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Abstracts

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Hepatitis A virus: correlation between clinical course, biochemical features and cellular immune responses

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Introduction: Hepatits A is a worldwide occurring disease with approximately 1,5 million cases par year.

The aim of the study: The role of cell-mediated immunity in HAV infection, correlation with clinical course, biochemical features and cellular immune responses.

Material and methods: HAV-infected 36 patients hospitalized in the Warsaw Medical University were aged between 17 and 40 years. Laboratory examination of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin levels. All results were compared to normal healthy controls. The analysis of CD4+T-cells, CD8+T-cells of AHA patients, CD4+/CD8+ and NK lymphocyte populations. Additionally in acute period of disease was made the allergy skin testing with 7 recall antigens.

Results: Among 36 patients with persistent symptoms, elevation of aminotransferase and total bilirubin for at least 5 months was present in 3 patients (P-AHA). In P-AHA the number and percentage of CD4+T-cells to remaining acute hepatitis (AHA) were significantly decreased, but CD*+T-cells for both groups AHA and P-AHA was normal, the CD4+/CD8+ ratio in P-AHA were lower as compared to AHA, NK lymphocyte in P-AHA were higher as compared to AHA. Considering smaller than 10 mm reactions against recall antigens was corresponded to higher AspAT levels, but not to the persistently time course of AHA.

Conclusions: the higher AspAT levels might be due to diminished cellular immunity responses. Higher levels of NK lymphocyte in persistent cases suggest that they play an important role in the pathogenesis of HAV infection. The allergy skin testing is reliable index of disorders reactivity of CD4+ T-cells.

Key words: hepatitis A, cell-mediated immunity, the persistently time course of AHA, allergy skin testing.

Hepatitis E seroconversion in HIV-infected patients from west-central Poland – preliminary study using a new automated test

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Introduction: West-central Poland seems to be an area of common exposure to hepatitis E virus (HEV) [Bura et al., Int J Infect Dis 2017; Grabarczyk et al., Transfusion 2018]. As HEV-3 infections most often go asymptomatically or with non-characteristic symptoms, it is difficult to identify patients in the acute phase of hepatitis. Anti-HEV IgG seroconversion may prove exposure to the virus.

The aim of the study: To determine the incidence of HEV infections in the group of people from Greater Poland living with HIV using a new automated assay for anti-HEV IgG.

Material and methods: From each of 50 HIV-positive patients (46 men) aged 22-55 years (median age – 38 years) two sera were obtained at intervals of 5-18 months (median – 12 months). Both samples were tested for the presence of anti-HEV IgG by the VIDAS Anti-IgG assay (BioMérieux, France).

Results: At baseline, HEV seroprevalence was 32% (16/50). The average age of seropositive patients (37.4 years) was not higher in comparison to those who were anti-HEV IgG-negative (39.1 years). In 31 patients (62%) both results were negative and in 14 persons (28%) both results were positive. Of the 34 initially seronegative patients, seroconversion was demonstrated in 3 persons (8.82%). None of the seroconverters reported any symptoms of hepatitis. The observation of these patients lasted a total of 377 patient-months, an average of 11.1 months (median 12 months). This corresponds to the seroconversion rate of 9.62% per year. In 2 cases (2/16 = 12.5%) the seroreversion was found.

Conclusions: Preliminary data obtained with the VIDAS Anti-IgG assay indicate that HEV seroconversion occurs annually in almost 10% of HEV-seronegative HIV-infected patients from Greater Poland. These HEV infections are subclinical.

Autoimmune liver diseases in a child with ulcerative colitis. Case presentation

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Introduction: Autoimmune hepatitis (AIH) and primary sclerosing cholangitis (PSC) tend to have similar clinical presentation. The overlap of these features, together with biochemical, immunological and histological features can be considered as autoimmune sclerosing cholangitis (ASC). Additionally PSC is sometimes associated with inflammatory bowel disease (IBD), which can occur even in 75% of overlap syndromes. We present a 13 years old patient with these three conditions treated in the Children's Memorial Health Institute.

Material and methods: In 2011, a five years old girl was admitted to the hospital because of the cholestasis, elevated transaminases: gamma globulins, GGTP and autoantibodies (ASMA 1 : 320, ANCA 1 : 1280), after exclusion of Wilson disease and viral hepatitis. During the treatment with Ursofalk (UDCA), the normalization of biochemical parameters was observed, and first after the recurrence of the disease, in 2013 (abnormal biochemical parameters and cholangiographic findings) liver biopsy showed histopathological changes characteristic for AIH/PSC (interface hepatits/fibrous obliterative cholangitis in small ducts). The patient followed Encorton with Immuran and Ursofalk treatment. Consecutive liver biopsies showed the remission of microscopical changes (in 2016 only mild inflammation and periductal fibrosis, in 2019 absence of inflammation, minimal fibrosis). However the endoscopic examination from 2017 revealed the presence of epithelioid granulomas, cryptitis and crypt abscesses in the sigmoidal and rectal region, which also disappeared after two years of treatment (Encorton, Immuran, Ursofalk, Pentase). Despite of the remission of the biochemical and microscopical parameters, the magnetic resonance cholangiopancreatography (MRCP) still show features of PSC (strictures and dilatations of the biliary three).

Conclusions: After nine years of the therapeutic modalities, the treatment of AIH/PSC/IBD, contributed to the remission of the clinical, biochemical and histopathological changes, which led us to discontinue immunosupression. MRCP features characteristic for PSC are present and the UDCA treatment should be continued.

Long-term outcomes in patients with compensated cirrhosis due to chronic hepatitis C after direct acting antiviral treatment

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The aim of the study: To analyzed the efficacy and clinical outcomes in hepatitis C (HCV) patients after direct acting antiviral therapy (DAA) based on selected blood and elastography parameters.

Material and methods: A total of 41 hepatitis C patients with compensated cirrhosis after successful DAA treatment were included. Selected blood parameters: platelets (PLT), alanine aminotransferase (ALT), prothrombin time (PT), glucose and elastography measurements: dynamic liver stiffness (LS) and controlled attenuation parameter (CAP) were performed 18-30 months after end of treatment and compared with baseline.

Results: We assessed blood and elastography parameters before and after HCV eradication. Mean follow-up period was 18-30 months after therapy. Our collecting data revealed that in long-term observation PLTs were higher by 26.8% ($p < 0.001$) [145.20 vs. 181.78 tys/ul] and glucose increased by 12.82% ($p < 0.001$) [109.46 vs. 118.58 mg/dl]. However, ALT decreased by 46.41% ($p < 0.001$) [80.84 vs. 25.32 IU]. The differences in PT was not significant. Elastography results revealed that liver stiffness decreased by 39.34% ($p < 0.001$) [20.57 vs. 14.54 kPa] while steatosis (measured by CAP) increased by 27.83% ($p < 0.05$) [261.41 vs. 288.03 dB/m].

Conclusions: Our research showed that HCV eradication improves clinical liver parameters in patients with compensated cirrhosis. We also observed regression of liver stiffness in elastography however, noticeable increased liver steatosis and level of glucose are matters of concern and require further investigation.

Multi-parametric MRI as a composite biomarker for classifying liver disease in paediatrics

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Introduction: The is a need for an alternative to biopsy in paediatric liver disease. MRI-derived iron corrected T1 (cT1) and proton density fat fraction (PDFF) are emerging techniques that have demonstrated utility in stratifying adults with liver disease. We explored the potential discriminative value in paediatric patients.

Material and methods: Sixty patients (28 male; mean age 13.0 [6-17 yrs]; AIH (n = 43), PSC (n = 9), Wilson's disease (n = 6), NAFLD (n = 2)) and 21 controls (9 male; mean age 13.8 yrs [9-17 yrs]) underwent multi-parametric MRI with LiverMultiScan™. cT1 and PDFF values were compared across groups using two-sided Kolmogorov-Smirnov (KS) tests and then combined into a probability risk score with multivariate logistic analysis with discriminative ability evaluated using ROC curves.

Results: Mean cT1 was significantly higher in AIH (763 ±87 ms) than controls (708 ±41 ms; $p < 0.01$) and elevated further in NAFLD and WD (883 ±38 ms; 890 ±60 ms, respectively, $p < 0.01$), but was not significantly elevated in PSC (734 ±66 ms). Mean PDFF was significantly elevated in NAFLD (18.3 ±6%, $p < 0.01$) and WD (19.9 ±8%, $p < 0.001$) compared to all other groups. A combined cT1 and PDFF score discriminated WD from other patients with a PPV of 67% and sensitivity of 100% (AUROC 98% [96-100%]).

Conclusions: Combining cT1 and PDFF within disease populations may assist in distinguishing between liver diseases, which may have the potential to aid paediatric clinical management and clinical trial enrolment. Further research in much larger samples is warranted.

This study was funded by The National Centre for Research and Development and InnovateUK under EUREKA/Eurostars project E!10124 "Kids4LIFe – Assessing Kids for Liver Inflammation and Fibrosis using noninvasive MRI".

