hepatic function and reduction of hepatic stiffness. However successful therapy did not prevent hepatic decompensation, HCC development or death in cirrhotics, that support need for longer than 2-year monitoring.

2nd Plenary Session
Hepatitis does not end with C

Hepatitis A – is there a new outbreak?

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Hepatitis A is a viral liver disease caused by the hepatitis A virus (HAV), member of the family *Picornaviridae*, identified in 1973. HAV is transmitted primarily by the faecal-oral route through consumption of contaminated food or water. Less often virus spread by direct contact with infected person, including sexual transmission, particulary among men who have sex with men. According to WHO reports approximately 1.2-1.4 million people are infected with HAV annually worldwide. The incidence of HAV in population correlates with socioeconomic conditions, access to clean water and sanitation; the endemicity is classified into low, intermediate, and high levels. The acute hepatitis A is usually mild, self-limited liver disease with good prognosis; the treatment is supportive and chronicity does not develop. The current strategies for control and prevention of HAV infection include adequate water supply, sanitation and personal hygiene; the most effective way to reduce hepatitis A incidence is vaccination. Through those activities rates of acute hepatitis A have steadily declined during last decades. Since summer 2016 the new outbreak of acute hepatitis A is observed in Europe, mainly among homosexual men, spreading by person-to-person contact. The part of this epidemy is increasing number of cases noted in our country since March 2017. 3072 cases of acute hepatitis A were reported by the end of 2017 in Poland, which is tens times more than last years.

The cure of HBV – are we getting closer?

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Chronic hepatitis B is still leading persistent viral infection worldwide with over 290 million cases as estimated recently by Polaris Observatory. Despite of lack curative therapies for HBV WHO recommends similar to HCV-infections goals of elimination by 2030. Taking into consideration elimination goals and large epidemiologic burden novel anti-HBV therapies are urgently needed. In the recent years several new anti-HBV compounds were studied in pre-clinical and clinical studies. Those include direct acting antivirals but also novel immunomodulators. Among DAA for HBV the most advanced are entry inhibitors for HBV/HDV, small interfering RNAs, HBV capsid inhibitors, HBsAg-secretion inhibitors and RNA-destabilizators. Entry inhibitor – Myrcludex B, already entered phase III studies, while several siRNAs and capsid inhibitors past phase II studies. Future anti-HBV therapies will indeed change therapeutic horizon, allowing therapy of patients with low HBV-DNA and introduction of treatment as prevention scenarios. But the most importantly, are supposed to induced durable HBsAg-loss and immune control of HBV and thus enabling reversion of fibrosis and deep reduction in HCC incidence. Those option will be further discusses as well as potential timelines will be presented.

HEV infection or hepatitis E?

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Hepatitis E virus (HEV) was discovered by Balayan in the early 1980s. At first it was thought that HEV is the cause of hepatitis in developing countries (genotype 1 and 2) but now we know that it is endemic in most high-income regions (genotype 3 and 4). In Europe HEV genotype 3 and occasionally genotype 4 cause zoonotic infection in human. Probably only 5% of infected patients develop symptoms of acute hepatitis. Progression to acute liver failure is rare. Interestingly re-infection with HEV is still possible despite immunity against this virus developed after primary infection. The main clinical problem with hepatitis E virus is possibility to develop chronic hepatitis in immunosuppressed patients. In some cases progression of liver fibrosis leading to cirrhosis is observed. HEV infection can be transmitted not only as zoonotic disease but also by transfusion of infected blood and blood products. Some countries have introduced screening for HEV in donors.

Severe clinical course and complications of current hepatitis A epidemic in Silesia

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Introduction: In the recent year unexpected HAV-epidemic spread through Poland. The most affected regions were Masovian and Silesia. We aimed to describe risk factors and compare clinical course of disease in immunocompetent and HIV(+) individuals.

Methods: 217 patients hospitalized with acute hepatitis A (acHAV) in two Infectious Diseases Departments in Silesia between 05.2017-03.2018 were included. 192 were HIV(–) and 25 HIV(+). Liver function tests, serology for HAV, HBV, HCV, EBV, syphilis and abdomen ultrasonography were obtained.

Results: 151 (69%) of subjects were male, median age of 38 (10-90% CI: 23-58 yo). History of travelling abroad was reported only in 18 (8%), while 37 (17%) declared MSM as potential route of infection. Median duration of symptoms before hospitalization was 7 (3-14) days. Among most frequent symptoms jaundice (95%), malaise (85%), vomiting (63%) and fever (57%) were noted. Interestingly, in HIV(+) acalculous cholecystitis (52% vs. 12.5%, $p < 0.001$) and diarrhea (28% vs. 13.5%, $p = 0.05$) were recorded more often. Four cases of acute EBV (3 HIV–), 4 HBV-infections (all in HIV–), 4 HCV-infections (3 in HIV+) and 3 cases of syphilis (2 in HIV+) were diagnosed. In the analyzed cohort there were 2 (0.9%) fatal cases due to the ACLF of acute HAV on alcoholic liver disease.

Conclusions: Current HAV epidemic comprises mainly of males in their late 30's. In almost one/fifth possible route of infection was MSM. In HIV(+) prevalence of cholecystitis and diarrhea during acHAV is higher, as HCV and syphilis. Importantly, mortality is higher than reported previously for acHAV, mainly involving patients with chronic liver disease.

Best of EASL

Systemic treatment of CCA. Which ways will we need to go?

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Cholangiocarcinoma (CCA) is the second most common cancer disease originating from the liver. However, there are broad differences in tumor incidences, ranging from less than 1 patient in 100,000 inhabitants in some parts of Europe until more than 10 patients in 100,000 inhabitants in Asia. CCA can be divided anatomically in different entities, namely intrahepatic CCA (iCCA), hilar CCA/Klatskin tumors (hCCA) and extrahepatic CCC (eCCA). Standard of care in patients with unresectable or metastatic disease is first-line chemotherapy with cisplatin and gemcitabine leading to a median overall survival of about one year. No standard palliative second-line chemotherapy is established. In patients with resected cancer disease adjuvant treatment with capecitabine increases recurrence-free as well as overall survival. In contrast the combination of gemcitabine and oxaliplatin did not show a relevant improvement in recurrence-free or overall survival in comparison to surveillance in patients with CCA in a multi-center trial. Genetically, CCA is a highly diverse entity, although genomic studies could correlate distinct mutational profiles with clinicopathological characteristics. Liver fluke-induced CCA have other mutational signatures (TP53) than non-liver fluke-induced CCA (BAP1, IDH1, IDH2). Likewise, certain mutated genes could be associated with chronic hepatitis-induced CCA (TERT, PBRM1) in comparison to hepatitis-negative CCA (KRAS, IDH1 / IDH2). Additionally, iCCA and eCCA strongly differ concerning specific mutations, namely FGFR2 fusions are mostly found in iCCA. Potentially actionable frequently mutated genes compromise proteins involved in tyrosine kinase signaling, glucose metabolism, chromatin remodeling and the PI3K/mTOR signaling pathway. Microsatellite instability which is associated in other cancer diseases with response to immunotherapy is rare in CCA and therefore, the potential of immunotherapy is still unclear. Presently, the most promising drug targets include IDH1, IDH2, and FGFR2. In conclusion, extensive characterization of the individual tumor entity will be even more important in CCA in comparison to other gastrointestinal cancer diseases as classical cancer driver genes are less prevalent in CCA.

Current and future treatment options for NASH

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Reduction of hepatocellular fat content represents a common mechanism of action of most of the drugs under study for nonalcoholic steatohepatitis (NASH). This can be achieved by reducing appetite and improving metabolic controls, as demonstrated in a proof-of-principle study for the GLP1 agonist liraglutide, which resulted in weight loss and a reduced rate of fibrosis progression [1]. An alternative approach for reducing systemic insulin resistance is targeting the adipose tissue with PPARγ agonists, such as pioglitazone. Glitazones improve insulin resistance, adiponectin secretion and hepatic steatosis in patients with NASH [2-4].

Novel approaches consist in targeting directly hepatic lipid metabolism. For example, the combined PPARα/δ agonist elafibranor resulted in amelioration of metabolic comorbidities and liver damage in a subset of patients defined post-hoc with more severe disease [5]. The most impressive results have been reported so far for the FXR agonist obeticholic acid, which led to amelioration of steatosis and regression of fibrosis [6]. FXR agonists directly act on hepatocytes and hepatic stellate cells, but part of their efficacy may be due to induction of FGF19 secretion by the intestine [7]. In keeping, an engineered FGF19 analogue that lacks the proliferation-promoting activity of the natural hormone, namely NGM282, has been shown the reduce hepatic fat accumulation and markers of fibrogenesis in patients with NASH [8]. Initial data suggest that NGM282 will also improve histological liver damage [9]. Alternatively, lipogenesis and lipolysis can be directly targeted by ACC inhibition [10]. ACC inhibitors have been shown to suppress lipogenesis in overweight individuals [11], and preliminary data suggest they may be effective in reducing hepatic fat and fibrogenesis in patients with NAFLD [12]. Similarly, administration of a pegylated FGF21 analogue or stimulation of thyroid receptor β led a decrease in both hepatic fat and fibrosis markers [13, 14].

Study on drugs that specifically target inflammation and fibrogenesis are yielding more disappointing results. Indeed, the chemokine receptor (CCR) 2/5 inhibitor cenicriviroc did not significantly improve liver fibrosis [15]. Similarly, the ASK1 inhibitor selonsertib was associated with a trend for improvement in liver fibrosis, but the difference was not statistically significant as compared to placebo, and should be confirmed in further studies [16].

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Management of HCV infection in patients with HCC history

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Direct acting antivirals (DAA's) have transformed treatment and enhanced treatment rates; treatment is currently limited only by clinical capacity, the availability of funds and the ability to diagnose and treat new cases. The treatment goals of direct acting anti-viral therapy extend beyond the attainment of a sustained virological response (SVR), and importantly, include the ability to reduce the incidence of hepatocellular carcinoma (HCC). Several large databases indeed indicate a beneficial effect of DAA treatment. There is clear evidence from large data sets that a DAA- induced sustained virological response is associated with a reduced risk of *de novo*, incident HCC.

Nonetheless there is a persistent risk of HCC in hepatitis C patients with cirrhosis, despite a SVR. The advent of the ability to treat cirrhosis has meant large numbers of patients with advanced liver disease have now been treated with DAA's. The success of DAA treatment in patient with cirrhosis has resulted in significant numbers of ageing, cirrhotic patients requiring follow-up and possibly management after an SVR. All cirrhotic patients should be closely monitored and followed after successful anti-viral therapy. It has been suggested that the risk of recurrent HCC is higher after DAA treatment than after interferon treatment. However accurate comparison requires statistical adjustment for independent risk factors that may explain any observed differences, as selection bias may play a role in evaluating the incidence of recurrent tumour in cohorts treated with DAA's compared to interferon.

There is a stated imperative to treat patients with advanced fibrosis because of the risk of progressive disease in such patients. An SVR will reduce the risk of de novo incident HCC. Considerable loss of life expectancy can be countered by DAA treatment of hepatitis C in those with advanced disease. Better definition of risk predictive host factors, for example advanced liver disease, age, accompanying metabolic disease including diabetes, and persisting hepatic inflammation and elevated alpha-fetoprotein as well as viral factors for example genotype 3 are required to determine the risk of HCC recurrence. In the absence of prospective controlled trials in patients with treated HCC, treatment of HCV could practically be deferred for 6 months in those with HCC, but the evidence base is weak.

3rd Plenary Session
Wilson's disease

Wilson's disease – diagnosis

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Wilsons' disease (WD) is exceptional rare genetic disorder. When properly managed survival is similar as general population, but in untreated cases disease progress leading to death in few years. Main causes of death is liver failure or progress of neurological symptoms causing immobility and medical complications. Despite in the progress of availability of diagnostic methods still is a gape lasting to few years between clinical first symptoms and diagnosis. Due to great diversity of disease clinical symptoms, diagnosis must be supported by laboratory methods, as study of copper metabolism (ceruloplasmin, copper execration with urine), DNA analysis. Additional methods as liver biopsy, liver and brain imaging, radioactive copper incorporation test are helpful. Currently WD diagnosis is based on Leipzig scores (see Table). Diagnosis should be performed also in all siblings of the index case – even asymptomatic, as well of other member of family if they despite of age have hepatic, neurological or psychiatric symptoms of untypical clinical course or etiology. Success of therapy depends in great part from disease advance at diagnosis.