A combined blood and MR imaging risk score for monitoring liver inflammation in paediatric AIH

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Management of autoimmune hepatitis (AIH) is highly variable in practice, with lack of consensus on optimal follow up strategies for patients, including the utility of on-treatment liver biopsy.

LiverMultiScan™ is a multiparametric MRI method which measures iron-corrected T1 (cT1). This has been shown to correlate with the key histological features of liver disease (ballooning, inflammation and fibrosis), and to predict clinical outcomes. Here, we evaluate the utility of cT1 in AIH, in combination with circulating biomarkers, for the stratification patients experiencing flares of liver inflammation.

Forty-six AIH patients (19 male; mean age 13.8 [6-18 yrs]; underwent LiverMultiScan™, with comparison to liver biopsy and liver enzymes (ALT, AST, GGT and bilirubin). Correlation with the imaging and blood biomarkers against biopsy was explored using Spearman's Rho. The ability of these biomarkers to identify individuals with histologically confirmed portal inflammation was evaluated using AUROC analysis, with step-wise logistic regression used to combine biomarkers into a risk score.

All biomarkers correlated with Ishak fibrosis and all except total bilirubin correlated with portal inflammation. Pairwise comparisons identified different patterns for cT1 compared to blood biomarkers, with stronger separation between Ishak scare 2-3 and 5-6 ($p < 0.001$) and equally a more stepwise pattern with portal inflammation. Independently, both cT1 and ALT were the best predictors of portal inflammation ≥ 2 (cT1 AUROC: 0.70 (0.55-0.85, se: 39%, sp: 100%, NPV: 61%, PPV: 100%)); ALT AUROC 0.73 (ci: 0.58-0.88), se: 61%, sp: 77%, NPV: 56%, PPV: 81%). Interestingly, the superior model with the strongest predictor of those with current portal inflammation ≥ 2 was a risk score combining cT1, total bilirubin and AST (AUROC of 0.84 (0.7-0.94)) that was able rule-in those currently experiencing a 'flare' with 100% specificity (PPV: 100%, NPV: 57%, sensitivity: 50%). Both ALT and cT1 are effective biomarkers for identi-

fying portal inflammation. This performance for identifying low level inflammation however is further enhanced when cT1 is used in composite with AST and total bilirubin, highlighting the potential of multiparametric MRI when used in conjunction with circulating markers of disease for monitoring paediatric patients with AIH. Further research is warranted.

Study funded by NCBiR, InnovateUK-EUREKA/Eurostars project E!10124-Kids4LIFe.

Quantitative MRCP imaging: preliminary observations in a cohort of paediatric patients with liver and biliary diseases

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Magnetic resonance cholangiopancreatography (MRCP) is commonly used for the evaluation of biliary disease but has significant limitations, including variable quality bile duct depiction and subjective assessment. This is particularly true in paediatric assessment, where biliary changes may be less advanced. We sought to understand the potential utility of quantitative MRCP (MRCP+™) in paediatric patients, particularly those with overlapping autoimmune hepatitis (AIH) and primary sclerosing cholangitis (PSC).

Recruited patients (6-18 yrs; AIH (51), AIH/PSC (10), Wilson's disease (6), other (7)) and 21 healthy controls underwent multi-parametric MRI with LiverMultiScan™ and heavily T2-weighted three-dimensional MRCP imaging for MRCP+ processing to enhance and quantify the tubular biliary structures and assess liver parenchyma. The underlying algorithms combine multi-scale Hessian analysis, gradient vector flow analysis, an intelligent path search algorithm and novel duct modelling algorithms.

PSC patients had an increased number of candidate strictures and dilatations (defined as a change in diameter > 30%) than healthy controls ($p = 0.007$) and AIH patients ($p = 0.019$). Furthermore, the percentage severity of strictures and total length of dilated and strictured regions were greater in PSC patients than healthy controls ($p = 0.019$; $p = 0.008$) and AIH patients ($p = 0.045$; $p = 0.035$). AUROCs of 0.80-0.95 were observed for a range of quantitative biliary metrics assessing AIH/PSC against Health or AIH patient groups. Increases in MRI-derived iron corrected T1 (cT1) whole liver inter-quartile range (which can reflect heterogeneity of fibro-inflammation) was associated with increases in the total length of dilated and strictured regions (Pearson's correlation $R = 0.88$; $p = 0.05$), suggesting parenchymal disease association with biliary metrics.

We report findings demonstrating that quantitative MRCP (MRCP+) provides measures that could objectively differentiate patients with PSC from healthy or other liver disease patients, with potential for monitoring and severity assessment applications.

This study was funded by NCBiR and InnovateUK under EUREKA/Eurostars project E!10124 "Kids4LIFe – Assessing Kids for Liver Inflammation and Fibrosis using noninvasive MRI".

Prevalence and risk factors of anti-HCV positivity among patients with cardiovascular diseases in Poland

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Introduction: Majority of HCV-infected in Poland remain undiagnosed and screening campaigns are urgently needed. Previous hospitalizations and medical procedures are leading risk factors of anti-HCV positivity. Precise risk of nosocomial exposure is largely unknown. HCV is also regarded as modifier of morbidity and mortality of cardiovascular disorders (CVD). We aimed to assess the prevalence and risk factors of anti-HCV and HBsAg risk factors and possible influence of viral hepatitis on CVD mortality.

Material and methods: The analysis included 8,646 patients tested for anti-HCV and 47,831 for HBsAg in Silesian Center for Heart Diseases between 2014-2017. Anti-HCV and HBsAg were tested with immunoenzymatic assays according to current guideline. Analyses included comorbidities and previous hospitalizations (ICD-10), previous medical procedures (ICD-9), liver function tests and follow-up data including mortality based on Silesian CVD Registry.

Results: The prevalence of anti-HCV was 1.1% (94/8,646) and HBsAg 0.3% (141/47,831) among patients with available hepatitis testing. Anti-HCV+ subjects were younger then HBsAg+ (60.0 ±14.4 vs. 56.4 ±14.4 yo, $p = 0.02$) but gender distribution was comparable. Heart transplant rejection (10.6% vs. 2.1%, $p = 0.01$) and heart insufficiency (54.3% vs. 39.0%, $p = 0.03$) was diagnosed more often in anti-HCV+ vs. HBsAg+. Subjects with anti-HCV+ had higher median number of previous hospitalizations (9.3 vs. 6.7, $p < 0.002$), blood transfusions (5.8 vs. 0.6, $p = 0.001$) and CVD-surgeries (16.6 vs. 4.8) comparing HBsAg+. Moreover, trends towards higher number of previous invasive diagnostic procedures (3.3 vs. 2.1, $p = 0.06$) and history of abdominal surgery (52 vs. 39%, $p = 0.06$) were observed in anti-HCV+. In Cox-regression model the highest hazard ratio for anti-HCV+ vs HBsAg+ was for history of liver disease HR 5.32 ($p < 0.001$), previous invasive diagnostics HR 2.99 ($p = 0.01$) and chronic kidney disease HR 1.95 ($p = 0.017$). Kaplan-Meier analysis showed higher mortality in anti-HCV(+) subjects vs. HBsAg+ in follow-up ($p = 0.009$).

Conclusions: History of liver disease, previous invasive diagnostic procedures and chronic kidney disease constitute of the most important risk factors of anti-HCV(+) in patients with CVD. Importantly, anti-HCV(+) was associated with higher mortality. Results of the study underline the necessity of HCV-screening and prompt therapy in patients with CVD to improve their prognosis.

Low risk of HBV reactivation in a large European cohort of HBV/HCV coinfected patients treated with DAA

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HBV reactivations during direct acting antivirals (DAA) for HCV were described in both HBsAg(+) and HBsAg(–)/anti-HBcIgG(+) patients. The rate of HBV-reactivation in HBV/HCV coinfection is poorly defined. The aim was to characterize HBV/HCV coinfection and the prevalence HBV-reactivation during DAA.

Analyzed population consisted of 6228 chronic hepatitis C patients (52% female, mean age 54 yo, 82% HCV-GT1b, 34% with liver cirrhosis) receiving DAAs in 2016-2017 included in EpiTer-2. DAA combinations consisted mainly of OBV/PTV/r ± DSV ± RBV (53%) and LDV/SOF ± RBV (28%). Prior to the DAA all subjects had HBsAg testing and ALT-activity eval-

uated every 4 weeks during DAA. Anti-HBc IgG was available in 742 patients without HBsAg.

70 of 6228 patients (1.1%) had detectable HBsAg. HBV/HCV patients were younger and more often infected with HCV-GT3-4 than HCV-group. They were also less often diagnosed with arterial hypertension (26% vs. 38%, $p = 0.04$), diabetes (6% vs. 15%, $p = 0.03$) and had lower BMI (24.5 vs. 26.0, $p < 0.01$). Prior to DAA only 21 of HBV/HCV required NA-therapy. DAA-therapy was continued according to plan in 96% (HBV/HCV) vs. 95% (HCV) of cases. Sustained virologic response (SVR) rates were similar in HBV/HCV and HCV-monoinfection (mITT 97% vs. 95%, $p = 0.7$).

In HBsAg(+) subjects only 3 (4.3%) HBV reactivations were observed, while none occurred in HBsAg(–)/anti-HBc(+) group. All subjects with reactivation were HBeAg(–), infected with HCV-GT1 and had advanced liver disease. One reactivation was clinically significant with HBV-DNA increase at wk5 and ALT-flare (1337 IU/m) requiring DAA discontinuation, while 2 remaining were subclinical with HBV-DNA increase form negative to 1.3 (wk12) and 3.2 log10 IU/ml (wk8). Interestingly, one case of HBV-reactivation occurred during LAM-therapy. During next phase of Epiter-2 study additional reactivation in subject with HBsAg(–)/anti-HBc(+) was diagnosed, which suggests that occult hepatitis B should be taken into consideration before DAA.

Data form a large cohort suggest that the risk of HBV-reactivation during therapy with DAA seems to be low in HBsAg(+) HBV/HCV subjects (< 5%), while probably minimal although existent in HBsAg(–)/anti-HBc IgG(+). Interestingly, subjects with HBV/HCV coinfection seem to less often present symptoms and complication of metabolic syndrome.

Liver function improvement after effective antiviral treatment in cirrhotic patients infected with hepatitis C virus

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Introduction: The new direct acting antivirals (DAA) have opened access to treatment also for patients with liver cirrhosis infected with hepatitis C virus (HCV). In this group of patients, the beneficial effect of viral eradication on the further clinical outcome is relatively assessed. The aim of this clinical, retrospective study was to analyse the potential influence of HCV eradication with DAA on liver function in patients with decompensated liver cirrhosis.

Material and methods: Twenty eight patients (16 M/13 F, mean age 59 ±14 years) with liver cirrhosis (median liver stiffness measurement (LSM) 29.1 kPa [21.30-4.30] evaluated with transient elastography) after successful therapy of HCV infection were analysed. Liver function tests, including alanine (ALT) and aspartate (AST) aminotransferase and gamma-glutamyltranspeptidase (GGT) serum activities, serum albumin and bilirubin levels as well as prothrombin time, were estimated before and at the end of treatment (EOT), 24 and 48 weeks after EOT. Severity of liver cirrhosis was estimated using Child-Turcotte-Pugh (CTP) classification in the same control points. LSM were conducted at baseline, 6 and 12 months after the end of therapy.

Results: During DAA therapy, serum activities of ALT, AST and GGT decreased significantly ($p < 0.001$, for each). Up to 48 weeks after EOT, albumin serum concentration increased significantly ($p < 0.001$) and bilirubin serum concentration decreased ($p < 0.05$) resulted in decreasing the CTP score ($p < 0.01$). LSM decreased in EOT24, but not significantly ($p < 0.07$). In EOT48, in 75% of patients LSM decreased significantly ($p < 0.01$) but in 25% increased.

Conclusions: Resolution of HCV-induced inflammation as a result of effective antiviral therapy caused gradual improvement in liver function and severity of cirrhosis during the one year after EOT. Longer observation is needed in order to assess the sustainability of this recovery. LSM improvement is not universal and further observation of liver stiffness is necessary.

Description of the innovative solution: "The system of mapping occurrences of echinococcosis in Poland"

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Echinococcosis is a parasitic disease caused by larval tapeworms of the Taeniidae family. There are four species known, however only *Echinococcus granulosus* and *Echinococcus multilocular* are of significant epidemiological and clinical significance. There are several new cases of echinococcosis in Poland annually, mainly in the Warmian-Masurian, Sub-Carpathian and Lesser Poland Voivodships.

Spatial analysis of patients with echinococcosis is a complex and time-consuming task. It requires the doctor to not only maintain a detailed history of the disease of many patients, but also to analyze them and to manually apply selected cases to the map. This approach is not efficient and results in a high probability of making a mistake.

Presented system answers above challenges by combining in one tool a comprehensive module for creating, editing and viewing disease history with a module for dynamically mapping selected aspects of the disease in a geographical context. It allows not only to store detailed data about patients but also to create summaries in terms of age, disease severity or hospitalization time. The system also provides an opportunity for visual representation of data in the form of thematic layers containing density of patients in various stages of the disease or statistical analysis of the number of cases in each city. Due to its high versatility, the system can also be used to analyze patients with a different disease entity.

It is an innovative solution that supports physicians in their daily work as well as in scientific research in a comprehensive way.

Agreement between clinical diagnosis and selected methods for causality assessment in drug-induced liver injury

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Introduction: Drug-induced liver injury (DILI) is a growing clinical problem resulting from the widespread use of drugs, dietary supplements and herbal products (HDS).

The aim of the study: To assess the agreement between clinical diagnosis and selected methods for DILI causality assessment (CAM). The agreement between CAMs was described using Cohen's kappa (κ) test. The κappa value ranges from −1 (perfect disagreement) to +1 (perfect agreement).

Material and methods: For each patient hospitalised between 2009 and 2018 who met criteria of DILI the causal relationship between the liver injury and the implicated drug/HDS was evaluated using selected CAMs: RUCAM (Russel Uclaf CAM), M & V (Maria & Victorino CAM), Naranjo (Naranjo Adverse Reaction Scale), WHO-UMC (World Health Organization-Russel Uclaf Monitoring Center). The agreement among scales was assessed using weighted coefficient Cohen's kappa (κ).

Results: The agreement between clinical diagnosis and Naranjo (κ = 0.178), WHO-UMC (κ = 0.157) and RUCAM (κ =0.021) scale was described as slight, and as "disagreement" for the M&V scale (κ = –0.012). The highest values of kappa coefficient: κ = 0.373 (95% CI: 0.305-0.441), κ = 0.368 (95% CI: 0.197-0.538) were found in the group of acute cholestatic and mixed hepatitis, in the Naranjo scale. Causality assessment by means of WHO-UMC scale correlated with clinical diagnosis in all analyzed sub-groups with exclusion of: mild course of DILI κ = –0.086 (95% CI: 0.257-0.309) and acute hepatocellular hepatitis κ = –0.039 (95% CI: –0.070 to –0.007).
Conclusions: Despite wide recommendations on importance of causality assessments in DILI diagnosis we found their limited application in clinical practice when used retrospectively. The Naranjo and WHO-UMC scales showed better correlation with clinical diagnosis than DILI-specific CAMs: RUCAM and Maria & Victorino.

A ten-year retrospective analysis of causes and clinical features of drug-induced liver injury in patients hospitalized in the Clinic of Infectious Diseases, Tropical Medicine and Hepatology in Warsaw

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Introduction: Drug-induced liver injury (DILI) is a growing clinical problem. DILI can be caused by any drug either due to its dose-dependent direct hepatotoxic effect or as a result of idiosyncrasy. The diagnosis of DILI is based on the exclusion of other causes of liver disease.

The aim of the study: To analyze the causes and clinical picture of DILI in patients hospitalized in the Clinic of Infectious Diseases, Tropical Medicine and Hepatology in Warsaw (CIDTM&H) between 2009 and 2018.

Material and methods: Relevant clinical data was abstracted from medical records of patients hospitalized in CIDTM&H between 2009 and 2018. Liver injury type, disease severity and Hy's rule were assessed for each patient. Logistic regression multivariant analysis was used to analyze factors associated with type of liver injury and severity of disease outcome.

Results: In the analyzed period, DILI was diagnosed in 79 patients: in 68 (86.1%) was caused by drugs, in 11 (13.9%) by herbs and dietary supplements (HDS). More than one drug contributed to DILI in 16 (20.3%) patients. 91.2% of patients presented with idiosyncratic DILI and 7 (8.8%) had intrinsic DILI. Leading causative agents were: amoxycillin/clavulanic acid – 13 (13.1%), anabolic steroids – 9 (9.2%), acetaminophen, estradiol – 6 each (6.1%). Antimicrobials were the most common class of causative drugs: 31 (35.6%). Based on multivariate analysis, the age ≥ 55 years and prolongation of the latency period were related to cholestatic/mixed type of liver injury. Moderate/severe DILI correlated with AST and GGTP values (p = 0.047 and p = 0.0196, respectively). Women compared to men and patients ≥ 55 years used a larger mean number of causative and associated drugs (p = 0.018 and p = 0.015, respectively).

Conclusions: Diagnosis of DILI in clinical practice requires assessment of disease-specific parameters which allow targeted diagnostic approach and predict disease outcome. Older age and prolonged latency period predispose to cholestatic and mixed liver injury.

Drug-induced liver injury associated with amoxycillin/clavulanic acid – review of 13 clinical cases

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Introduction: Amoxicillin with clavulanic acid (AC) is one of the most commonly prescribed antibiotics and a leading cause of idiosyncratic drug-induced liver injury (DILI) worldwide. Liver injury appears primarily due to the clavulanate component.

The aim of the study: To analyse clinical course of AC-related DILI in patients hospitalized in the Clinic of Infectious Diseases, Tropical Medicine and Hepatology in Warsaw (CIDTM&H), between 2009-2018.

Material and methods: Cases of DILI related to AC were selected from the electronic data base of the CIDTM&H. Relevant demographic, laboratory and other clinical data were collected for each patient.