Pharmacological treatment of Wilson's disease

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Wilson's disease (WD) is an inherited disorder of copper metabolism that can be successfully treated with pharmacological agents. The aim of such treatment is to create the negative copper body balance, what stop the pathological copper accumulation in different tissues as well as lead to clearing affected or-

Table. Diagnostic scoring system developed at the 8th International Meeting on Wilson disease, Leipzig 2001

Typical clinical symptoms and signs		Other tests	
Kayser Fleischer rings		**Liver copper (in the absence of cholestasis)**	
Present	2	> 250 µg (> 4 µmol)/g dry weight	2
Absent	0	50-249 µg (0.8–4 µmol)/g	1
Neurologic symptoms**		Normal: < 50 µg (< 0.8 µmol)	–1
Severe	2	Rhodanine-pos. granules*	1
Mild	1	**Urinary copper (in the absence of acute hepatitis)**	
Absent	0	Normal	0
Serum ceruloplasmin		1-2 × ULN	1
Normal (> 0.2 g/l)	0	> 2 × ULN	2
0.1-0.2 g/l	1	Normal but > 5 × ULN after d-penicillamine	2
< 0.1 g/l	2	**Mutation analysis**	
Coombs-neg. haemolytic anaemia		On both chromosomes detected	4
Present	1	On 1 chromosome detected	1
Absent	0	No mutations detected	0

Total score	**Evaluation:**
4 or more	Diagnosis established
3	Diagnosis possible, more tests needed
2 or less	Diagnosis very unlikely

ULN, upper limit of normal.
**If no quantitative liver copper available; **Or typical abnormalities at brain magnetic resonance imaging.*

gans of copper overload. Currently two groups of drugs are used: 1) chelators (d-penicillamine and trientine) which act by inrease of copper urinary excretion; and 2) zinc salts, which decrease the copper absorption from digestive tract through induction of metallothioneins in enteroctytes, which binding copper with high affinity helds their transfer to blood stream form intestinal cells. Due to lack of prospective clinical trials comparing the different WD pharmacologic treatment options, the use of different drugs as well as current recommendations according to WD depend mainly on centers experience and drug accessibility in different countries. Netherless, the different expert opinion and experience regarding to choice of anti-copper drug, few axioms regarding the WD treatment are common. The treatment should start immediately after WD diagnosis, should be lifelong and compliance with treatment as well as treatment monitoring (copper metabolism, liver and hematologic tests, neurologic and psychiatric examinations) are the key points for treatment success. Other drugs proposed for WD treatment (e.g. tetrathiomolybdate) are in clinical trials or in preclinical phase (e.g. curcumin, metanobactin). Finally, presenting the pharmacological treatment of WD, the another important issue is an additional symptomatic treatment of liver, neurological or psychiatric symptoms.

Wilson disease – liver presentation

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There are two major clinical presentations of Wilson disease – liver and neurological (rare in children). Liver symptoms may vary in severity – from asymptomatic forms, to cirrhosis and acute liver failure. There are adult guidelines (edited by EASL) and recently elaborated pediatric position paper on diagnosis and therapy of Wilson disease (edited by ESPGHAN). The diagnostic criteria for adult, pediatric, neurological and liver presentations are similar and use the same scoring system, which is a combination of different clinical symptoms and laboratory tests (ceruloplasmin concentration, 24 h urinary copper excretion, copper content in the liver and molecular analysis). Diagnostic testing for WD initially should include liver function tests (serum transaminases, conjugated and total bilirubin; alkaline phosphatase and prothrombin time/INR), serum ceruloplasmin, and 24-hour urinary copper. Mutation analysis of the *ATPB7* gene may facilitate the diagnosis. WD should be considered in the differential diagnosis of children already above the age of 1 year and in adults presenting with any sign of liver disease ranging from asymptomatically increased serum transaminases to cirrhosis with hepatosplenomegaly and ascites or acute liver failure. Biochemical tests may be less sensitive in very young children. Pharmacological therapy is mainly based on chelating agents like penicillamine and trientine and zinc preparations. It was proven to be very effective but the major problem on long term is poor compliance. Chelating agents should be preferably used in patients with signs of significant liver disease, such as cirrhosis or abnormal INR. Zinc salts could be used in pre-symptomatic patients identified through family screening, or as maintenance therapy after de-coppering with chelators as long as serum transaminase levels remain normal. Liver transplantation is indicated only in selected cases, mainly with acute liver failure and the medical decision can be based on a special prognostic scoring system of King's College.

LTx for Wilson disease

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Liver transplantation (LTx) for Wilson disease (MW), is an indication in cases of acute liver failure or advanced stage of liver dysfunction (disease) when conservative treatment options fail. MW is a rare autosomal recessive disorder of copper metabolism with a prevalence of 1 in 30 000 in population. Liver transplantation in principle allows to correct the underlying hepatic metabolic defect (impaired biliary copper excretion) of MW. The author discusses contemporary views on the current status of LTx for MW, indications, focusing on controversies in patients with neuropsychiatric symptoms. Next review issue is the choice of diagnostic modality in identification of acute liver failure (ALF) cases related to MW. Early identification of ALF is key as mortality is 100% without emergency LTx. The indication for LTx in MW patients presenting solely with progressive neurological deterioration remains highly debated. Finally, the results of liver transplantation in Wilson disease from local perspective are discussed. Wilson disease in our center accounted for 4.3% (26/600 cases) of indications for LTx. Distant LTx results are excellent, correcting copper metabolism and ending complications of MW with 1, 5 and 10 year survival 92.3%, 92.3% and 90.9% respectively.

Liver transplantation for Wilson's disease – case study

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Wilson's disease (WD) is an autosomal recessive disease caused by a mutation of the *ATP7B* gene, resulting in abnormal copper metabolism. The major clinical features of WD include liver disease, neurologic, or psychiatric disturbances, or a combination of these, in individuals ranging from age three years to older than 50 years. Asymptomatic patients are most often detected by family screening.

Liver disease includes recurrent jaundice, simple acute self-limited hepatitis-like illness, autoimmune-type hepatitis, fulminant hepatic failure, or chronic liver disease. Neurologic presentations include movement disorders (tremors, poor coordination, loss of fine-motor control, chorea, choreoathetosis) or rigid dystonia (mask-like facies, rigidity, gait disturbance, pseudobulbar involvement). Psychiatric disturbance includes depression, neurotic behaviors, disorganization of personality, and, occasionally, intellectual deterioration. Kayser-Fleischer rings, frequently present, result from copper deposition in Descemet's membrane of the cornea and reflect a high degree of copper storage in the body.

Diagnosis is difficult and involves blood tests (serum ceruloplasmin and copper levels), urine tests (a 24-hour urinary copper excretion), an ocular slit-lamp examination and a liver biopsy. Genetic testing may be used to screen the family members of those affected.

Existing therapies comprise treatment with either zinc salts or copper chelators. Copper chelating agents increase urinary excretion of copper. High-dose oral zinc interferes with absorption of copper from the gastrointestinal tract and is most effective after initial decoppering with a chelating agent. Treatment is life long. While these drugs allow for sufficient control of the symptoms, they do not cure the disease. Additionally, chelators induce multiple severe toxicities, requiring discontinuation in approximately 30% of patients.

The psychiatric symptoms of WD are poorly controlled by available drugs.

Liver transplantation (LT) is a treatment option for the most severe cases of WD. LT is a curative therapy, with biliary Cu excretion being restored, neurologic and psychiatric disease stabilizing or improving, and Kayser-Fleischer rings disappearing over time.

I present a case study of 30-year-old woman with liver cirrhosis owing to Wilson disease underwent liver transplantation in 2010.

LiverMultiScan™ in Wilson's disease in children: early observations from a larger trial into paediatric liver disease

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Introduction: Wilson disease (WD) is a rare autosomal recessive inherited disorder of copper metabolism that is characterized by excessive deposition of copper in the liver, brain, and other tissues. Diagnosis may be difficult and often involves a combination of blood tests, urine tests, and a liver biopsy, as well as genetic testing. Since severe liver damage can occur before there are any other signs of the disease. The ability to distinguish WD patients who present with liver symptoms from those with other liver-related disease would be beneficial to the early detection and thus treatment of the disease. Liver biopsy is the gold standard for evaluating liver pathology, but it is risky, costly and lacks validation in pediatric populations. MRI-derived iron corrected T1 (cT1) is a promising technique that has demonstrated utility in stratifying patients with liver disease in adults. This study (NCT03198104) is aimed at evaluating this MRI based technique in a large sample of children with a variety of liver diseases.

Methods: We investigated 54 paediatric patients (30 female; mean age 13.4 [range 6-17 yrs.], 5 with WD (mean age 9.1 [7-10]) and 49 others with various liver diseases (AIH (n = 38), PSC (n = 6), other (n = 5)). All participants underwent multi-parametric MRI with the LiverMultiScan™ protocol (acquisition time < 10 mins) from which cT1 maps, and also a measure of liver fat (PDFF) were derived. cT1 has been shown to correlate with fibro-inflammatory disease and predict liver-related outcomes in adults. Comparisons

between groups for cT1 and % liver fat were performed using two-sided Kolmogorov-Smirnov (KS) tests, and cut-offs that could separate WD from other liver diseases explored.

Results: WD group had significantly higher cT1 ($p < 0.01$) and PDFF ($p < 0.001$) compared to the other liver diseases. In an enrichment analysis designed to classify the groups from each other, a cut-off of liver fat ≥ 10% and cT1 ≥ 750 ms, successfully separated the WD from the other patients.

Conclusions: Early results indicate that LiverMultiScan™ may be a promising, fast and non-invasive technique for stratifying children with WD from other types of liver disease.

4th Plenary Session
HCC

HCC treatment in the future

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The current treatment of HCC is the result of a major research effort that has taken place during the last 30 years. The clinical decision-making using evidence-based data allows a structured approach in conventional care and the identification of the unmet needs that should be faced. The BCLC model [1] provides an easy and clear strategy for the management of the patients and is recommended by the majority of scientific associations.

The major niches of research should tackle prevention of recurrence after successful resection/ablation/transplantation, improvement of the efficacy and impact in survival by transarterial chemoembolization and finally, enhancement of the effectiveness of systemic therapy. This last aspect has sharply changed since the introduction of sorafenib. Now we have additional agents that provide survival benefit in 1st line (lenvatinib) or 2nd line (regorafenib, cabozantinib, ramucirumab). Major hope is placed in immune agents that may induce a significant number of long-lasting responses with encouraging survival. Ongoing trials should demonstrate if such agents surpass the benefits of already available options and likely, transition into combination strategies.

Research has to be prospective with trial design evolving according to novel concepts. In addition, it is expected that a better knowledge of the molecular events that trigger cancer development and progression will ultimately provide the tools to stratify patients according to prognosis and potentially, link this assessment with the most adequate treatment option. Unfortunately, this is not yet the case in HCC and thus, this neoplasm has not reached the situation of other entities such as breast, lung or colorectal cancer.

As a whole, the landscape of HCC treatment has abandoned a grim situation and patients diagnosed with such disease in the future will benefit from a large array of effective therapies.

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Treatment of advanced HCC in Poland according to the reimbursement from the National Health Fund

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Hepatocellular carcinoma (HCC) is the third cause of death due to cancer worldwide. Progress in the therapy of advanced HCC has come with the clinical development of sorafenib – a multikinase inhibitor of proliferation and angiogenesis. Multicenter, prospective, placebo-controlled phase III trial SHARP was designed to evaluate the efficacy and safety of sorafenib administration in advanced HCC. In 2008 final analysis of SHARP trial has shown that sorafenib improved overall survival (OS) of patients in comparison with placebo (median OS 10.7 vs. 7.9 months, HR = 0.69, $p < 0.001$). Median time to progression (TTP) was longer and disease control rate (DCR) was also higher in sorafenib arm (TTP 5.5 vs. 2.8 months, $p < 0.001$ and DCR 43% vs. 32%, $p = 0.002$, respectively). The total incidence of serious adverse events was similar in both arms (52% vs. 54%), however in sorafenib group the following G3/G4 adverse episodes were significantly more frequent: weight loss (2% vs. 0%), diarrhea (8% vs. 2%), and hand-foot skin reaction (8% vs. 1%). Since then sorafenib has become a new standard for the treatment of advanced/metastatic HCC, and has served as a reference regimen for future clinical trials.

In Poland the reimbursement from the National Health Fund does not include a treatment with sorafenib of HCC patients with extrahepatic dissemination. However, the SHARP study did not stratify patients due to the presence or absence of cancer spread outside the liver. In a situation where the study was not designed for patients with dissemination outside the liver and was discontinued before termination, it can't be unequivocally stated that the lack of statistical significance indicates a lack of efficacy of sorafenib therapy. In 2012 Bruix *et al*. found that sorafenib consistently improved the median OS and DCR compared to placebo in patients with advanced HCC, regardless of: etiology of cancer, baseline tumor burden, performance status, cancer advancement and prior therapy.

Reasons for failure of liver transplantation for HCC

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Hepatocellular cancer (HCC) is one of the most frequent tumors in humans and its strict association with cirrhosis makes the therapeutic approach a still controversial problem. The incidence of HCC is significantly increasing worldwide. Liver resection is the treatment of choice for the Child A patients with the tumor limted to 1-2 liver segments, without portal hypertension.

Liver transplantation is well established treatment for selected patients with hepatocellular cancer in cirrhotic liver. Removal of the tumor and cirrhotic liver provides very good results in terms of long-term and recurrence-free-survival. The criteria of the oncological radicality are fulfilled and certainly there is no chance for the liver cirrhosis progression.

Contemporary, the selection of patients with HCC for transplantation is based on widely accepted by the liver transplant community Milan criteria, proposed and published by Vincenzo Mazzaferro in 1996 (single tumour less than 5 cm in diameter or 2-3 tumours less thean 3 cm in diameter). 5-year survival reaches about 75%. Modest expansion of selection criteria is allowed within limits (i.e. up-to-7, UCSF) and depending on local conditions, however any expansion increases the need for donor organs and by this, is likely to further lengthen waiting periods, increase drop-out rates and impairs outcomes.

In the assessment of liver transplantation failure for HCC patients, the obvious factor is the quality of the transplant centre (volume, standards of organ allocation, pre- and posttransplant care, including immunosuppression, surgical technique).

The crucial problem in liver transplant recipients for HCC is the tumor recurrence, reaching 15%. The most important factor is overall burden of disease at the moment of transplantation. Other factors include: lack of standardized methods of follow-up in the risk groups, quality of imaging (50% – tumor over- or underestimation), HCC biomarkers (currently used biologic surrogates of tumor behaviour i.e. AFP, should be included in predicting scores and algorithms of decision making in order to decrease the recurrence rate), lack of pre- and posttransplant combined therapy programs (downstaging strategies allow selection of tumors with more favorable biology and could improve the results), limited access to targeted therapy.