Results: Between 2009 and 2018, 13 cases of AC-related DILI were diagnosed. AC was the main cause of all DILI cases reported within this period (13/79, 16.4%). The mean age of patients was 56.8 years (SD 13.9), 77% were women, mean latency period was 8.3 days (SD 7.6). Six patients had hepatocellular type of liver injury, 7 – mixed and cholestatic. In 8 cases disease had moderate severity. All patients had symptoms of DILI: jaundice (77%), itching (46%). All but one patient had concomitant diseases, 10/13 took other than offending drugs. Laboratory mean values were: ALT 664, 7 IU/l ±SD 514.4; FA 274.7 ±SD 137.3; total bilirubin 70.9 μmol/l ±SD 22.9; AST 371 IU/l ±SD 450.7; GGTP 457.7 IU/l ±SD 345.1. One patient had DILI due to re-exposure to AC.

Conclusions: Amoxycillin and clavulanic acid was the most common cause of DILI in the analysed period. AC-related DILI was predominately in women and manifested as hepatocellular and mixed/cholestatic type of liver injury.

From kidney to liver – unusual manifestation of systemic sarcoidosis. Case presentation

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Introduction: Sarcoidosis (Besnier-Boeck-Schaumann disease) is a systemic disease. Main clinical manifestations, include lungs (90%), eyes and skin. Diagnosis of sarcoidosis is still a challenge, frequently remaining a diagnosis of exclusion. It is important to mention, that other conditions, with similar symptomatology must be consider in the differential diagnosis such as, tuberculosis, Wegener's granulomatosis, cancer or lymphoma.

Case presentation: We report a 34-year-old man with a 3 months history of acute kidney injury of unknown etiology with enlarged peripheral lymph nodes. Laboratory tests revealed hypercalcemia, increased activity of liver enzymes and elevated serum kappa/lambda ratio. Multiple hypoechoic nodules in the liver, kidney, spleen and pulmonary parenchyma as well as hepatosplenomegaly and concomitant lymphadenopathy in thorax and abdominal computed tomography were found. Result of bone marrow biopsy did not confirm multiple myeloma and histological examination of the external axillar lymph node and liver parenchyma demonstrated the presence of nonceasing granulomas, typical for sarcoidosis. Gluocorticosteroid therapy caused rapid reduction of the lymph nodes dimensions as well as improvement of kidney function. Despite the treatment, supplemented by ursodeoxycholic acid, activity of liver enzymes was still elevated, however patient remained asymptomatic.

Conclusions: Hepatomegaly and liver dysfunction are found in ca. 10% of a patients and hepatitic sarcoidosis represents only a small percentage of causative hypercalcemia. Increased risk for cancer or lymphoma in affected organs in patients with sarcoidosis should be taken into consideration, however longer follow up is needed.

Phytotherapy in hepato-oncology

Paweł Słodnik

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Hepatocellular carcinoma is a primary liver tumor. The risk factors to develop this cancer are infection with hepatitis virus, alcoholism and liver diseases. The prognosis of this disease is poor.

In the last years, the resistance of tumors against therapeutic procedures is increasing. So many new oncologic drugs obtain from plants. Well known are also dietary supplements which showed already antineoplastic potential such as trans-resveratrol and a pine bark extract. In the literature are described in-vitro studies with both agents with HT1080 fibrosarcoma cell line. It was already showed that trans-resveratrol modulates sphingolipid metabolism in hepatocellular carcinoma cells, inhibits the progression of human hepatocellular carcinoma via regulating p53 and the phosphoinositide 3-kinase/protein kinase B pathway. Trans-resveratrol also modulates PI3K/AKT Signalling through SIRT1 modification. Also hepatic stellate cells play a crucial role in resveratrol-induced inhibition of hepatocellular carcinoma cell growth. Resveratrol showed also anti-metastatic activity in hepatocellular carcinoma through SP-1 modulation. Oxyresveratrol inhibits hepatocellular carcinoma growth via modulation of angiogenesis and lymphangiogenesis. Pine bark extract showed already an inhibitory effect on hepatitis C virus replication so on one of risk factors of hepatocellular carcinoma. In the literature was also described a synergistic effect of piperine and curcumin *in vitro* and *in vivo* on the suppression of hepatocellular carcinoma cells.

Nowadays already many natural compounds showed in *in vitro* but also *in vivo* study antineoplastic activity against hepatocellular carcinoma cells. It is possible that such agents could in the future be used as supportive therapy in hepato-oncology.

Acute hepatitis A in children – own observations

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The aim of this study was to analyze the clinical course of acute hepatitis A in children. Retrospective analysis of medical records of 25 children hospitalized due to hepatitis A from the March 2017 to the March 2019 was taken. Among analyzed group there were 12 girls and 13 boys in the age of 1-17 years (mean 10 years). In 21/25 (84%) the infection was transmitted via household contact. None of children were earlier vaccinated against hepatitis A. The most frequent symptoms were abdominal pain in 12/25 (48%), fever – 11/25 (44%), change in the color of urine and/or stool – 10/25 (40%), diarrhea – 9/25 (36%), nausea and vomiting – 8/25 (32%), loss of appetite – 6/25 (24%) and itching – 4/25 (16%). Hypertransaminasemia (17-2932 U/l) was reported in 22/25 (88%) children, with mean ALT activity 1109 U/l, ALT > 30× normal in 13/25 (52%) and mean AST level 908 U/l (34-2918 U/l). Increased GGTP level was observed in 21/25 (84%) patients (8-498 U/l, mean 145 U/l, in 6/25 (24%) > 4× normal). Jaundice was observed in 16/25 (64%) patients with mean total bilirubin level 3.76 mg/dl (0.77-8.94 mg/dl) and a predominance of direct bilirubin. Splenomegaly was found in 12/25 (48%) patients and hepatomegaly in 11/25 (44%). In 8/25 (32%) children cholecystitis was described. None long-term sequels were observed. Hepatitis A infection is a self-limiting disease, with a diversified clinical manifestation and usually complete recovery. It is necessary to promoting pre- and postexposure vaccinations, especially among household of children with hepatitis A.

Efficacy and safety of HCV treatment in hemodialyzed patients – analysis of EpiTer-2 database

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Introduction: The decision of treatment in HD patients is slightly more complicated. Apart from DDIs and renal insufficiency, the pharmacokinetics and distribution of antiviral medications had to be considered.

Material and methods: EpiTer-2 project is a real-world, investigator-initiated study. The group that was analyzed started HCV treatment before January the 1st 2018. Among 6229 patients in EpiTer-2 database we identified 334 patients with any kidney disease. Among 77 patients with eGFR < 30 ml/min/1.73 m^2 53 patients were on dialysis – 21 women (39.6%) and 32 men (60.4%). The mean age was 50.28 ±12.80 years. Females were younger (47.3 ±10.88 years) than males (52.4 ±13.67 years).

Results: Predominant genotype was 1b – 45 pts (84.9%). Three pts were infected with genotype 1a (5.7%) and 5 with genotype 4 (9.4%).

Advanced liver fibrosis was found in 14 pts – F4 (26.4%) and in 9 pts – F3 (17.0%). In 19 pts (35.8%) F1 and in 11 pts F2 (20.8%) were diagnosed. At the baseline in 3 cases there was a history of liver decompensation.

In group of HD patients 10 underwent kidney transplantation and 4 of 10 had acute graft rejection. The explanation for 40% graft rejection in this group is obvious, due to transplantation failure they continued replacement therapy.

The most often regimen was OBV/PTV/r ± DSV – in 30 pts (56.6%). GZR/EBR was used in 15 pts (28.3%), ASV/DCV in 4 pts (7.5%), GLE/PIB in 1 (1.9%) and aLDV/SOF in 3 pts (5.7%). In 1 patient with genotype 1a physician decide to add reduced dose of RBV (200 mg) to OBV/PTV/r ± DSV for 12 weeks. Two patients with G1a were treated with GZR/EBR for 16 weeks and OBV/PTV/r ± DSV for 24 weeks without RBV.

There was 1 episode of ascites, but the patient continued the treatment. In 4 patients anemia occurred, 2 had pruritus and 2 jaundince. All adverse events did not lead to therapy modification.

All HD patients achieved SVR 12 and/or SVR24.

Conclusions: HD patients require close monitoring but they can be treated with efficacy and safety comparable to general population.

Primary Health Care (PHC) as the first step in identification of non-alcoholic fatty liver disease (NAFLD) patients

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The aim of the study: The aim of the study was to determine if primary care practitioners (PCPs) take care of non-alcoholic fatty liver disease (NAFLD) patients and properly manage patients with suspected non-alcoholic steatohepatitis (NASH).

Material and methods: The tool used to carry out the research was a questionnaire consisting of 19 questions. General practitioners worked in Lublin Voivodeship participated in this research. Our study had been accepted by the Bioethics Committee.

Results: 64 PCPs in Lublin Voivodeship responded to the questionnaire. The age of the respondents ranged from 28 to 75. Twenty one percent of PCPs took care of patients with diagnosed NAFLD, while only 7% of them treated patients in everyday medical practice in primary care units. Twenty eight percent of respondents referred patients with fatty liver to further specialist evaluation. Forty percent considered screening for NAFLD, i.e. level of liver enzymes or ultrasonography examination, as important in a group of patients with obesity or metabolic syndrome. Twenty four percent of PCPs knew transient elastography e.g. FibroScan system and 26% were aware of diagnostic possibilities offered by this technique.

Conclusions: Although PHC is thought to be the first step in diagnosing NAFLD, only few doctors were aware of treating patients with this disease. Less than half of respondents paid attention to introduce screening tests. Improving the level of knowledge about NAFLD in general practitioners should be the necessary activity for the near future.

The role of Primary Health Care doctors in direct acting antiviral therapy of HCV infection – interview survey

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Introduction: HCV infection is considered a significant epidemiological problem in Polish population. Considering wide use of direct acting antiviral (DAA), we can expect increasing number of patients after oral therapy of HCV infection that are under control of Primary Health Care (PHC) providers.

The aim of the study: To gain information on the extent of knowledge the primary health care doctors have about DAA therapy of HCV infection. Enhancing awareness of general practitioners on the basis of current guidelines of Polish Association of Study of the Liver (PASL).

Material and methods: We distributed paper questionnaire to 64 primary health care doctors aged between 28 and 75 years working in Lublin and surrounding area. Survey was focused on HCV infection diagnostics and DAA treatment in Poland. After responding the questionnaire we provided doctors with a brochure with basic information about HCV diagnosis and DAA therapy.

Results: The results indicate that diagnostics, treatment and supervision of HCV-infected patients is not currently considered common knowledge for PHC doctors. Even though four out of five doctors knew how to interpret laboratory tests for HCV infection, one in three does not realize that infection can be effectively cured using oral therapy and half of them never heard about DAA therapy. 95% of responders think that knowledge about modern HCV therapy should be widened in the group of general practitioners.

Conclusions: Recent developments in HCV therapy made specialists to place particular emphasis on the role of primary health care doctors in screening of HCV infection and after treatment management. In the age of effective antiviral treatment, significant decrease in number of infected people can be reached mostly by education of health care workers, including general practitioners.

Neutrocyte to lymphocyte ratio predicts the presence of a replicative hepatitis C virus strand after therapy with directly acting antivirals

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The aim of the study: Residual HCV-RNA can persist in liver tissue and peripheral blood mononuclear cells (PBMCs) long after antiviral therapy of chronic hepatitis C in patients repeatedly negative for viral RNA in serum. This occult infection associates with impaired immune response and the risk of lymphoproliferative disorders or progressive liver disease. There are currently no monitoring strategies for patients after treatment. We investigated if serum inflammation markers and interferon lambda (IFNL) genotype can be predictors of the presence of HCV-RNA and the replicative, HCV-RNA(–) strand in patients who reached sustained virological response after interferon-free therapy.

Material and methods: Forty two consecutive patients who remained HCV-RNA negative in serum 24 weeks after end of treatment (EOT) and during the follow-up were enrolled. Total HCV-RNA and HCV-RNA(–) strand were detected using ultrasensitive RT-PCR in PBMCs collected 12-15 months after EOT. Polymorphisms within IFNL3-IFNL4 region (rs12979860 and ss469415590) were genotyped with allele-specific PCR.

Results: Viral RNA was found in PBMCs from 31 (74%) patients, and of those 29 (69%) were also positive for HCV-RNA(–). Neither normalization of alanine aminotransferase nor IFNL genotype predicted the presence of residual HCV-RNA. Significantly higher neutrocyte to lymphocyte ratio (NLR) 24 weeks after start of treatment, predicted elimination of replicative HCV-RNA strand (OR = 0.23; 95% CI: 0.10-0.86; p = 0.019). Patients with no HCV-RNA(–) in PBMCs showed greater increase in neutrocyte count between EOT and baseline (p = 0.028).

Conclusions: Lack of significant elevation of NLR after therapy with directly acting antivirals could predict the presence of residual replicative HCV-RNA strand in PBMCs.

Real world experience of chronic hepatitis C retreatment with genotype specific regimens in non-responders to previous interferon-free therapy

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The development of interferon free regimens improved efficacy of antiviral treatment for HCV, but failures still occur. The aim of our study was to evaluate the efficacy of retreatment with genotype specific direct acting antivirals based regimens in non-responders to previous IFN-free therapy.

Studied population consisted of 31 non-responders to interferon-free regimen, which received second interferon-free rescue therapy, selected from 6228 patients from a large database EpiTer-2. Age, gender and genotype in this group were similar to whole population, but included patients demonstrated more advanced fibrosis. Primary therapy was discontinued in 12 patients recognized as non-virologic failures, whereas virologic failure was recognized in 19 patients which completed therapy.

Overall SVR rate was 81% and 86% in intent-to-treat (ITT) and modified ITT analysis, respectively (74% and 78% in virologic failures, 92% and 100% in non-virologic failures). There were no significant differences in SVR rate after the rescue therapy related to the type of administered primary or rescue regimen. All non-responders to rescue therapy were cirrhotics. SVR in cirrhotic virologic failures was 62%, whereas vs. non-virologic failures and non-cirrhotics achieved 100%. Resistance associated substitutions testing was carried out in 8 virologic non-responders, three of them had risk for failure related to NS5A, but two of them achieved SVR.

Concluding, rescue therapy with genotype specific regimens can be considered in non-virologic failures related to discontinuation of primary therapy and in non-cirrhotics, but should be avoided in cirrhotics after virologic failure. RAS testing is not essential after the first failure of treatment.

Comparative effectiveness of 8 versus 12 weeks of ombitasvir/paritaprevir/ritonavir and dasabuvir in treatment-naïve patients infected with HCV genotype 1b with non-advanced hepatic fibrosis

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Introduction and aims: Since 2016 treatment-naïve patients with chronic hepatitis C virus genotype 1b infection with minimal or moderate fibrosis can be treated with ombitasvir/paritaprevir/ritonavir and dasabuvir (OprD) for 8 weeks according to Summary of Product Characteristics updated based on results of Garnet trial. The aim of our study was to assess the comparative efficacy of 8 and 12-week treatment duration of OPrD in patients with none, minimal or moderate fibrosis (F0-F2) treated in real-world setting.

Material and methods: We analysed data of 3067 HCV genotype 1b infected patients treated with OPrD between 2015 and 2017 obtained from EpiTer-2 database.

Results: A total of 800 patients with not advanced fibrosis were enrolled to the study, that included 223 (29%) treated for 8 weeks and 577 patients fulfilling criteria for shorter treatment but assigned to 12-week regimen. Majority of patients had no or minimal fibrosis, and they were more frequently treated for 8 weeks (80%) than 12 weeks (61%). Longer treatment duration was more often administered in patients with comorbidities (56% vs. 31%), concomitant medications (45% vs. 30%), HIV coinfected (0.7% vs. 0%) and HBV coinfected (11.6% vs. 7.2%). SVR was achieved in 211 (95%) patients treated for 8 weeks and 561 (97%) for 12 weeks ($p = 0.09$). After exclusion of lost to follow up patients, SVR rate reached 96% and 98%, respectively, and the difference was statistically significant according to the Fischer analysis ($p = 0.02$). All 10 non-responders from the 8 weeks group were naïve to DAA and demonstrated viral load below 6 million U/l. All except one demonstrated minimal fibrosis (F1) and 9 were males. We were not able to identify factors associated with non-response in this group.

Conclusions: We confirmed high effectiveness of 8 and 12-weeks regimens of OPrD in genotype 1b HCV infected patients with non-advanced fibrosis and supported no need of 12-weeks therapy in large majority of such patients. Further analysis of growing population treated for 8 weeks is necessary to identify possible factors responsible for non-response.

Efficacy of 8 versus 12-weeks treatment with ledipasvir/sofosbuvir in chronic hepatitis C patients eligible for 8-weeks regimen in real world setting

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Introduction and aims: Non-cirrhotic treatment-naive hepatitis C patients infected with genotype 1 can be treated with ledipasvir/sofosbuvir (LDV/SOF) for 8 weeks according to Summary of Product Characteristics, but in real world practice this regimen is frequently extended up to 12 weeks. The aim of our study was efficacy comparison of 8 and 12-weeks regimens in patients eligible for 8 weeks therapy.

Material and methods: Data of HCV genotype 1 infected patients treated with LDV/SOF between 2015 and 2017 and included into the EpiTer-2 database were analysed in respect to patients characteristics and length of treatment.

Results: Among total of 1718 patients treated with LDV/SOF, 679 were included in the analysis and 238 (35%) received 8-weeks regimen, whereas 441 patients were treated for 12-weeks although fulfilled criteria for a shorter LDV/SOF course. Majority of patients were infected with genotype 1b (89%) and demonstrated minimal fibrosis (55%). Twelve weeks regimen was assigned significantly more frequently to patients with comorbidities (71% vs. 45%), concomitant medications (69% vs. 39%), advanced liver fibrosis (32% vs. 1%), HIV coinfected (7.9% vs. 2.5%) and HBV coinfected (13.4% vs. 4.6%). Sustained virologic response rate was similar after 8 (98%) and 12 (97%) weeks of therapy according to intent-to-treat analysis and reached 99% in both groups after exclusion of patients lost to follow-up.