Liver registries in Poland. Trends and results of liver transplantation in HCC, HCV and HBV recipients

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Introduction: Poltransplant's registries collects information about and transplantations with outcomes.

Aim: Registries give possibility for data processing in liver transplant profiles and outcomes. We present current (February 2018) analysis for the years 2002-2011.

Method: Indications for 1846 primary liver transplantations were divided into groups: HCC, HCV, HBV and non-HCC, HCV, HBV and 2002-2006 vs. 2007-2011. Numbers, trends and 5-year graft survival were compared.

Results: 1. The total number of HCC increases (3% to 9%, $p < 0.0001$), with insignificant decrease of transplants in patients with HCC without hepatitis and insignificant increase of patients who, in addition to HCC, have HCV or HBV cirrhosis. 2. The total number of HCV transplants does not increase (25% vs. 26%); in this group number of patients with HCV/HCC increases significantly (4% to 16%, $p < 0.0001$), this is balanced by a decrease (83% to 74%, $p = 0.02$) of transplants, where HCV occurs without associated disease; 3. HBV transplants does not increase (11%); although in this group significantly increases the number of patients with HBV/HCC (4% to 13%, $p = 0.005$), this is balanced by decrease in the number of patients with HBV/HCV cirrhosis (29% to 18%); 4. The frequency of not-HCC, HCV, HBV has not changed (65% vs. 62%). 5. Total 5-year graft survival reached 70%. 6. In HCC (61%) and in HCV (66%) results were worse

(p = 0.02-0.03). Not-HCC, HCV, HBV group had better results (73%, p = 0.0005). Results for all groups got worse: 72% vs. 69%. In HBV this was significant (80% vs. 62%, p = 0.03).

Conclusions: 1. The number of HCC recipients is increasing, this depends on increasing number of HCV/HCC and HBV/HCC combinations, not HCC alone. 2. The numbers of HCV and HBV are stable; numbers of HCV or HBV alone are decreasing but number of cases with HCC combinations is increasing. 3. HCC and HCV are associated with worse and non-HCC, HCV, HBV with better outcomes. 4. There is not progress in long term graft survival for last years; in HBV results are worse.

5th Plenary Session
Complications of cirrhosis

Spontaneous bacterial peritonitis

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Spontaneous bacterial peritonitis (SBP) – the term used to describe acute bacterial infection of ascites without an obvious clinical or identifiable source of infection in patients with decompensated liver cirrhosis. SBP is most commonly (75%) caused by gram-negative micororganisms with the dominant role of *Klebsiella pneumoniae* (about 50%). Infection with gram-positive cocci is rare – mostly due to *Streptococcus* spp.

Anaerobic infection is unusual because of high oxigen tension in ascitic fluid.

Patients who experience SBP have decompensated liver cirrhosis with Child-Pugh classification of C; ranking 10-15 points.

Risk factors of SBP include: a previous history of SBP, low complement level, reduced synthetic hepatic functions, and long proton – pump inhbitors therapy which promotes gut bacterial gowth and translocation.

SBP in adults is usualy seen in patients with abdominal ascites; in children with SBP ascites is rare.

The latest data on SBP diagnosis and therapy will be presented.

Bacterial infections and hepatic encephalopathy in patients with liver failure – a new prophylactic and therapeutic approach

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The discovery of the important role of microbiome as a necessary element of the human organism is one of the breakthrough of modern biology, ergo medicine. The summary approach to changes in the microbiome is dysbiosis proven in liver cirrhosis (compensated, decompensated, severe failure) and other pathological states. One of the drugs that have beneficial effects in liver cirrhosis and its complications like hepatic encephalopathy, bacterial peritonitis, and esophageal variceal haemorrhage is rifaximin-α with statistically significant effect on the above-mentioned complications of liver cirrhosis, and above all statistically significantly prolonging the life of patients. Due to its unique action, rifaximin-α is now treated not only as a conventional antibiotic, but also has eubiotic properties, connected with the meaning of the intestinal microbiome, a coordinate structure with other human organs.

The effectiveness of the influence of rifaximin-α on Hepatic Encephalopathy (HE) in the author's review of the literature concerned the assessment of 5062 patients observed in several dozens of clinical centers, including under controlled conditions. In some of them, lactulose or placebo was used as a control. Administration of rifaximin-α in doses of 1100-1200 mg/d for a period of up to 280 days has been statistically significant in:

- decrease in the concentration of ammonia in the peripheral blood,
- delay in the onset of the first episode of encephalopathy in liver cirrhosis (22% versus 40% in those not treated in this way, statistical significance),
- favorable changes in the composition of the microbiome with colonization of "physiological" bacterial species, such as *Eubacteriaceae*,
- reduction of the rate of encephalopathy recurrence,
- reduction of the frequency of bleeding from esophageal varices,
- reduction in mortality.

In controlled studies in patients with Spontaneous Bacterial Peritonitis (SBP), in the number of 817 in various clinical series, the use of rifaximin-α in a dose of 1100 mg/d in summary terms caused (statistical significance):

- reducing the risk of occurrence by 62%,
- preventing the first episode in 47% and re-occurring in 74%,
- reduction of mortality risk by 14% (24% when using an absorbable antibiotic from the gastrointestinal tract).

6th Plenary Session
Benign liver tumours

Point of view of the pediatric hepatologist and the oncologist

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Focal nodular hyperplasia (FNH) of the liver is a benign tumor with an unclear etiology. Until recently FNH was thought to be almost exclusively an adult problem because reports of pediatric cases have been limited to individual ones. FNH is usually found incidentally in asymptomatic patients but it is often an occasional finding in a patients imaged for other reasons. In the last few years we observed increased frequency of FNH in pediatric population especially in children after neoplastic disease, chemotherapy, radiotherapy and who underwent hematopoietic SCT (HSCT), after bone marrow transplantation, especially in long survivors. Liver lesions (very often multifocal) in children with malignant tumors in the anamnesis are generally suspicious for metastases.

In my presentation I pay attention to this problem, concerning the literature data and discussing the diagnostic algorithm.

In conclusion, I would like to emphasize that FNH should be considered in a patient with a history of malignancy (with chemotherapy and/ or radiotherapy or after SCT) who developed liver tumor(s).

Liver echinococcoses – spreading threat of public health from the parasitologist's point of view

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Human echinococcoses are zoonotic diseases occurring with very high prevalence in parts of Eurasia, north and east Africa, Australia and South America, rising also in Poland. In the Classification of harmful biological factors, they are placed in Group 3 of the hazard as "Factors that can cause severe diseases in people, are dangerous to employees, and their spread in the human population is very probable". Cystic and alveolar echinococcoses are caused by the larval stage of *Echinococcus*. Typical intermediate hosts of *E.granulosus* complex are various herbivorous mammals, *E. multilocularis* – rodents. Human is an atypical, accidental intermediate host, for whom the source of echinococcosis are typical final hosts: dogs in the *E. granulosus* infection, foxes in the infection with *E. multilocularis*. Oral rout of infection occurs: directly from dogs or foxes, indirectly: with water, food, fruits of the forest floor, contaminated excrement of final hosts, containing parasite infective eggs with oncospheres. Approximately 70% of larvae developing from the oncospheres reveal a liver location. Human echinococcoses may develop over years as clinically non-pathognomic. In late diagnosed, advanced cases, surgical treatment is undertaken, taking into account the threats resulting from the specificity of species parasites. Morphological studies, including molecular, of the material obtained intra-operatively, are helpful in diagnosis verification.

In recent years, *Echinococcus* has undergone taxonomic revision: G1-G3 genotypes have been grouped as *E. granulosus* sensu stricto, G4 as *E. equinus*, G5 as *E. ortleppi*, G6-G10 as *E. canadensis*, *E. felidis* strain was distinguished. The main etiological factor of cystic echinococcosis is *E. granulosus* G1, while in Poland, as shown by the latest molecular studies, the genotype G7 dominates. In alveolar echinococcosis, diagnostic mistakes due to, among others, similarity of larval development to neoplastic changes, ambiguity of imaging results, cross reactions in serological tests, delay detection of the infection, increasing the risk of its spreading to various tissues and organs, decreasing the effectiveness of pharmacotherapy and the conditions of surgical treatment. Expectations concern the early implementation of adequate therapy, therefore a comprehensive action is necessary: parasitological, histopathological, morphological, and especially molecular techniques in diagnosing echinococcosis. The correct identification of genotypes will improve the choice of therapeutic treatment and, as a result, increase its effectiveness.

Assesment of parasitological, morphological and molecular techniques in terms of their usefulness for diagnosis and therapeutic management of human liver echinococcoses

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Cystic and alveolar echinococcoses are emerging zoonotic diseases caused by the larval stage of the *Echinococcus granulosus* complex, developing in ruminants and omnivores, and *E. multilocularis*, which inhabits rodents. Cestode eggs are dispersed in the environment with the feces of typical definitive hosts: dogs for *E. granulosus* and foxes for *E. multilocularis*.

Humans become accidental intermediate hosts by direct infection from dogs or foxes, and indirectly from food, water, wild fruits, or fungi contaminated with soil or feces containing tapeworm infective eggs. Larvae in man develop mainly in the liver (70%), then lungs (20%), and other organs.

The disease may develop asymptomatically for years and clinically is non-pathognomic. Surgical removal of hydatid cysts and even liver transplantation are used in advanced cases.

Echinococcosis is considered as an emerging disease with the highest prevalence in parts of Eurasia, north and east Africa, Australia and South America.

Echinococcus species have been recently taxonomically revised: the genotypes G1-G3 grouped as *E. granulosus* sensu stricto, G4 as *E. equinus*, G5 as *E. ortleppi*, G6-G10 as *E. canadensis* and the 'lion strain' as *E. felidis*. The major causative agent of cystic echinococcosis that develops in man is *E. granulosus* G1, while in Poland it is G7 genotype, recently confirmed by molecular studies. Diagnostic mistakes due to cancer like *E. multilocularis* growth and cross reactions in serological tests imply the urgent need for parasitlogical, morphological and especially molecular techniques application in echinococcoses diagnosis.

It should be taken under consideration that proper genotype identification will impact on better option for treatment management and furthermore increased therapeutic efficacy.

Presentation of the most interesting/difficult patient cases – interactive session

A Janus-faced hepatitis C virus. Can we forget about it?

Joanna Musialik

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Hepatitis C virus (HCV) is both hepatotropic and lymphotropic virus that causes liver as well extrahepatic manifestations (EHMs). The clinical outcomes of the hepatic manifestation of HCV are well known and include cirrhosis and hepatocellular carcinoma leading to liver transplantation or liver-related mortality. The most frequent and studied extrahepatic condition is mixed cryoglobulinemia. Cryoglobulins can be detected in 25 to 30% of HCV-positive patients, but in asymptomatic cases, treatment is unnecessary. Cryoglobulin-related illness, known as cryoglobulinemic vasculitis, appears in a minority (10 to 15%) of patients and includes a spectrum of symptoms ranging in severity from mild (sporadic purpura) to life-threatening. The syndrome is characterized by the typical clinical triad – purpura, weakness, and arthralgias, low complement C4 fraction serum level and various visceral organ involvement, including renal, neurological, cardiac or digestive disease. Different clinical manifestations may coexist in the same patient thus, the correct approach to patients with HCV-EHMs requires a multidisciplinary management. Specialists of different medical areas challenging with specific HCV-EHMs should take into account the pathogenetic role of HCV in different underlying pathological processes.

On an example of case presentation, a complexity of the problem will be illustrated. The diagnostic difficulties and attempt to therapy in patient with advanced liver disease (infected with GT3) and coexisting renal and cardiac insufficiency due to cryoglobulinemic vasculitis will be discussed.

7th Plenary Session
Diseases of the liver and biliary system in the aspect of disorders of metabolic parameters, gut flora, and immune and endocrine systems

Microbiome in inflammation bowel diseases and risk of liver disorders

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The intestinal microbiota plays a crucial role in the organism homeostasis by participating in immunity development and protecting against colonisation and invasion of the intestine by pathogenic microorganisms. Epithelial cells of the intestinal mucosa are the first line of contact with microbiota and protect against translocation of pathogens and their metabolites to the organism. The inflammation in the intestinal wall leads to severe damage of the intestinal barrier. Inflammation bowel diseases (IBD), such as Crohn's disease, ulcerative colitis, are usually accompanied by microbiome composition disturbances. Increased number of *Faecalibacterium prausnitzii* of *Firmicute* genus plays a significant role in the patogenesis of Crohn's disease while some bacteria of *Enterobacteriacae* family increase the risk of ulcerative colitis. Mucosal barrier damage, disturbances of secretion of secretory IgA, decrease in immunological possibilities of the intestine favors dysbiosis with the advantage of pathogenic bacteria, mainly anaerobic ones G (–). A link between intestinal microbiota and the liver, a so-called intestinal-liver axis has been noticed recently. Increased permeability of the intestine (a so-called "leaky gut") favors bacteria and their metabolites translocation to the systemic circulation. The first barier eliminating toxins from the blood is the liver. An increased toxins, including polysaccharides, stimulates the activity of satelite cells and cytotoxic lymphocytes T in the liver. The liver diseases, such as hepatitis, primary sclerosing cholangitis, non-alcoholic fatty liver disease, and thrombosis, are frequently observed in patients IBD in clinical practice. Therefore, all the factors inducing dysbiosis should be eliminated and physiological intestinal flora should be restored in patients with IBD.