Conclusions: We confirmed high and the same efficacy of 8 and 12-weeks regimens of LDV/SOF in non-cirrhotic chronic hepatitis C patients infected with genotype 1 which fulfilled criteria for 8 regimens according to current label and expert guidelines. This real-world study confirmed no need of 12-weeks therapy with LDV/SOF in this population.

New palliative therapies in HCC

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In 2008 analysis of SHARP trial showed that sorafenib improved overall survival (OS) of patients with advanced HCC (aHCC) in comparison with placebo (median OS: 10.7 months vs. 7.9 months, HR = 0.69, $p < 0.001$). Since then sorafenib has become a new standard for the treatment of aHCC, and has served as a reference regimen for future trials. In 2017, the results of REFLECT trial were released and showed that lenvatinib in comparison to sorafenib was a non-inferior first-line treatment option for patients with aHCC. The median OS with lenvatinib was 13.6 months compared with 12.3 months for sorafenib (HR = 0.92, 95% CI: 0.79-1.06). Until 2016 there were no accepted second-line treatment options for patients with aHCC. The first positive was the RESOURCE trial, which demonstrated regorafenib efficacy compared with placebo in second-line therapy. The median OS for regorafenib group was 10.6 months, and for placebo group was 7.8 months, and 38% reduction in the risk of death for patients treated with regorafenib (HR = 0.62, 95% CI: 0.50-0.78, $p < 0.001$). The second positive trial was the CELESTIAL trial. This trial, conducted in patients with aHCC who had progressed following at least one prior systemic therapy including sorafenib, showed that cabozantinib significantly improved median OS over placebo (10.2 months vs. 8.0 months, HR = 0.76, 95% CI: 0.63-0.92, $p = 0.0049$). Molecules that inhibit the PD-1/PD-L1 receptor seems to be valuable treatment option in advanced HCC. A phase I/II CHECKMATE 040 trial with nivolumab confirmed characteristic feature of anti-PD-1 molecules i.e. the persistence of a long-lasting clinical response (ORR) with a median of 17 months, and the long OS of 28.6 months for first-line therapy and 15.6 months for patients who progressed on sorafenib. In the phase II KEYNOTE-224 trial pembrolizumab induced ORR of 17% among patients previously treated with sorafenib, with median OS 12.9 months. Although, the KEYNOTE-240 confirmatory trial showed that the pembrolizumab improved OS vs. placebo (HR = 0.78, 95% CI: 0.611-0.998, $p = 0.0238$), it was not deemed statistically significant. Combination therapy using targeted agents with immune checkpoint inhibitors is expected to yield even better effects, and many trials are ongoing.

Four years of Polish experience with direct acting antivirals in HCV infection

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Interferon-free regimens based on direct acting antivirals (DAA) became available in Poland since mid 2015. Untill the end of 2018 10 166 patients were included in the EpiTer-2 study. Analysis of this database resulted with five already published articles. This real world experience provide huge source of informations about Polish HCV infected patients and changes in their profile between 2015 and 2018. Comparison of patients characteristics did not demonstrate changes in gender distribution, but significant reduction of age, as well as prevalence of overweight, accompanying diseases and concomitant medications were observed. Genotype 1b was predominant, but decreasing tendency from 87% in 2015/2016 to 78% in 2018 was observed. Increasing proportion of treatment naïve and non-cirrhotics were noticed. Despite of significantly reduced number of cirrhotics (from 44% to 15%) less patients have decompensation history, Child-Pugh > A, MELD > 15 and history of liver transplantation. In 2017 and 2018 propotion of HIV coinfected patients increased from 1.4% to 3.9%. Ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin (OPrDR) was the most frequent regimen till 2017, followed by ledipasvir/sofosbuvir ± ribavirin (LSR), but in 2018 the leading became grazoprevir/elbasvir ± ribavirin (GER). SVR rate after OPrDR was higher (97%) than LSR (95%) and GER (95%). SVR of 96% in non-cirrhotics was significantly higher than in cirrhotics (92%). Among 83 patients treated with pangenotypic regimens (available from mid 2018) with available efficacy data at the moment of the abstract submission, SVR was achieved in 93% only. It was due to administration to cirrhotic non-responders to previous DAA based therapies mostly.

Hepatology presentation of nonhepatotropic virus infection in immunocompetent subjects

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The lecture discusses the hepatology presentation of nonhepatotropic viruses infections. The literature search shows that wide group of viruses can cause liver disease including CMV, EBV, adenovirus, parvovirus B19, TTV and VZV. Most of the viruses listed above are common in population. In immunocompromised patients they may induce serious clinical course leading to severe hepatitis with acute liver failure. Nonhepatotropic infections in immunocompetent subjects are usually asymptomatic however increase of ALT and bilirubin may be present. In rare cases the infection may be the reason for acute liver failure and death. Nonhepatotropic viruses infection do not have specific clinical signs or symptoms allowing for easy differentiation from other causes of liver disease. Thus these infections should be taken into account in subjects with unexplained liver pathology. Detection of viral etiology of liver disease allows to modify the therapy with the limitation of the use of surgery or antibiotics.

Hepatological aspects of Epstein-Barr virus infections in children

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Epstein-Barr infections in children are usually asymptomatic. If the infection occured at a later age, in adolescents and adults, it can lead to infectoius mononuckleosis (IM). Over 95% of adults worldwide are infected with this virus and about half of the population has primary Epstein-Barr virus (EBV) infection until 5 years of age in developed countries. In the acute phase of primary EBV infections, hepatic involvement is common. Mild to moderate elevations of liver enzymes concern up to 80-90% of patients. Cholestatic EBV hepatitis is a rare presentation and severe cholestasis is seen in 5% of cases. Hepatic failure has rarely been reported. An atypical presentation of primary EBV infection is also acute acalculous cholecystitis, isolated gallbladder wall thickening or hydrops. In light of the sporadic presentation of AAC, the etiologic pattern and clinical spectrum of the disease in childhood have not been well established. The presence of Gilbert's syndrome in patients with cholestasis of infectious origin (EBV-infection) could also play a role in the development of gallbladder abnormalities. The incidence of Gilbert's syndrome may contribute in the pathogenesis of ACC in children with EBV infection. Infection-induced acute hepatitis complicated with acute pancreatitis is associated with hepatitis A virus, hepatitis B virus or hepatitis E virus. Although rare, EBV infection should be considered also in the differential diagnosis if the patient has acute hepatitis combined with pancreatitis. The mechanism of the relation with development of pancreatitis associated to infectious hepatitis are unknown and likely multifactorial. The reliable confirmation of infectious mononucleosis, as primary EBV infection, is detection of specific IgM antibodies or heterophile antibodies tests. There is also the possibility of false negative results, mainly in children. In these case real-time PCR is a reliable tool for diagnosis of primary EBV infection early in the course of disease. In addition, EBV DNA detection may serve as a useful diagnostic supplement in serologically indeterminate EBV infections.

Should the hepatitis B virus infection therapy be interrupted?

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Long-term therapy with nucleos(t)ide analogues is a corner stone of chronic hepatitis B management due to effective control of HBV replication and favourable safety profile. It reduces risk of liver related complications such as cirrhosis and hepatocellular carcinoma. The accepted endpoint for treatment discontinuation is hepatitis B antigen seroclearance but whether analogue therapy can safely be stopped before HBsAg loss is a subject of debate. The arguments for therapy cessation are: cost reduction, safety issues in the elderly, in patients with co-morbidities and HIV coinfection, procreation plans in young patients, risk of poor adherence over time, and chance for HBsAg seroclearance. The arguments against treatment discontinuation are: high probability of virological relapse, biochemical and clinical rebound with risk of hepatic decompensation and the frequent need for retreatment.

HDV – diagnostic and therapeutic challenge

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Coinfection and particularly superinfection with hepatitis D virus (HDV) of HBV-infected patients is considered important threat for their liver condition. It may cause the most severe form of chronic viral hepatitis with earlier development of liver cirrhosis, significant risk of hepatocellular carcinoma development and increased liver-related and overall mortality. Additional problem is lack of standardized diagnostic methods and poor correlation between anti-HDV positivity and HDV-RNA presence. In addition, treatment options for hepatitis D are currently limited. So far the standard of care might be pegylated interferon alpha treatment that was proved to suppress HDV replication in about 25% of patients but only a minority of patients can be treated with interferon-based therapies.

Altogether is a reason of doubtful real diseases burden assessment and difficulties in management standards development.

We have assessed the prevalence of anti-HDV in HBsAg-positive patients using different tests (both quantitative and qualitative) with PCR diagnosis of HDV replication in anti-HDV positive patients. The lack of repeatability of results with the use of different tests makes us look very critically at the usefulness of particular tests in the diagnosis of active HDV infection. The accurate diagnosis is important also because of expected new therapies within next a few years.

The key problems that have to be answered:

1. Choosing a serological test.
2. What test for HDV-RNA determination, as many of used in labs are home-made.
3. In whom anti-HDV testing should be obligatory (in all HBsAg+?).
4. In whom HDV-RNA testing as there are reports of HDV-RNA positive results in seronegative patients.
5. What HBV treatment and when (since the low/negative HBV-DNA viral load is not a sign of inactivity).
6. The role PEG-IFN and upcoming new therapies awaiting approval.

Epidemiology of hepatotropic virus infections in Polish blood donors

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The knowledge about the epidemiology of hepatotropic viruses in blood donors in Poland is based on the results of obligatory serological (HBsAg, anti-HCV) and molecular (HBV DNA, HCV RNA) screening, additional testing of plasma for fractionation (RNA HAV) and emerging pathogens monitoring in blood donors (anti-HEV and RNA HEV). During the presentation epidemiological trends will be discussed (number of infections/100,000 donors, 95% confidence interval, CI) in years 2005-2018, and for HEV in 2015.

The frequency of confirmed anti-HCV results decreased significantly from 368 (342-394) in 2010 to 105 (89-121) in 2018 in first-time donors and from 12.9 (8.7-17.1) in 2006 to 5.2 (3.1-7.3) in 2018 in repeat donors. In first-time donors, a significant decrease was noted in the age groups below 50 years-old.

The frequency drop for seropositive HBV infections was found among both, first-time: from 601 (567-635) in 2005 to 126 (109-145) in 2018 and repeat blood donors: from 7.6 (4.9-11.7) in 2005 to 0.2 (0-1.2) in 2018, RR 0.21 (0.18-0.24) and 0.03 (0-0.21) respectively. So far, 2017 was the first and the only one year without HBsAg-positive infections in repeat donors. The most significant decrease of HBsAg detection among first-time donors was recorded in the age group up to 20 years (RR = 0.01 (0-0.03)), significant changes were not noticed in donors over 50 years old.

For 14 years, the majority seronegative infections were detected for HBV: 184 occult infections (OBI) (frequency/1 million donors, 95% CI: 22.7, 19.7-26.3) and 47 in serological window period (WP) (5.8, 4.4-7.7). During this period 75 HCV WP (9.3, 7.4-11, 6) were identified.

HAV infections were not detected until the outbreak. In 2017-18, 17 infected donors (2.6/100,000 donors, 1.4-3.7) and two likely transmissions via transfusion were identified.

In 2015, the frequency of HEV RNA was 47.4 (21.7-103.3)/100,000 first-time donors, and anti-HEV IgG antibodies were found in 43.5% (41.8-45.3) donors.

Currently, the highest risk of transfusion-transmitted infection (TTI) concerns HEV, following HAV during the epidemic period (up to several cases per year). The risk of HBV transmission is mainly associated with OBI. For HCV, TTI is estimated to may occur no more frequently than once every few years.

Nephropathies: different pictures of the disease (nephrological part)

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Ciliopathies, the defects of organ microstructure with cystic phenotype, include renal damage among several organs. The presence of renal cysts has several phenotypic patterns and those which are of genetic background are divided, in terms of localisation, volume and clinical consequences, to recessive and dominant polycystic kidney disease (ARPKD, ADPKD), various types of medullar cystic pathologies (nephronophtysis) and cystic disease accompanying tuberous sclerosis (TSC). Simple cysts as well as cysts present in some cases of renal cancer or congenital kidney diseases (CAKUT) are of separate pattern. Several ciliopathies are limited to the kidneys, while in remaining ones the several variable extrarenal symptoms, including hepatic, CNS, large vessels, pancreas and intestine pathologies accompany the presence of renal cysts. The diagnostic algorithm starts with detailed defining of phenotype and ends with genetic evaluation, which confirms final diagnosis (especially in syndromic cases), indicates the need for additional diagnostic procedures in cases when some potentially important clinical symptoms are not overt yet and determines the outcome, at least in terms of renal survival. The clinical diagnostic sequence starts with evaluation of renal function (filtration rate and tubular functions), then goes to the imaging procedures: renal USG, evaluating numer, size and localisation of the cysts; CT or MRI evaluating the volume of the cysts and it's progression over time and presence/development of solid changes inside the cysts; and (upon additional indication) radiologic evaluation of pathology of great vessels and cerebral circulation (in ADPKD). The management is variable and may include ongoing correction of homeostasis disturbances (nephronophtysis), renoprotection with ACEi or blocking of vasopression receptors with tolvaptan (ADPKD), use of mTORi (sirolimus or everolimus) in TSC and finally the isolated kidney or combined/sequential liver-kidney transplantation in severe cases of ARPKD. Distinct management based on radiologic intervention or surgical treatment of arterial wall abnormalities (coarctation or aneurysms), secondary to the defect of polycystin (relevant both to cysts formation and arterial wall defects) is necessary in some cases in ADPKD.

Non-alcoholic fatty liver disease (NAFLD) in lean subjects

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Non-alcoholic fatty liver disease (NAFLD) in people with normal body weight often remains unrecognized. Epidemiological studies, albeit few in number, suggest that this problem may affect from several to more than a dozen percent of people in the general population with a normal body mass index (BMI). The pathogenesis of lean NAFLD seems to differ from the disease in obese people, but the consequences in the form of cirrhosis, as well as the risk of developing hepatocellular carcinoma are analogous. In view of the few studies, it is difficult to unequivocally assess the specificity of metabolic disorders, as well as extrahepatic risk, the effectiveness of therapeutic treatment, including the essential for the treatment of NAFLD in obese people, weight reduction. It is emphasized in people with visceral obesity. Further research on therapies, including metabolic disorders disturbed by their distinctness and genetic determinants, are necessary to determine the proper algorithm of management. For the clinician, the most important issue is that people with normal BMI may be at risk of fatty liver disease and require diagnostic procedures similar to those with obesity and metabolic syndrome. Diagnosis of the disease, even in the absence of pharmacotherapy, allows the implementation of appropriate measures limiting the negative effects of the disease.

Dietary factors associated with the development of NASH

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Nonalcoholic steatohepatitis (NASH) is a disease that affects an increasing part of the population around the world and is associated primarily with environmental factors such as diet and its effect on metabolic changes in the body, which is a trigger mechanism for the induction of fatty liver. NASH is considered a type of chronic hepatitis reminiscent of the changes occurring in people who abuse alcohol, but the cause is completely different factors. It is regarded as a progression of non-alcoholic hepatitis and is a risk factor for the

development of liver cirrhosis and hepatocellular carcinoma. According to the latest literature data, the most important in the development of the disease are carbohydrate-related disorders of insulin resistance type, resulting in the accumulation of fat in hepatocytes and their steatosis. As a result of chronic oxidative stress, lipid peroxidation occurs with the production of proinflammatory cytokines and the development of hepatitis (NASH). Numerous dietary factors leading to steatosis are primarily simple sugars found in food products, especially glucose-fructose syrup and a diet rich in carbohydrates and simple sugars, including natural (e.g., juices, fruits, honey, sweetened beverages). Hepatic metabolism disorders on this background concerning glycogenolysis, glyconeogenesis and fat metabolism favor the rapid development of hepatocyte reversal and steatosis, even in lean patients. Effective dietary intervention involving a long-term change in eating habits has a huge impact on the reduction of liver steatosis, is the only prophylactic action, and while maintaining dietary regimen, including liver regeneration capabilities, allows the retreat of even advanced NASH changes, confirmed in both laboratory and available non-invasive methods (e.g., fibroscan, ultrasound).

HCV infection and metabolic/ cardio-vascular risks

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Liver steatosis is a common disorder in chronic HCV infection, affecting from 40% up to 80% patients. HCV-dependent fatty liver is linked to particular virus genotype. Metabolic steatosis prevails in infections due to viruses of not genotype 3, while in viral one viruses of genotype 3 are apparently responsible. In the latter some virus sequences were shown to induce lipid accumulation in hepatocytes. Moreover, fatty change in liver was found to be correlated with viral replication. Some liver proteins such as seipin participate in the formation of cellular large lipid droplets. HCV-dependent liver steatosis appears to be promoting factor for insulin resistance, leading to diabetes, liver fibrosis and hypo-beta lipoproteinemia. Blood laboratory findings show high triglyceride and insulin levels but low values of adipokines and especially adiponectin. It is of interest, that in patients treated by DAA new cases of insulin resistance and type II diabetes were practically not found. In HCV infection lipid accumulation affects also cardiovascular system manifested by arteriosclerosis, coronary arteries of heart, internal carotid arteries and brain ones, the latter often leading to a stroke. Thus, close attention to metabolic lesions during HCV+ liver disease seems to be mandatory.