Liver diseases in immunocompromised patients

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Most cases of immunodeficiency are acquired (secondary) but some people are born with primary defects in their immune system. The latter are rather rare including, ataxia-telangiectasia, Chediak-Higashi syndrome, complement deficiencies, DiGeorge syndrome, hypogammaglobulinemia and many more. The form of immune disturbances may be a dominant factor for the type of liver disease. Patients with more common combined variable immunodeficiency disease are prone to have abnormal liver tests, particularly raised alkaline phosphatase levels. Some have nodular regenerative hyperplasia in liver biopsy with unexplained pathology.

More common acquired immunodeficiency includes HIV infection, but also drug-induced, autoimmune disorders and splenectomy, diabetes mellitus, cancer, and many more.

The course of hepatropic virus infections may be completely different from those in immunocompetent host. Occult HBV infection may reactivate during immunosuppressive therapy. Chronic courses of HEV infections with potentially life-threatening complications within immunosuppressed patients have been also described. The reliable diagnosis of infections is a challenge, as serologic tests do not reflect the status of infection. Opportunistic infections may affect liver and require extensive treatment with potentially hepatotoxic medications.

Another problem is hepatocellular cancer that could be the consequence of HBV and/or HCV infection. Some other uncommon tumors are described in immunocompromised patients. For example primary liver lymphomas are accounting for only 0.4% of all the extra nodal lymphomas. There are some reports of primary liver Burkitt's lymphoma that is extremely rare. The definitive diagnosis is based on biopsy.

Metabolic syndrome and the risk of cardiovascular complications after pediatric liver transplantation

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Introduction: Post-transplant metabolic syndrome (MS) is an important issue in pediatric recipients, however the real risk of organic damage in not established as yet. Diabetes, arterial hypertension, renal dysfunction, obesity and lipid disturbances may result from long-term immunosuppression. The aim of this study was to investigate components of MS and other risk factors of cardiovascular complications (CVC) in long-term pediatric liver transplant recipients.

Methods: We evaluated 105 patients (64 females) at the mean age of 14 years (range 10-18), 10.5 years after LTx (range 5.1-16.8) with long-term stable graft function and no significant changes in immunosuppression for at least 12 months (tacrolimus in 90%). We measured MS parameters, carotid intima-media thickness (cIMT), arterial stiffness by pulse wave velocity (PWV), left ventricular mass index (LVMI-S), relative wall thickness (RWT), lipid profiles including apolipoproteins, renal function, markers of oxidative stress glutathione (GSH), glutathione peroxidase (GPx), asymmetrical dimethyl arginine (ADMA) and oxidized low-density lipoprotein (oxyLDL). Biochemical results were compared to reference values or age and sex matched healthy control group (age 13.7, range 10-18; 57 females) as appropriate.

Results: Overall, at least one of MS component was present in 39% of patients however diagnostic criteria for MS were fulfilled in 6.6%. BMI was > 90th percentile in 14.2% and was more prevalent in males (21.9% vs. 9.3%), mean BMI-Z-score was 0.00671.1. Waist circumference > 90th percentile was in 16.4% and positively correlated with BMI. 8.5% of patients were hypertensive (SBP/DPB 1068.6/617.6 mmHg), fasting plasma glucose was ≥ 100 mg% in 17.1% (91.58.7), HOMA-IR was > 3.1 in 9.5% (2,050,73), triglycerides > 150 mg% in 4.7% (86.24.5) and HDLc < 40 mg in 12.3% (51.912.3). Median cIMT was normal in all patients (mean 0.370.03), PWV was > 95th percentile in 21.9% (mean 5.31.1), LVMI-S was > 95th percentile in 5.7% (mean 27.46.1) and RWT was > 4.1 in 6.6% (0.320.05). Renal function by cystatine-c was > 95th percentile in 10% (0.860.21) and did not correlate with GFR and creatinine. Extended lipid profiles were not significantly disturbed except ApoE which was lower in the study group (9.93.4 vs. 12.44.9, $p < 0001$). Oxidative stress markers were disturbed in the study group: ADMA 0.520.16 vs. 0.300.01 ($p < 0.0001$), GSH ($p < 0.001$) but not oxyLDL ($p = 0.51$) and GPx ($p = 0.14$).

Conclusions: Patients after paediatric liver transplantation present with increased risk of MS and cardiovascular disease. Increased arterial stiffness with concurrent normal cIMT requires further investigations to establish clinical significance. Some markers of oxidative stress which potentially plays role in atherosclerosis were increased in the study group.

8th Plenary Session
Varia

Does NAFLD, the growing global problem of indications for transplantation not apply to the Polish population?

Wojciech Lisik

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Nonalcoholic fatty liver disease (NAFLD) is an organ-specific manifestation of metabolic syndrome. The spread of this pathology is called a global epidemic, what, in consequence, may lead to that in the coming years its consequences will become the leading indication for liver transplantation. According to the guidelines of the American Association for the Study of Liver Disease (AASLD), NAFLD is caused by excessive accumulation of fat within the liver and covers a wide spectrum of pathologies ranging from simple mild steatosis, nonalcoholic steatohepatitis (NASH), to cirrhosis and even hepatocellular carcinoma (HCC). NASH is seen as an aggressive form of NAFLD, with a higher rate of complications and mortality, particularly in those with progressive fibrosis. NAFLD is not only a manifestation of the metabolic syndrome, but also a disease that promotes the onset of type 2 diabetes and cardiovascular complications. The prevalence of NAFLD is estimated at around 25% of the global population, and NASH at 2-5%. NAFLD in patients with type 2 diabetes mellitus (DM2) or pathological obesity reaches over 50% and 90% respectively, and NASH in this population increases to approximately 40%.

It is anticipated that by 2030, NAFLD will be the leading indication for liver transplantation. That is why so important from the point of view of both the patient and clinician becomes early identification of potentially high-risk groups and to develop appropriate therapeutic strategies.

Acute hepatic decompensation in peritransplant period – acute-on-chronic liver failure

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In 2013 a group of investigators under auspices of the European Association for the Study of the Liver (EASL), called EASL Chronic Liver Failure Consortium (EASL-CLIF Consortium), published the results of a large multicenter European study on acute decompensation of cirrhosis known as an acute-on-chronic liver failure (ACLF). The group proposed a new evidence-based definition and diagnostic criteria of ACLF which distinguish this dramatic condition from traditional decompensated cirrhosis. According to EASL-CLIF Consortium the term ACLF means acute complications of cirrhosis accompanied by multiorgan failure and high short-term mortality. It should be considered as a new clinical entity, because it differs from decompensated cirrhosis in many aspects:

- concomitant failure of at least one organ other than liver,
- higher short-term mortality in comparison with traditional decompensated cirrhosis,
- younger age at the time of decompensation,
- alcoholic etiology of cirrhosis in most instances,
- higher frequency of some precipitating events (sepsis, active alcoholism),
- higher level of systemic inflammation.

Not always the development of ACLF can be attributed to sepsis or active alcoholism; in many cases the etiology of ACLF remains unknown.

There are two other definitions of ACLF: one proposed by the North American Consortium for the Study of End Stage Liver Disease (NACSELD) and the other given by the Asian Pacific Association for the Study of the Liver (APASL). They are largely converging with the EASL-CLIF Consortium statements with a few exceptions: cirrhosis is not required to diagnose ACLF (NACSELD) and frequent precipitating factors can be chronic HBV infection and surgery but not sepsis (APASL). Central focus in all definitions is liver dysfunction defined as jaundice (serum bilirubin $\geq$ 5 mg/dl) and coagulopathy (INR > 1.5 or prothrombin activity < 40%). Acute hepatic insult is complicated within 4 weeks by ascites and/or encephalopathy.

Diagnostic criteria of extra-hepatic organ failures include:
– respiratory failure (mechanical ventilation),
– renal failure (dialysis),
– circulatory failure (shock),
– neurologic failure (grade 3-4 hepatic encephalopathy, HE).

ACLF is not diagnosed if the patients with cirrhosis have no organ failure(s) or there is single-organ failure (liver, coagulation, circulation, lungs) in patients with serum creatinine levels < 1.5 mg/dl and no hepatic encephalopathy, or there is single cerebral failure in patients with serum creatinine levels < 1.5 mg/dl. ACLF can be divided into 3 different groups – from grade 1 to grade 3 (Table 1).

Table 1. Definition and grades of ACLF

Definition	28-day transplant-free mortality risk (%)
No ACLF	4.7
Grade 1 ACLF Single kidney failure Single-organ failure (liver, coagulation, circulation, lungs) in patients with serum creatinine levels ranging from 1.5 to 1.9 mg/dl and/or grades 1-2 HE Single cerebral failure in patients with serum creatinine levels ranging from 1.5 to 1.9 mg/dl	22.1
Grade 2 ACLF Two organ failures	32
Grade 3 ACLF Three or more organ failures	78.6

The precipitating factors of ACLF (according to EASL-CLIF Consortium) can be the following:
– bacterial infection (spontaneous bacterial peritonitis – SBP, pneumonia, urinary tract infection, skin inflammation, etc.),
– active alcoholism within last 3 months,
– gastrointestinal haemorrhage (relatively rarely).

In approximately 45% of patients admitted to the hospital with ACLF there is no identifiable trigger for this syndrome.

It is worth mentioning that ACLF is not simply an end-stage cirrhosis. In almost half of the cases the ACLF develops despite the absence of a prior history of decompensation or develops shortly (< 3 weeks) after the first symptoms of liver failure. Interestingly, patients with no history of decompensation usually present with more severe form of ACLF in comparison with decompensated subjects.

The most important in the management of ACLF is prevention of precipitating events. It includes:
– earlier treatment of AKI,
– non-selective beta-blockers to prevent variceal haemorrhage,
– albumin infusion to prevent SBP.

Treatment of choice is liver transplantation, however, there is a high mortality on the waiting list and the surgery is considered a high risk procedure with a significant short-term mortality. A lot of controversies are around transplantation for ACLF related to active alcoholism.

References

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Heart failure patients qualified for liver transplantation

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The liver and the heart are organs that are closely related both in health and disease. The cardiac causes of hepatic dysfunction include constrictive pericarditis, severe arterial pulmonary hypertension, and congenital valve disease. All of these causes can lead to passive congestion due to the elevated right ventricular pressure and right sided heart failure. In chronic heart failure the increase venous pressure caused by RV dysfunction leads to the atrophy of hepatocytes and causes perisinosidal oedema, which can impair the diffusion of oxygen and nutrients to the hepatocytes. The stagnant flow favors thrombosis within sinusoids, hepatic venules and portal tracts; thereby contributing to liver fibrosis. Chronic cardiac hepatopathy is common in patients evaluated for heart transplantation, and liver dysfunction predicts an adverse outcome following transplantation.

Chronic liver diseases may affect cardiac functions in the absence of other heart disease. These effects are called cirrhotic cardiomyopathy and may aggravate the course during orthotopic liver transplantation. In patients with advanced liver disease, cirrhotic cardiomyopathy may develop including hemodynamic changes, diastolic and systolic dysfunctions, reduced cardiac performance and electrophysiological abnormalities. Cardiac evaluation is important for patients with liver diseases especially before and after liver transplanta-

tion. Liver transplantation may lead to the improvement of all cardiac changes and the reversal of cirrhotic cardiomyopathy. There are many systemic diseases that affect both the liver and the heart. The spectrum of theses diseases includes congenital (f.e. Allagile syndrome), metabolic (hemochromatosis, Wilson disease) and infections (cytomegalovirus, sepsis) causes. Collaboration between haptologists and cardiologists is needed in these categories of patients for better diagnosis, treatment and prognosis.

HCV treatment after liver transplantation

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Direct acting antivirals (DAA) used to treat HCV infection in transplanted liver recipients are characterized by very high efficacy and low side effects.

The choice of treatment regimen depends on several factors, such as the viral genotype, failure of previous treatment, renal function, and in the case of cirrhosis of the transplanted liver, the clinical stage of its advancement. The choice of drugs should also take into account the potential interactions with the medicines used by the patient, especially calcineurin inhibitors (cyclosporine, tacrolimus). Glecaprevir with pibrentasvir is recommended for all genotypes in patients without decompensated cirrhosis and can be used in patients with advanced chronic kidney disease. Ledipasvir with sofosbuvir and ribavirin can be used in all patients with a genotype other than 2 and 3. This is the best treatment regimen in patients with cirrhosis, and the only currently recommended in cases of clinically advanced cirrhosis (Child and B grade C). However, this regimen can't be used for chronic kidney disease in stages 4 and 5. Daclatasvir with sofosbuvir and ribavirin is recommended for the treatment of patients with genotypes 2 and 3 and cirrhosis of the transplanted liver.

Due to drug interactions, the use of cyclosporine with glecaprevir/pibrentasvir is not recommended. It is also important to remember about potential DAA interactions with other drugs often used in patients with liver transplantation, such as statins, calcium channel blockers or azole antifungals.

The choice of the time to start treatment after liver transplantation depends on the course of hepatitis C after transplantation but should be started as soon as stable immunosuppression is obtained.

There is much controversy about the increased risk of hepatocellular carcinoma (HCC) recurrence in liver transplant patients after DAA treatment, possibly related to changes in the immune system due to rapid HCV elimination.

The introduction of highly effective therapies has also opened up a field for discussing the possibility of liver transplantation from HCV-infected donors.

Ciclosporin A induces remission in steroid resistant AIH and AIH/PSC overlap syndrome

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Introduction: Autoimmune hepatitis (AIH) is a progressive inflammatory liver disease of unknown origin. Up to 49% of AIH cases may be concurrent with primary sclerosing cholangitis (PSC). Response to initial treatment is achieved in 90% AIH patients. In cases refractory to steroids, cyclosporin A (CsA) is introduced to induce remission. Our aim was to assess its efficacy in such an indication.

Methods: It is a retrospective, single center study. We describe a clinical characteristic of 33 children (18 F, 15 M), mean age 14 years, mean disease duration 37 months who underwent CSA treatment in the course of AIH and AIH/PSC in years 2005-2015. The primary endpoint was biochemical and histological remission/response at month 24 and the secondary one – liver transplantation rate. The clinical outcomes were related to biochemical, histological and demographic data at the beginning of CsA therapy.

Results: Biochemical and histological remission was achieved at month 24 in 11 out of 33 cases (33%). Liver transplantation has to be performed in 6 out of 33 (18%) cases. Statistical analysis showed that remission group had significantly higher number of platelets than group with no remission at the beginning of the CsA therapy: 215; 103; 343 vs. 91; 65; 186 [median; q1; q3] respectively.

Conclusions: CsA leads to remission in up to one third of AIH, AIH/PSC cases refractory to steroid therapy. Liver transplantation rate in his group is 18%. Patients with symptoms of hypersplenism have worse prognosis of CsA therapy.

POSTER PRESENTATIONS

The abstracts are printed in the form sent by authors, accepted by the Scientific Programme Committee.

Pediatric liver diseases

[1] Fatal rituximab-induced pulmonary fibrosis in a child with giant cell hepatitis with autoimmune hemolytic anemia

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Giant cell hepatitis with autoimmune hemolytic anemia (GCH with AIHA) is a rare, aggressive disease of young children with humoral immune mechanism. Conventional immunosuppressive treatment is often unsuccessful. Rituximab, an anti-CD-20 monoclonal antibody was described as effective, well tolerated, and safe in patients with GCH with AIHA so far.

13-month-old girl with cholestasis and anemia due to GCH with AIHA was treated initially with glucocorticosteroids and azathioprine, however with no effect. Four doses of rituximab (4×375 mg/m^2) were ordered and resolution of cholestasis and hematologic improvement were achieved.

The first symptoms of respiratory tract infection occurred three weeks after the last dose of Rituximab. Despite antibiotics treatment the girl developed pneumonia with pneumothorax and increasing respiratory failure and required mechanical ventilation.

Mycoplasma, *Pneumocystis carinii* and *Chlamydia pneumoniae* were excluded. Repeated CT scans revealed grand-glass opacity assessed as progressive interstitial pneumonitis after Rituximab treatment. Despite a variety of antibiotics, antimycotic drugs, methylprednisolone pulses, aggressive ventilation and ECMO (extracorporeal membrane oxygenation), respiratory failure worsened and the girl died 2 months after Rituximab treatment. We present the case as the first RALI (Rituximab-associated lung injury) in a patient with GCH with AIHA.

[2] Genetic variability of Polish pediatric patients with Wilson's disease

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Introduction: Wilson's disease is an autosomal recessive disorder of copper metabolism. The underlying cause is a mutation of ATP7B gene located on 13 chromosome. There are over 800 hundred mutations described to evoke WD. The aim of this study was to analyze the frequency of particular ATP7B mutations in relative big cohort of Polish pediatric population with WD.

Methods: 151 Polish children with WD diagnosed according to Ferenci scoring system had molecular analysis of ATP7B gene by direct sequencing of exons 1-21 performed.

Results: 284 mutated alleles with 41 different mutations were identified among investigated samples. In 18 children only one mutated allele was found. 189 out of 284 (66.5%) was p.H1069Q, 26 (9.1%) was p.A1135fs, 10 (3.5%) was p.Q1351X and 5 (1.8%) was W779X and p.R969Q (each). 3 further mutations (p.N1270S, p.G1158fs, p.E507fs) were found in 3 alleles (1.1%), 8 in 2 alleles and 24 in one allele each. 59 patients were homozygous for p.H1069Q mutation, 4 for p.A1135fs and 1 for Q1351X, R778G and G1158fs (each). Using the three most common mutations 86 of 151 (57%) children were diagnosed with two mutations in both alleles.

Conclusions: p.H1069Q is the most common mutation in Polish pediatric population with WD (with frequency up to 66%). Over 3/4 of all mutations are the three most common: p.H1069Q, p.A1135fs, p.Q1351X and using those mutations allow diagnosis in more than half of the patients. 44% Polish children with WD are homozygous.

[3] Phenotypic expression of various mutations in children with Wilson's disease

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Introduction: Wilson's disease is an autosomal recessive disorder of copper metabolism. The underlying cause is a mutation of ATP7B gene located on 13 chromosome. There are over 800 hundred mutations described to evoke WD and mutations within ATP7B are very heterogeneous. They can be divided into missense, nonsense and frameshift ones. The two last ones are regarded as severe because of more substantial changes in ATP7B protein. The aim of this study was to compare phenotypic expression of various types of ATP7B mutations in Polish children with WD.

Methods: Among 151 patients, 98 children had two missense alleles or only one missense allele detected without second mutation (mild group) and 53 remaining had at least one frameshift or nonsense mutation (severe group). The demographic (age at onset and age at diagnosis), clinical (hepatomegaly, splenomegaly, ascites, jaundice), laboratory (AlAT, AspAT, INR, bilirubin, complete blood count, albumins) and copper metabolism (ceruloplasmin, 24h-urine copper, liver copper) data before pharmacological therapy was started was compared between both groups. *U*-Mann-Whitney test was used and $p < 0.05$ was regarded as significant.

Results: No changes were found between demographic, clinical and laboratory data between both groups. Severe group had significantly lower concentration of ceruloplasmin: 9; 3; 11 [median; Q1; Q3] vs. 15; 11; 18. No differences in 24h-urinary and liver copper were found.

Conclusions: Nonsense and frameshift mutations disturb copper metabolism more than missense ones. They have no influence on clinical presentation of WD in Polish children.

[4] Biliary atresia coexisting with Gilbert's syndrome – diagnostic and therapeutic difficulties

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7.5-year-old girl with hyperbilirubinemia was admitted to the Department of Gastroenterology, Hepatology, Feeding Disorders and Pediatrics, The Children's Memorial Health Institute for further investigation. In the neonatal period, she was diagnosed due to hyperbilirubinemia. Clinically, she had jaundice and acholic stools. The laboratory tests showed cholestasis with elevated bilirubin level total (19.8 mg/dl) and conjugated (4.6 mg/dl). In abdominal ultrasound gall bladder was not found. Liver biopsy was performed and histopathological examination confirmed biliary atresia. The infant had undergone Kasai procedure in the 5th week of life. Despite a good response to the surgical treatment, elevated total bilirubin level and unconjugated bilirubin level as well as a periodic increase in transaminases and GGT activity were observed. The girl twice had cholangitis. She is under the care of the nephrologist because of the horseshoe kidney and the otolaryngologist due to bilateral hearing loss. Due to persistent hyperbilirubinemia, with other laboratory tests within normal limits and without clinical symptoms, a molecular examination was performed in which variant (TA) 7 in the UGT1A1 gene was detected. On this basis, Gilbert's syndrome was diagnosed. This syndrome may accompany other liver diseases and very often goes asymptomatically.

[5] Allopurinol administered with azathioprine for autoimmune hepatitis (AIH) treatment allows do decrease azathioprine dose – case report

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Allopurinol, alters azathioprine metabolism and allows to decrease dose of azathioprine.

We present a case of 6 years old girl with acute onset of autoimmune hepatitis [hepatosplenomegaly, hypertransaminazemia (ALT 2100 U/l), hyperbilirubinemia (3.9 mg%), positive LKM (1 : 81820) increased concentration of IgG (2200 mg/dl), gamma-globulins (25.7 g/l) and biopsy proven high inflammation and mild cirrhosis (G3/S1 according to Batts and Ludwig scale)]. Patient received standard prednisone and azathioprine therapy with rapid decrease of liver function tests and reduction of the therapy to maintenance doses of prednisone and azathioprine.

Three years later liver function tests deteriorated. Patient had mild steroid-related symptoms thus over the next 6 months the azathioprine dose was increased under control of blood 6-thioguanine level from 37.5 mg (1.5 mg/kg) to 150 mg (5.5 mg/kg) but therapeutic concentration of 6-thioguanine in blood was not achieved and ALT activity remained increased. Due to inadequate therapeutic effect we decided to modify therapy. The steroids was continued, azathioprine dose was lowered to 25 mg/d and allopurinol (25 mg/d) was added to increase azathioprine metabolites. This approach increased blood 6-thioguanine levels to therapeutic values however ALT was not normalized and ALT flares requiring increase of steroid doses were noted. Four years after diagnosis liver biopsy showed mild inflammation and fibrosis (G1/S1) and patient continues on deflazacort, low dose of azathioprine (25 mg/d) and allopurinol (25 mg/d).

The case presents that allopurinol can alter the azathioprine metabolism allowing for decrease of the azathioprine dose but it does not necessarily effect in normalization of ALT.

[6] LiverMultiScan™ – non-invasive assessment of paediatric liver disease

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Introduction: Liver biopsy is the gold standard for evaluating liver pathology, but it is risky, costly and lacks validation in paediatric populations. MRI-derived iron corrected T1 (cT1) is a promising technique that has demonstrated utility in stratifying patients with liver disease in adults. This study is aimed at evaluating this MRI based technique in a large sample of children with liver disease. Here we present the preliminary results.

Methods: We investigated 35 paediatric patients (14 male; mean age 12.7 [range 6-17 yrs] with various liver diseases (AIH (n = 24), AIH/PSC (n = 3), Wilson disease (n = 2), other (n = 7)), and 8 healthy controls participants (3 male; mean age 13.6 yrs. [range 7-18 yrs.]). All patients received liver biopsy to stage for Ishak fibrosis and grade for steatosis, lobular and portal inflammation, and ballooning. A composite disease score was also calculated as the sum of these pathology grades/stages. All participants underwent multi-parametric MRI with the LiverMultiScan™ protocol (acquisition time < 5 mins) from which cT1 maps were derived. High cT1 indicates inflammation and/or fibrosis, with cT1 > 875 ms correlating with liver-related outcomes in adults. Correlations between variables were performed using Spearman's Rho, and comparisons between groups were performed using two-sided Kolmogorov Smirnov (KS) tests.

Results: cT1 was significantly higher in patients (876 ms) versus controls (781 ms; $p < 0.01$). cT1 correlated with ballooning (rho = 0.52; $p < 0.001$), liver fibrosis (rho = 0.51; $p < 0.001$), the composite disease score (rho = 0.50; $p < 0.001$), portal inflammation (rho = 0.47; $p = 0.0014$) and lobular inflammation (rho = 0.43; $p = 0.0042$). cT1 had an AUROC of 0.91 (95% CI: 0.75-1) for discriminating patients from controls, with a sensitivity, specificity, PPV and NPV of 0.7, 1.0, 1.0 and 0.5, respectively, at a threshold of 815 ms.

Conclusions: Early results indicate that LiverMultiScan™ is an effective, fast and non-invasive technique for stratifying children with liver disease.

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[7] Recurrent acute liver failure triggerd by acute pancreatitis in 3-year old girl – case report

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Introduction: Acute liver failure (ALF) in children is a very rare and life-threatening condition. In about 50% of cases, the etiology remains unknown, which makes it difficult to make decisions about the best treatment method, including liver transplantation. We present the case report of recurrent ALF triggered by acute pancreatitis and succesfully treated medically.

Case report: We present 3-years old girl who was hospitalized in 2014 for the first time, because of vomiting and abdominal pain. She was admitted to the hospital in serious general condition with progressive deterioration of neurological state. The results of laboratory tests showed hypoglycemia, hyperamylasemia, severe coagulopathy, hyperammonemia, high lactate and slightly increased ALT/AST activity and bilirubin. She was transferred to Intensive Care Unit because of worsenig clinical condition, symptoms of encefalopathy, heart arythmia and cerebral edema. CT scan showed hepatomegaly, fatty liver and enlargement of the pancreas. Treatment with glucose infusion, plasma, coagulation factors, proton pump inhibitors and mannitol was started. Due to the unclear background of the observed disorders and the suspicion of mitochondrial DNA depletion, a liver biopsy was performed in which hepatic steatosis was found. So far, there were 9 similar episodes of ALF, each accompanied by pancreatits. Early introduction of medical treatment, including stimulation of anabolism by intensive glucose infusions, prevented from neurological deterioration and successfully ameliorated liver crises. Exome sequencing detected SPINK1 mutations responsible for pancreatic flares. No mitochondrial disorder was confirmed so far but additional genetic studies are planned.

Summary: Recurrent ALF in children is rare but severe condition, usually triggered by infections We presented unique fenotype were recurrent ALF was induced by pancreatits. Early introduction of treatment stimulating anabolism is crucial in effective treatment.

[8] 13-year-old boy with FNH, after treatment for retinoblastoma

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Focal nodular hyperplasia (FNH) is a benign, solid hepatic tumor of so far unknown pathogenesis. In children it is approximately 2-7% of all tumors of the liver. In the pediatric population with oncological history, after radio- or chemotherapy, the risk of developing FNH is up to 10 times higher than in the healthy population.

The described case concerns a 13-year-old boy being treated for sporadic binocular retinoblastoma diagnosed in the 8th month of life. Numerous chemotherapy protocols were used in the treatment. Due to the complications of chemotherapy, the boy required an enucleation of the left eye. When he was about 3 years old, there was a recurrence of the tumor in the right eye. The patient was qualified for brachytherapy. Despite the treatment, the right eye enucleation was necessary. At the age of nearly 9 years, an abdominal ultrasound was performed in which numerous focal lesions of the liver were described. The boy did not report any complaints. The level of alpha-fetoprotein was normal. In CT scan four hyperdense areas, poorly distinguishing themselves after administration of contrast agent, the largest with a diameter of 33 mm, were visualized. To verify the diagnosis, a liver laparoscopic biopsy was performed. Microscopic analysis confirmed the diagnosis of FNH. The patient remains under observation.

In most cases, diagnosis of FNH is possible on the basis of imaging studies, however, in patients with a history of cancer, it may require invasive diagnostic methods.

[9] Is there an increased risk of liver steatosis in children with type 1 diabetes mellitus?

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Introduction: Adult patients with type 1 diabetes mellitus (DM) are at an increased risk for non-alcoholic fatty liver disease (NAFLD). At present NAFLD detection is based on ultrasound (US) and elevated levels of ALT. Due to limited sensitivity of this assessment we applied transient elastography of FibroScan® with option Controlled Attenuation Parameter (CAP). The aim of our study was to find out whether pediatrics patients with type 1 DM have liver steatosis in FibroScan® measurements and compared the results with overweight/obese patients. As recent studies in large pediatric population assessing hepatic steatosis in children using different tools and FibroScan® with CAP found that optimal threshold to detect steatosis is CAP > 249 dB/m with sensitivity 72% and specificity 98%.

Methods: In all groups of patients (type 1 DM, overweight/obese and lean control) NAFLD was primarily excluded based on normal US and ALT value. We used liver steatosis measurements by FibroScan® with CAP option for more precise assessment of hepatic steatosis and stiffness of the liver in 3 groups of patients matched for age (age 8-18 years). The anthropometric measurements (BMI, waist and chest circumference) and body composition (BC) like lean body mass (LBM) and adipose tissue (AT) were also done in type 1 DM and overweight/obese patients. We analyzed 37 patients with type 1 DM, 43 patients with overweight/obesity and 21 lean controls. For group comparison we used Mann-Whitney *U* test and Kruskal-Wallis test and simple linear regression for correlation analysis.

Results: There were no differences in age among groups overweight/obese patients and with type 1 DM (median age 13.4 yrs vs. 14.1 yrs). The control group was slightly younger (median age 12.1 yrs). The median steatosis measured by CAP in group overweight/obese patients was significantly higher – 242 dB/m (range 126-400) than in patients with type 1 DM – 202 dB/m (range 102-318) and controls – 200 dB/m (range 132-261) ($p < 0.05$). There were no significant difference between patients with type 1 DM and controls ($p = 0.9393$). There were no significant difference in liver fibrosis (E) measured by FibroScan® between all groups. Median SDS BMI in overweight/obese patients was 1.98 (range 1.21-3.26), in type 1 DM patients –0.06 (range –2.26-2.23) and in controls median was –0.55 (range –2.26-0.77). In children with type 1 DM CAP values correlated with age and all anthropometric parameters (BMI, waist circumference, %LBM and %AT) (r2 range 0.12 to 0.16, $p < 0.05$). There were no significant correlation compering E values with this parameters ($p > 0.05$). 28% (12/43) patients with overweight/obesity, 19% (7/37) patients with type 1 DM and 9.5% (2/21) controls received CAP > 249 dB/m using FibroScan® which is suspected to be early stage of liver steatosis.

Conclusions: 1. Children with type 1 DM do not indicate a significantly increased prevalence of NAFLD compared to lean controls. 2. Increased risk of liver steatosis in children with type 1 DM is associated with unfavourable anthropometric factors.

Other liver disorders

[10] Ataxia telangiectasia as a rare cause of non-alcoholic steatohepatitis

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Introduction: Ataxia telangiectasia (A-T) is an autosomal recessive disorder characterized by cerebellar degeneration, telangiectasia, immunodeficiency, cancer susceptibility and radiation sensitivity. We present a case of a 21-year-old women with A-T and non-alcoholic steatohepatitis (NASH).

Case presentation: Patient with a height of 160 cm and body mass index of 21 kg/m^2 was referred to hospital for elevated serum transaminases (ALT 112 U/l, AST 81 U/l). She was diagnosed with A-T in infancy. Her history included acute hepatitis due to EBV infection and recurrent sinusitis. Following abnormalities were found in laboratory tests: alpha-fetoprotein level (AFP) > 1000 IU/ml, GGTP 205 U/l, cholesterol 235 mg/dl, triglycerides 404 mg/dl and elevated serum glucose level. Diabetes mellitus (DM) was diagnosed and insulin therapy was started. In abdomen ultrasound hepatomegaly and liver steatosis were described. Liver biopsy showed characteristic features of NASH: activity score 7 (steatosis grade 3, lobular inflammation 2, hepatocellular ballooning 2) and fibrosis score 2. Other chronic liver diseases (Wilson disease, HBV and HCV infection, autoimmune hepatitis, α-1 antitrypsin insufficiency) were excluded.

Conclusions: High level of AFP is typical for the majority of individuals with A-T. Metabolic disorders are already observed in adolescent A-T patients. The screening tests for DM, liver involvement and dyslipidemia should be performed regularly in those patients. Dietetic modification and appropriate treatment should be started if needed.

[11] Serum irisin level a new possible marker of HCC progression

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Introduction: Hepatocellular carcinoma is 5 most common cancer in the world. The main factor related to oncogenesis is liver cirrhosis, with many etiology among them NAFLD. Irisin is adipomiokine with anabolic activity, it serum level raises in after physical activity, in metabolic syndrome, diabetes, obesity. The aim of this study was assume serum level of irisin among patient with liver cirrhosis and liver cancer.

Methods: 79 patients with liver cirrhosis, 48 with liver cirrhosis and HCC and control 21 patients with liver cirrhosis was included. Measurement of fasted irisin level was made with irisin Elisa test (Biovendor, Cze), Skanit RE for Multiscan GO3.2. Statistica analyses and test TIR Turkyea were performed.

Results: 69 patients: 54 men (78.3%), 15 women (21.7%). Patients with HCC were divided in 3 groups: BCLC A – 12 patients (25%), B – 20 patients (42%), C – 16 (33%) patients. Patients were classified in CHP: A – 36 patients (52,18%), B – 27 (39.1%), C – 5 (8.9%). 29 had raised glucose level (42%), diabetes were confirmed in 27 patients (39%), BMI higher than 30 in 30 patients (43%). Medium irisin level among all patients was 2.73 (min 0.411 – max 4.75 μg/ml), among BCLC A m = 3.2972 μg/ml, BCLC B m = 2.5409 μg/ml, BCLC C m = 2.1058 μg/m; difference between BCLC A and C was significant ($p = 0.02$), less between A and B ($p = 0.47$).

Conclusions: Serum irisin level may be useful in assessment liver progression patients with hepatocellular carcinoma with liver cirrhosis and progression from stage to stage in BCLC scale.

[12] Late-onset lysosomal acid lipase deficiency – clinical outcome in 19 Polish patients

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Introduction: Lysosomal acid lipase deficiency (LAL-D) is a rare autosomal recessive lysosomal lipid storage disorder that results in an early-onset, severe and lethal phenotype, known as Wolman disease, or a late-onset, attenuated phenotype, cholesteryl ester storage disease (CESD). The aim of our study was to describe the clinical outcome of CESD, focusing on the first noted abnormalities in patients. A diagnostic algorithm of CESD was also proposed.

Methods and results: This is a long-term, observational, one-centre study of 19 Polish patients with late-onset LAL-D. The mean age at which the first symptoms were reported was 4 years and 6 months. A mild hepatomegaly was the most common initial abnormality observed in all (100%) patients. Seven (37%) patients were noted to have mildly to moderately elevated serum transaminases. At the time of first hospitalization in our clinic, all (100%) patients presented with hepatomegaly, 15 (79%) patients presented with elevated serum transaminases and all (100%) patients had dyslipidemia. The mean age at the time of CESD diagnosis was 7 years and 2 months. Diagnoses were based on a deficient LAL activity in leukocytes (in all patients) and the LIPA gene mutations (in 47% of them). All the patients were carriers for the mutation c.894G>A in the LIPA gene. There was approximately a 3 year delay from initial symptoms to final diagnosis.

Conclusions: Hepatomegaly constitutes the most common presenting clinical symptom of CESD. Hepatomegaly and dyslipidemia defined as elevated serum total and LDL cholesterol, elevated triglicerydes and normal to low HDL cholesterol, comprises the most characteristic symptom at CESD diagnosis.

[13] Long-term follow-up of Polish transaldolase deficient patients

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Introduction: Transaldolase deficiency (TALDO) is a rare inborn autosomal recessive error of the pentose phosphate pathway that, to date, has been diagnosed in 33 patients. There are few reports regarding the long-term follow-up of these patients. The aim of our study is to present the disease progression in the form of a systematic long-term follow-up of four Polish patients with TALDO.

Methods and results: We report four patients who manifested early onset TALDO. They were monitored with systematic clinical and laboratory examinations for 4-13 years. The dominant feature was an early liver injury, with subsequent renal tubulopathy. All patients presented with osteopenia and poor physical development. Our data shows that polyol concentrations seem to decrease with age.

Conclusions: In our patients, a progressive coagulopathy was the most sensitive parameter of liver dysfunction. Nodular fibrosis of the liver developed over the natural course of TALDO. This is the first report of long-term systematic clinical and biochemical monitoring of the disease progress in patients with TALDO.

Liver cirrhosis and its complications

[14] HCC radio-frequency ablation outcome – one center experience

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Introduction: Radio-frequency ablation (RFA) is a surgical procedure with well-proven effectiveness comparable to resection. It is a preferable method in patients with progress of liver cirrhosis due to higher risk of liver failure after resection. RFA is also less invasive and better tolerated by patients in worse general condition. However, HCC has a poor prognosis with one-year overall survival less than 50%. We present the RFA operations' outcome, differentiating on primary or recurrent tumor character.

Methods: 98 patients were qualified for RFA in years 2012-2017. Main etiology was HCV (74.5%) infection, HBV (7.1%), and combined HBV+HCV (6.1%). Primary tumors were in 64 (65.3%) patients and recurrent in 34 (34.7%). Mean total tumor diameter was 3.1 cm (0.8-11.5 cm). Twenty-five (25.5%) patients were in "0" BCLC group (less than 2 cm). In 13 (13.3%) cases multiple lesions were noted.

Results: In the whole observed group one-year recurrent-free survival (RFS) reached 61.6%, and two-year – 31.3%. Mean time to recurrence was 344 days (56-1342). In the group of 44 (68.8%) primary tumors recurrences were found after mean time of 370 days. In the group of operated recurrent tumors – 20 (58.8%) secondary relapses were observed after mean time 287 days. No statistically significant differences were found between both recurrence ratios (58.8% vs. 68.8%, $p = 0.33$) and time periods of tumor reappearance (287 vs. 370 days, $p = 0.09$).

Conclusions: Although, the recurrence rate is high the RFA outcome is better than overall HCC patients' survival. Prognosis is similar for primary and secondary operations.

[15] Nonalcoholic fatty liver disease, obesity and diabetic polyneuropathy

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Introduction: NAFLD (non-alcoholic fatty liver disease) is a serious public health problem. Prevalence of the disease increases parallel with type 2 diabetes mellitus (DM2T) and metabolic syndrome. NAFLD is associated with increased morbidity and mortality and is directly related to the occurrence of cardiovascular diseases. The aim of the study was to detect the incidence of severe liver fibrosis and diabetic polyneuropathy (DN) in patients with DM2T with overweight/obesity.

Methods: In 2017 we examined 185 patients with DM2T in our clinic. We performed by each of them: ultrasonographic examination of abdominal cavity (USG), transient elastography, ECG, differential diagnostics of liver diseases. We completed a standardized Michigan questionnaire and screening test to detect diabetic polyneuropathy (Neurotest).

Results: We investigated a total of 185 patients (103 women/82 men). Overweight had 65/185 patients (35.2% – BMI 27.5 kg/m^2), obesity 120/185 patients (64.8% – BMI 35.4 kg/m^2). All patients had liver steatosis in the USG. The Fibroscan examination was performed in 165/185 patients (89%), severe fibrosis was detected in 109/165 patients (66.1%). Arterial hypertension occurred in 133/185 patients (72%), dyslipoproteinemia in 179/185 patients (96.7%). The presence of DN was detected in 59 patients (32%).

Conclusions: NAFLD is a multisystem disease which plays an important role in the development of atherosclerosis, DM and other cardiometabolic diseases. DM 2 type and arterial hypertension are the most important risk factors for the progression of NAFLD. It is necessary to educate diabetics about NAFLD, metabolic syndrome and DN in multiple ambulances.

[16] The occurrence of autoantibodies in patients with primary biliary cirrhosis in different stages

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Introduction: The detection of autoantibodies and typical liver histology in patients with chronic cholestatic disease belongs to the most important criteria the in diagnosis of primary biliary cirrhosis (PBC). The aim of this study was to analyze the presence and pattern of serum autoantibodies in 35 patients with PBC by indirect immunofluorescence (IIF) and immunoblotting technique in comparison the liver microscopical changes.

Methods: A total of 35 PBC patients with a liver biopsy were included in the study. We analyzed the presence of serum autoantibodies in 18 patients, who were AMA positive and in 17 patients, who were AMA negative by IIF. The immunoblotting technique showed that out of 17 IIF AMA negative patients, 6 were positive for antibodies against M2-3E (BPO) and 4 were positive for AMA M2. Patients positive for AMA M2 were also positive for autoantibodies against M2-3E(BPO). In addition, the detection of antinuclear and anticytoplasmic autoantibodies by immunoblotting techniques allowed to diminish the group of autoantibody negative patients – finally only 5 patients with the clinical and histologically proven PBC diagnosis did not show any serum autoantibodies.

Results: The histological stage of the disease did not correlate with the presence of autoantibodies.

Conclusions: We concluded that immunoblotting techniques proved to be an effective alternative method to IIF in the diagnosis of PBC. The determination of AMA M2 and antibodies against M2-3E(BPO) as well as antinuclear and anticytoplasmic autoantibodies by immunoblotting may provide reliable diagnostic support especially in seronegative PBC patients.

Varia

[17] Effectiveness of lifestyle modification on treatment of metabolic syndrome

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Introduction: Metabolic syndrome significantly increases morbidity and mortality, impairs quality of life and brings serious socio-economic problems. The aim of the study was to find out whether the non-pharmacological treatment of metabolic syndrome will positively affect values of total CHOL, triglycerides (TG), HDL LDL, uric acid (KM) and glycemia. We have also been interested in the question of possible correlation between severity of obesity and the presence of liver fibrosis.

Methods: We developed a complex specialized two-week stay aimed at weight reduction. During this stay clients gain new knowledge regarding proper diet and physical activity while being under medical supervision. During the stay they undergo testing for early detection of cardiovascular disease and liver diseases (ultrasound scan of the abdominal cavity and examination on Fibroscan 502 touch device).

Results: 184 clients has completed the weight reduction stay. Average weight loss was 3.8 kg, waist circumference was reduced by an average of 5.5 cm. The values of weight loss and waist circumference reduction were highly statistically significant ($p = 0.001$). Transient elastography was applied on clients at the beginning of the course. It could be realized with 165/184 clients (89.6%). We conducted a correlation analysis of the relation of BMI and the degree of liver fibrosis. The degree of fibrosis increases with the increasing degree of obesity. We took clients control samples at the end of their weight reduction stay. The values of decrease in total CHOL, TG, LDL, and blood glucose levels were highly statistically significant ($p = 0.001$).

Conclusions: The most effective method in the prevention and treatment of metabolic syndrome is targeted intervention aimed at improving dietary habits, increasing physical activity and overall change of ones' lifestyle.

[18] Urinary kynurenine in alcohol-dependent persons

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Background: Kinurenine (KYN) present in the urine, is a product of the kynurenic pathway of tryptophan (TRP). The concentration of the urinary kynurenine depends on the amount TRP in diet, efficiency of the kynurenine pathway and renal excretion. There are currently no scientific reports about the impact of ethyl alcohol abuse on kynurenine concentration in urine, which became the reason for our research.

Material and methods: Control group was 10 healthy men, not abusing alcohol at the age of 36.0 ± 13.9 years and research group was 10 addicted men, aged 36.1 ± 9.0 years, admitted to hospital at the end of multiple alcohol intoxication (150-800 g of ethanol/day). The urine was collected on day 1 and 10, after stopping alcohol intoxication. The concentration of urinary kynurenine was analyzed fluorimetrically by measuring the fluorescence at 330/415 nm (Borys *et al*. 2017) and was expressed in arbitrary fluorescence units (AFU). $P < 0.05$ was considered statistically significant.

Results: There were no significant differences in concentration of kynurenin in the urine of men in the 1th day of abstinence compared to healthy men who do not abused alcohol. Urine kinureniun concentration significantly increased at 10th day of abstinence ($p < 0.05$) as compared to healthy, non-abusing males ($p < 0.001$).

Conclusions: The study presents proof that withdrawal of alcohol and its metabolites from the organism increases the formation and/or urinary excretion of kynurenine.

[19] Liver condition and alcohol intake – analysis of autopsy cases

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Material and method: 235 autopsy protocols of people who were known to be alcohol addicts or died because of alcohol intoxication were analysed. Autopsies were performed in 2015 and 2016 in Forensic Medicine Department, Wroclaw Medical University. In each case a liver sample was collected and detailed histopathology was performed. In 163 cases blood samples (taken during medico-legal autopsies) were analysed with immunoenzymatic assay in VIDAS system, for presence of HBsAg, anti-HBc Total IgG and anti-HCV. Autopsy protocols were checked for signs of alcoholic disease, comorbidities, blood alcohol concentration and death circumstances. In the research group, 54 were women; the cadavers' age ranged from 24 to 81, average was 52.

Results: 49/235 (20.9%) had 0 or 1st degree of steatosis (in Dixon scale), 29/235 (12.3%) – 2nd degree, 55/235 (23.4%) – 3rd, 103/235 (43.8%) – 4th. In most cases both micro- and microvesicular steatosis was found. Inflammation (grading) was diagnosed in 105/235 (44.7%); 2nd and 3rd degree in 27/105 (25.7%); fibrosis in 93/235 (39.6%); 3rd degree – 6/93 (6.5%), 4th – 28/93 (30.1%). 28 cadavers (10 women) had liver cirrhosis, 8 had decompensated cirrhosis (6 ascites, 4 variceal bleeding). 20/232 (8.6%) were cachectic, but most od cadavers were overweight (55/232; 23.7%) or obese (45/232; 19.4%), 20/28 had 4th degree of steatosis. During the death 157/228 (68.9%) people were intoxicated by ethanol, 5 by non-consuming alcohol; 29 had severe metabolic acidosis due to earlier alcohol intake. In the whole group anti-HCV was found in 9/163 (5.5%), HBsAg in 35/163 (13.2%), 19/163 (7.2%) had markers of occult HBV infection.

Conclusions: In a group of patients with alcohol addiction typically severe liver steatosis (grade 3 and 4) is observed. Nearly half of those patients are overweight or obese. In almost 1/5, an additional factor damaging the liver is a hepatitis viral infection. In half of the cases of sudden deaths in alcohol-addicted patients, intoxication was determined to be the initial cause of death.

Infections (viral, bacterial, parasitic)

[20] Interferon-free therapy with and without ribavirin for genotype 1 HCV cirrhotic patients

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Introduction: In the interferon era patients with HCV-related cirrhosis were considered hard to treat due to contraindications to therapy, safety issues and poor response. We have investigated interferon-free regimens in cirrhotic patients in real-world practice.

Methods: We analysed data of HCV infected patients with liver cirrhosis conducted in 22 Polish hepatology centers. They were assigned to treatment schedule based on physician decision. Data were collected retrospectively using the online questionnaire.

Results: A total of 1113 patients infected with genotype 1 HCV were enrolled to the analysis, 96.6% presented GT1b infection. 56% of them were treatment-experienced, mostly with PegIFN+RBV. 77.2% presented comorbidities with the most frequent hypertension and diabetes. 73.2% patients were treated with concomitant medications. 31% of study cohort was assigned to RBV-free regimen, majority of them to OBV/PTV/r+DSV. Overall, 94.7% patients achieved the sustained virological response in intent-to-treat analysis, with comparable rate for RBV-free and RBV-containing options (94.2% vs. 94.9%). Treatment course was more often modified in RBV-containing group, whereas rate of discontinuation was the same for both cohorts. Adverse events were observed in 41% with the most common weakness/fatique; more frequently in RBV-containing regimens (43% vs. 36.6%). Serious adverse events were reported in 4.1% patients, more often in RBV-free cohort (4.9% vs. 1.2%). Sixteen deaths not related to study drugs were documented, mostly in RBV-containing group.

Conclusions: We confirmed effectiveness of the interferon-free regimens without ribavirin in real-world cohort of cirrhotic patients with chronic HCV infection genotype 1. Therapy was well tolerated with infrequent adverse events.

[21] Efficacy of paritaprevir/ritonavir/ombitasvir+dasabuvir and ledipasvir/sofosbuvir is similar in patients who failed IFN-based treatment with first-generation protease inhibitors

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Introduction: According to EASL and AASLD guidelines, the recommended treatment for patients who failed to achieve a sustained virologic response (SVR) on prior interferon-based triple therapy with protease inhibitors (PI), is a combination of sofosbuvir and NS5A inhibitors. Polish national recommendations also allow the use of paritaprevir/ritonavir/ombitasvir +dasasbuvir ribavirin (PrODR) in this group of patients. The aim of the study was to evaluate the efficacy and safety of PrODR vs. ledipasvir/sofosbuvir RBV (LSR) in PI-experienced patients in real-life setting.

Methods: Our analysis included patients registered in the nationwide, investigators initiated, multicentre EpiTer-2 database. Among 4530 patients registered, 335 with genotype 1 (95% 1b) were previously treated with IFN-based regimens with PIs: 127 with boceprevir (BOC), 208 with telaprevir (TVR). Patients with advanced fibrosis (F3/F4) were significantly predominant (BOC 28.4%/61.4%, TVR 18.8%/64.4%, respectively). Subjects were assigned to IFN-free retreatment as follows: BOC – 64 (50.4%) PrODR and 63 (49.6%) LSR; TVR – 103 (49.6%) PrODR and 105 (50.4%) LSR.

Results: SVR rates were similar for particular groups: BOCíPrODR – 100%; BOCíLSR – 97%; TVRíPrODR – 97%; TVRíLSR – 97% (intent-to treat analysis – ITT) and BOCíPrODR – 100%; BOCíLSR – 98%; TVRíPrODR – 99%; TVRíLSR – 98% (modified intent-to treat analysis – mITT).

Conclusions: Both treatment regimens had a favourable safety profile. Adverse events (AEs) were generally mild or moderate in severity. Two deaths were reported (not treatment-related). The treatment was stopped due to AEs in five patients (three treated with PrODR and two with LSR). Efficacy and safety of treatment with PrODR and LSR is similar in BOC or TVR-experienced patients.

[22] Decreased hepatocellular carcinoma (HCC) recurrence rate after postoperative direct-acting antivirals treatment

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Introduction: Recently administrated new interferon-free direct-acting antiviral (DAA) therapy caused major progress in HCV treatment. Although the outcome is promising, there are reports of increased number of HCC recurrence after surgery in patients treated with DAAs. Influence of DAA therapy on timing and frequency of the recurrence after surgical treatment needs further observation.

Methods: One hundred six patients with liver cirrhosis caused by HCV and a history of previous surgical treatment for HCC in 2012-2017, were analyzed in a case-control study. 26 (24.5%) patients received DAA therapy after tumor remission achieved by surgery and 80 (75.5%) of them didn't (NDAA group). Follow up included multiphase CT-scan or MRI of the liver and AFP level in 3- to 6-month intervals.

Results: Positive response for DAA treatment, defined as SVR, was noted in all cases (100% SVR). HCC recurrence was observed in 9 (32%) patients from DAA group and in 55 (69.1%) from NDAA group ($p = 0.02$). Relapse occurred within 295 days after surgery in DAA group vs. 414 days in NDAA group ($p = 0.089$). One-year recurrence-free survival (RFS) rate was 75% vs. 62% respectively DAA and NDAA group ($p < 0.05$).

Conclusions: There is a lot of reports that show opposite results of DAA treatment use according to HCC recurrence. This study proves significantly decreased recurrence rate after DAA therapy. However, tumor relapse may occur faster than in no DAA group. Therefore, there is a need to perform multi-center study concerning more factors to allow multivariate analysis of bigger patients' groups.

[23] "Exotic" hepatomegaly: case of severe visceral leishmaniasis in a traveler after stay in India

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Introduction: In recent years South-East Asia, including India has become one of the most popular destination for Polish tourists. Indian subcontinent is an endemic region for visceral leishmaniasis (kala-azar disease), multiorgan disease which is a life-threating condition. Due to severity of clinical course and poor prognosis, visceral leishmaniasis, apart from malaria, must be included in differential diagnosis of patient with hepatomegaly and fever after stay in tropics.

Methods: In May 2017 there was an urgent admission to the Department and Clinic of Tropical and Parasitic Diseases in Poznan of a 41 y.o. patient (R.C.) who suffered from general malaise, fever to 40°C, chills, intensive sweating and diarrhea that had lasted for 3 weeks before admission. In epidemiological anamnesis there had been a motorcycle tour across India between 15th and 30th of March 2017. In pre-travel preparation, patient had undergone vaccinations recommended in international tourism. During his trip he took antimalarial chemoprophylaxis, but did not used mechanical barriers against bites of flying bugs. On the basis of the epidemiological anamnesis, clinical picture, pathological laboratory results (pancytopenia, increased inflammatory markers, hipergammaglobulinaemia, hipertransaminasemia, hepatosplenomegaly) and positive result of Western blot patient was diagnosed with severe visceral leismaniasis. Intravenous amphotericine B that was used in causal treatment was tolerated well and caused clinical recovery and improvement of laboratory tests.

Conclusions: The main role in reduction of the risk of acquiring visceral leishmaniasisis is non-pharmacological prophylaxis that is based on protection against insects. Differential diagnosis of hepatosplenomegaly should include exotic parasitic diseases.

[24] Hepatitis E virus (HEV) seroprevalence in Wielkopolska Region, west-central Poland: a comparison over a 6-year period (between 2009 and 2015)

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Introduction: There is emerging evidence that hepatis E virus (HEV) infection is an under-recognized issue in Poland. Moreover, Wielkopolska Region (west-central Poland) seems to be a hyper-endemic area for this virus. Reports from some European countries have shown changing HEV seroprevalence over time. The aim of the present study was to assess the evolution of HEV seroprevalence among blood donors (BDs) from Wielkopolska Region over a 6-year period.

Methods: Three hundred fifty-five BDs (M – 244, F – 111) aged 18-58 (32.4 ± 10.1) from the Regional Blood Center in Poznan were tested for anti-HEV IgG with a sensitive commercial assay (Wantai Biological Pharmacy, Beijing, China). Serum samples were collected in 2009 (n = 103) and in 2015 (n = 252).

Results: Overall, 191/355 (53.8%) BDs tested were anti-HEV IgG-positive, including 64/103 (62.1%) samples from 2009 and 127/252 (50.4%) samples from 2015 (p = 0.0412). HEV-seropositive participants of the study were significantly younger than seronegatives (34.6 ± 10.3 vs. 29.4 ± 8.9 years; $p < 0.0001$). Seroprevalence was similar in men (135/244; 55.3%) and women (56/111; 50.5%) and in residents of cities or towns (150/281; 53.4%) vs. persons living in the country (41/74; 55.4%) (for both comparisons $p > 0.05$). For comparison between samples from 2009 and 2015, we observed a significant decrease of HEV seroprevalence among younger (aged 18-28) participants of the study (from 54.5% in 2009 to 31.9% in 2015, $p = 0.0068$), but not among older BDs (70.8% vs. 60.9%; $p > 0.05$).

Conclusions: Recent changes in HEV infection pressure among BDs from Wielkopolska Region were observed. Younger BDs showed declining HEV seroprevalence in the recent past.

[25] In the search for cross-reactivity between anti-HAV and anti-HEV IgM antibodies in patients with symptomatic hepatitis A from Wielkopolska Region, west-central Poland

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Introduction: Some viral infections can induce cross-reactions with diagnostic tests for other infectious diseases. The objective of this study was to assess cross-reactivity between class IgM antibodies to hepatitis A virus (HAV) and hepatitis E virus (HEV) in a subset of patients with symptomatic hepatitis A hospitalized at the Department of Infectious Diseases in Poznan (west-central Poland) during the 2017 outbreak.

Methods: We examined 100 patients (M – 93, F – 7) aged 20-64 (mean 33.8 ± 10.9; median age – 29.5 years) who were hospitalized at the Department of Infectious Diseases (the Jozef Strus Multidisciplinary Municipal Hospital in Poznan) in 2017 with the final diagnosis of hepatitis A. The disease was confirmed by the presence of anti-HAV IgM (Abbot Laboratories, Germany). IgM antibodies to HEV (anti-HEV IgM) were searched for using a commercial sensitive assay (Wantai Biological Pharmacy, Beijing, China).

Results: The majority of patients (80%) had no history of any recent (3 months before admission) travel abroad. Peak ALT, AST and total bilirubin levels were 158-12289 IU/l (median-2847 IU/l), 75-9840 UI/l (median-1427 IU/l) and 0.26-33.06 mg/dl (median – 9.8 mg/dl), respectively. Peak INR value higher than 1.5 was observed in 28% of patients. None of the study participants had detectable IgM class antibodies to HEV.

Conclusions: Hepatitis A confirmed with anti-HAV IgM testing done by the Abbott assay does not induce false positive cross-reactivity with anti-HEV IgM as tested with the Wantai assay.

[26] Role of diagnostic ultrasound in the assessment of alveolar echinococcosis. The most frequent hepatic ultrasound findings observed in patients hospitalized in University Centre of Maritime and Tropical Medicine in Gdynia, Medical University of Gdansk in the years between 2000-2016

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Alveolar echinococcosis (AE) is a rare, but potentially life-threatening parasitic disease caused by infection with the larval stage of the cestode tapeworm *Echinococcus multilocularis*. Early diagnosis of AE improves prognosis and gives chance for radical resection.

The aim of this work is to present the most frequent hepatic ultrasound findings observed in patients with confirmed and probably diagnosed alveolar echinococcosis. Therefore 58 ultrasound results of patients hospitalized in University Centre of Maritime and Tropical Medicine in Gdynia, Medical University of Gdansk, in the years between 2000-2016 were analysed according to *Echinococcosis multilocularis* Ulm classification-ultrasound. This classification distinguishes five sonomorphological patterns of AE hepatic lesions. In this study the most common pattern was the hailstorm pattern (56.9%), followed by pseudocystic appearance (36.2%) and hemangioma-like (3.4%) and ossification pattern (3.4%).

Suspicion of hepatic AE, raised during ultrasound scanning improves diagnosis and helps to avoid invasive diagnostic procedures like liver biopsy or exploratory laparotomy. Such procedures performed without antiparasitic therapy pose a risk of disseminated disease.

[27] Stage of liver injury in patients with congenital haemorrhagic diathesis and HCV infection

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Introduction: Hepatitis C virus (HCV) is the major cause of chronic liver disease in patients with hemophilia. In Poland there have been no studies assessing the stage of hepatic injury in patients with congenital haemorrhagic diathesis and HCV infection. The aim of the study was the epidemiological assessment of concomitant viral infections, evaluation of liver fibrosis stage and risk factors of its progression.

Material and methods: 71 individuals, the majority of whom were male (94.36%), who had congenital heamorrhagic diathesis (60 had hemophilia A, 5 had hemophilia B, and 6 had other factor deficiencies) and HCV infection, defined as the presence of positive anti-HCV antibodies, were included in this study. The procedures involved a survey, physical examination, biochemical and virological blood tests, and non-invasive methods of liver fibrosis assessment: FibroTest and SWE (shear wave elastography).

Results: The study shows that spontaneous elimination rate of HCV RNA was 29.6% and the most common HCV genotype among the infected was genotype 1 and 3. 74.6% of patients had serologic markers of HBV infection and the prevalence was significantly lower among those born after 1972 compared to patients born before 1972 (61.9% vs. 93.1%). In 9.9% of the patients the infection was still active. Only 18.3% of the subjects were successfully vaccinated. The presence of HIV antibodies was observed in one patient. The prevalence rate of past infection with HAV was 30.9% with a higher prevalence in older patients. The percentage of patients with cirrhosis or significant fibrosis (Metavir > F2) was 26.8%. Fibrosis stage depended on age and estimated duration of infection ($p < 0.001$). Active and past HBV infection did not have impact on fibrosis. Fibrosis was significantly lower in patients with a spontaneous clearance of HCV.

Conclusions: Patients with congenital haemorrhagic diathesis require a strict hepatological supervision. That necessity is dictated by higher rate of infections with hepatotropic viruses (particularly with HCV and HBV) compared to the general population. Non-invasive methods for assessment of the stage of hepatic fibrosis constitute an important supplement to the hepatological diagnostics.

[28] Third recurrence of a hepatocellulare carcinoma in patient with cirrhosis due to perinatally acquired HBV and HCV, after DAA therapy: a case report

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Background: Hepatocellular carcinoma (HCC) is the fifth most prevalent cancer worldwide Chronic HBV and HCV infections are major etiological factors of HCC (80%). Many reports show the increased rate of HCC occurrence and recurrence after DAA therapy.

Case report: 37-year-old male patient with mixed HBV/HCV cirrhosis, 12 MELD, 448 AFP was admitted in January 2018 for a resection of recurrent HCC tumor in VII liver's segment. In history: chronic perinatal HBV and HCV infections acquired through blood transfusions. Portal hypertension with esophageal varices haemorrhage. Patient also underwent Warren's operation. In 2015 he underwent anti-HBV Entecavir therapy and was excluded from liver transplantation due to portal vein thrombosis. First diagnosis and resection of HCC in VI liver segment was conducted in January 2016. DAA treatment was implemented after surgery and HCV was eradicated. In November 2016, CT scan showed recurrent HCC in VII liver segment (342 AFP). Radiofrequency ablation (RFA) was performed. In March 2017, new lesion, in VII segment was detected (230 AFP), but CT did not confirm HCC. Finally, the third recurrence of HCC was detected. The non-anatomical resection was performed. Control CT scan is planned in next 3 month, however AFP level in March 2018 reached 1306 ng/ml.

Conclusions: HCC recurrence after DAA therapy appears to be a significant problem. The liver transplantation as a prevention from HCC development after DAA should be considered. Follow up with CT or MRI scan every 3 to 6 months after DAA especially in patients with HCC tumors history is required.

[29] Cytomegalovirus disease after liver transplant – a description of a treatment resistant case

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Cytomegalovirus infection is a common complication in solid organ transplant recipients. In patients receiving immunosuppressive treatment may lead to life-threatening organ complications or graft loss. We describe a case of 31-year-old CMV seronegative patient who underwent liver transplant from a CMV seropositive donor with an early acute resistant rejection of the transplanted organ followed by primary cytomegalovirus infection, despite prophylaxis, and its severe organ complications. Routine treatment of acute allograft rejection through increasing the base immunosuppression and then administering methylprednisolone infusions did not yield significant therapeutic effect. This resulted in anti-thymocyte globulin and ultimately proteasome inhibitor introduction. The cholestasis remitted and liver parameters improved. But 4 weeks later the patient was admitted again due to incorrect liver function tests. Blood tests revealed high CMV viral load and primary cytomegalovirus infection was diagnosed. On diagnosis patients was treated with ganciclovir intravenously. As ganciclovir resistance was suspected based on clinical premises, foscarnet and leflunomide were implemented with concomitant cautious immunosuppression reduction due to the history of recent graft rejection. Despite aggressive treatment introduction viral clearance was not obtained. Ultimately the patient died due to respiratory distress resulting from lung fibrosis, most probably owing to cytomegalovirus diseases with *Pneumocystis jiroveci* coinfection. The presented case proves how important is strict following of the rules of prophylaxis, especially in patients with a high risk factor of CMV infection development. A quick diagnosis, implementation of appropriate treatment and fast re-

action to the lack of satisfying therapeutic effect can be key to a successful treatment.

[30] Incidence of HCV related HCC in non-cirrhotic liver in patient with colorectal cancer history

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Introduction: Hepatocellular carcinoma (HCC) is a primary malignancy of the liver and develops predominantly in patients with underlying chronic liver disease and cirrhosis. HCC is now a 2nd leading cause of death due to cancer worldwide causing 788 000 deaths in 2015. Colorectal cancer (CRC) is another major cause of morbidity and mortality worldwide, and in 2015 was a 3rd leading cause of death due to cancer.

Case presentation: We report a case of 71 year old woman with chronic hepatitis C virus and previous history of colorectal cancer. She underwent bowel resection followed by chemiotherapy courses 11 years ago. Her last colonoscopy that she had 5 years ago was clear and CEA level was not elevated. HCV antibodies were detected 9 years ago. Patient did not receive antiviral therapy. The patient was admitted to our Unit for resection of liver lesion of heaptic seg VI detected in regular ultrasound. Subsquent CT scan confirmed the nodule which did not meet criteria for recognition of HCC tumour and was most consistent with metastastic lesion. Otherwise patient liver function tests were within normal range and AFP level was 6,03 IU/ml. Patient underwent non-anatomical resection of hepatic seg VI. Histological examination revealed unifocal yellow-green HCC trabecular pattern tumour. Surrounding liver tissue was significant for portal fibrosis with rare septa (Ishak 2, MATAVIR-F2). Following surgery patient was doing well and was discharged home with follow up in 3 months.

Discussion: Our case presents HCC that developed in non-cirrhotic liver in patient with history of colorectal cancer and HCV related hepatitis. We report this case to emphasis difficulties that may be encountered in evaluation of focal liver lesions in patient with chronic hepatitis. In this case the background factors: HCV related hepatitis, low AFP level, history of colorectal cancer, non-specific imaging findings may contribute to complexity of the precise diagnosis. Our case is also another example of a patient with history of CRC and no metastases to the liver with chronic disease.

[31] Treatment difficulties of patients with advanced liver alveococcosis – Poznań Tropical and Parasitic Clinic experiences

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Echinococcus multilocularis infection leads to the development of alveococcosis, which is the cause of focal lesions located in the liver. The long-term asymptomatic course of the disease delays the diagnosis and proper treatment, which is the resection of the parasite pathologic mass. In advanced cases the lifetime intake of albendazole is the treatment of choice. The lack of proper diagnosis and the initiation of treatment leads to liver dysfunction resulting in the cirrhosis, as well as to the parasitic metastases in distant organs. In this research we will present two cases of patients with advanced liver alveococcosis disqualified from the surgical intervention. These patients required an individualized approach and monitoring at the Department of Tropical and Parasite Diseases, Medical University of Poznan, which as the National Alveococcosis Diagnostics and Treatment Reference Center has much experience in this medicine field.

A 30-year-old-man diagnosed on the basis of the characteristic radiological images (USG, MR) and positive serological tests (ELISA, Western-Blot, ELISA-Em2) remaining in the clinic's long-standing observation, with disease progression due to the irregular intake of albendazole. Progression of the parasitic process led to the liver cirrhosis and lesions infiltrations in the diaphragm, the parasite implants into the lower lobe of the right lung and inferior vena cava thrombosis.

26-year-old-woman diagnosed with the liver alveococcosis, disqualified several times from surgery due to the extent and localization of the parasitic lesions, with signs of disease progression resulting from albendazole intolerance. Due to its hepatotoxicity, resulting in liver function deterioration and transaminase elevation, the dose of the anthelminthic was modified. In the absence of an alternative to the pharmacological treatment, it was necessary to radically reduce the drug dose under strict liver function control. Finally, the patient was again evaluated for surgery and decided to perform palliative partial resection of the liver tumor.