Role of ethanol in cancerogenesis

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Ethanol is responsible for the development of diseases of many organs and it is the reason for the development of 3.6% of cancers. There is no safe dose of alcohol with respect to risk of cancer development. The carcinogenic activity of ethanol is based on the toxic effects of acetaldehyde, which has mutagenic effects on DNA. Ethanol is metabolized to acetaldehyde through three metabolic systems: cytochrome CYP2E1, alcohol dehydrogenase and catalase. Microbiota has a significant impact on the development of metabolic diseases and cancer. A significant change in microbiota composition leading to dysfunction of intestinal barrier is observed in patients chronically ingesting ethanol, obese and with diabetes. There is a clear relationship between chronic ethanol consumption and the development of tumors of the upper gastrointestinal tract and liver. More and more evidence points to an increase in the development of colon and pancreatic cancer for the people consuming ethanol. The role of alcohol in the development of pancreatic and gastric cancer is still not fully understood and can be modified by environmental, genetic and dietetic factors. Further studies are necessary to better explain and understand the role of ethanol in pathogenesis of cancer development and progression.

Renal activity in liver transplant recipients

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Improved long-term survival after liver transplantation (LTx) has led to increased prevalence of late complications after LTx such as chronic kidney disease (CKD). CKD has become one of the leading causes of morbidity and mortality after LTx. The reported prev-

alence of CKD after LTx ranges between 10% and 45%. Although calcineurin inhibitor-toxicity is typically considered a major contributor, other risk factors for CKD include perioperative acute kidney injury, HRS, preexisting CKD, diabetes mellitus, hypertension and chronic hepatitis C infection, donor factors. Decreased GFR < 30 ml/min is a risk factor of mortality after LTx. Renal biopsy can be relatively safe population with liver failure, may help elucidate the etiology of renal failure, may predict post-LAT kidney function, and may be helpful in kidney allocation for liver transplant candidates, but little data exist to validate the usefulness of kidney biopsies in this patient population. Frequent diagnosis includes glomerulonephritis, ATN, thrombotic microangiopathy. Renal biopsy in patients with CKD after LT should be performed, it seems safe and may offer specific therapeutic options. Furthermore, unnecessary changes of immunosuppression can be avoided in a considerable number of patients. Recommendations of ILTS for immunosuppression modification are presented below. In the peri-operative period to optimize renal function induction therapy (interleukin-2 receptor antibodies or short-term of antilymphocyte/thymocyte antibody preparations) combined with cortiosteroids and MMF/MPA and reduced dose or delayed initiation of CNIs is associated with superior renal function and less need for renal replacement therapy than early initiation and standard dosing of CNIs. mTORis should be avoided in the first postoperative month. Early institution at one month of EVL in combination with low dose TAC (5 ng/ml) results in a significantly better renal function than is achieved with standard dosing of TAC. This strategy is particularly beneficial in patients with CKD ≥ stage 3 (eGFR < 60 ml/min). CNI minimization should attempted in patients with CKD in the late postoperative period. Late (> 1 yr) conversion to mTORis is of unclear effect on renal function, particularly in patients with CKD > 3.

Extracorporeal therapies in liver failure

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Albumin dialysis is the best-studied extracorporeal nonbiologic liver support system as a bridge or ultimate therapy for patients with liver failure awaiting liver transplantation or recovery of liver function. Nonbiologic systems use artificial membranes and adsorbents to detoxify the blood in patients with liver failure. Albumin dialysis is based on the removal of albumin-bound and water-soluble substances, such as bilirubin, bile acids, ammonia, nitrotyrosine, and fatty acids. There are three available albumin dialysis systems: the molecular adsorbent reticulating system or MARS (Teraklin, Rostock, Germany), single-pass albumin dialysis (SPAD), and the Prometheus system (Fresenius, Bad Homburg, Germany). Use of albumin dialysis as a supportive treatment for liver failure is successful at removing albumin-bound molecules, such a bilirubin and at improving hepatic encephalopathy. However, survival benefit has not been established yet, after the analysis of 10 randomized control trials (7 of MARS and 3 of Prometheus, no trial of SPAD), and 2 head-to-head trials comparing MARS to Prometheus, with 3688 participants. In our single-center experience SPAD was used in acute-on-chronic patients with acute kidney injury. The results were summarized in the already submitted paper, entitled "Intermittent high-flux albumin dialysis with continuous venovenous hemodialysis for acute-on-chronic liver failure and acute kidney injury" by G. Niewiński, J. Raszeja-Wyszomirska, M. Hrenczuk, A. Rozga, P. Malkowski, J. Rózga. In patients with severe ACLF and acute kidney injury, renal replacement therapy coupled with high-performance albumin dialysis improved estimated 28- and 90-day survival and laboratory parameters. We also published our unique experience with treatment of intractable pruritus and analyzed the efficacy of plasmapheresis in a cohort of patients with primary biliary cholangitis (PBC) in article entitled "Plasmapheresis exerts a long-lasting antipruritic effect in severe cholestatic itch" by M. Krawczyk, R. Liebe, M. Wasilewicz, E. Wunsch, J. Raszeja-Wyszomirska, P. Milkiewicz (Liver Int 2017; 37: 743-747; doi: 10.1111/liv.13281). After the series of plasmapheresis mean pruritus decreased in the entire and antipruritic effect persisted throughout the 90-days follow-up. Thus, there is a need for a large, multicenter, randomized control trials of efficacy and safety of SPAD therapy in acute-on-chronic liver failure, especially with renal complication, with novel filters dedicated to remove proinflammatory cytokines (e.g. the Ci-Ca®CVVHD EMiC®2 kit) and with other indication, i.e. intractable pruritus.

Psychological aspects of addiction therapy

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Alcohol dependence and abuse is one of the most costly health problems in the world from both a social and

an economic point of view. It is a widespread problem, focusing attention not only psychiatrists but also doctors of other specialties. Patterns of drinking appear to be changing throughout the world, with more women and young people drinking heavily. Even risky drinking is a potential health risk, while chronic alcohol abuse contribute to the serious physical and mental complications. Alcohol used disorders associated with alcohol-induced brain damage include: withdrawal state, delirium tremens, alcoholic hallucinosis, alcoholic paranoia, Korsakoffs psychosis, alcoholic dementia, alcoholic depression. On the other hand, mental disorders as panic disorder, social anxiety disorder, agoraphobia, depression, bipolar disorder, schizophrenia, personality disorder most frequently comorbid with alcohol abuse or they trigger alcohol.

The most common liver tumors – the management

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Of the liver focal lesions, the most common are benign tumors: hemangiomas, cysts, FNH and HCA. Malignant lesions are metastases and primary carcinomas of the liver: HCC and cholangiocarcinomas. After finding the focal lesion in ultrasonography, the basic role in the diagnosis of liver tumors is performed by three-phase CT and magnetic resonance with contrast. Biopsies are less frequently performed only in unclear cases. Cancer markers (AFP, CA19.9, CEA), co-morbidities (HCV, HBV infection) and possibly oncological history of the patient may be helpful in diagnosis. Benign lesions rarely require treatment. The problem is to recognize them clearly. In metastases, depending on the size and number of tumors, we use resection, RFA along with chemotherapy. The possibility of surgical treatment concerns only the metastases of colon cancer and neuroendocrine tumors. In the case of HCC, we base our qualification for treatment on the Barcelona classification. Intrahepatic cholangiocarcinoma is an indication for resection.

PET/CT in diagnosis of primary liver tumours and liver metastases

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Hepatocellular carcinoma (HCC) is the fifth most common neoplasm in the world and the leading cause of death among cirrhotic patients. The radiologic modality most widely used contrast-enhanced CT has sensitivity around 70%, and MRI, around 80%. Positron emission tomography (PET) imaging using fluorodeoxyglucose (18F-FDG) wildly use in oncological disease, but in liver cancer has remained limited The sensitivity of 18F-FDG PET for detecting HCC is not better than conventional imaging (50-70%), mostly because well-differentiated HCC has a high rate of gluconeogenesis comparable with normal liver tissue, resulting in similar uptake of 18F-FDG. PET tracers of lipid metabolism have been proposed as a better method for the detection of HCC. 11C-labeled acetate was reported to be beneficial because of its better sensitivity, as high as 87%, for the detection of low- and intermediate-grade HCC. Choline is one of the components of phosphatidylcholine, an essential element of phospholipids in the cell membrane. 18F-fluorocholine for the detection of intrahepatic HCC is close to published values for 11C-acetate, with a sensitivity ranging from 75% to 87%. The liver is the most frequent site of metastases after the lymph nodes and at the same time the main organ, where the dissemination occurs through blood vessels. 18F-FDG PET/CT is the most sensitive method for the detection of liver metastases especially from multiple gastrointestinal origins, with a mean weighted sensitivity of 90-92%. However 18F-FDG PET/CT has limited utility in cancers with low rate of glucose metabolism as a neuroendocrine tumor, bronchoalveolare carcinoma, mucous cells carcinoma, iodine-avid diff. thyroid cancer, clarocellurare carcinoma and prostate cancer. The eighties brought the discovery of somatostatin receptor(SSTR) overexpression on neuroendocrine tumors. It allows the receptor imaging with radiolabeled somatostatin analogs and somatostatin based radiopeptide therapy as a next step. 111In-(DTPA)–pentetreotide and 99mTc-HYNICTOC are registered for use in Europe, where SPECT/CT equipment is now widely available in many hospitals. 68Ga-DOTATATE PET/CT offers higher spatial resolution and performs better than conventional SSTR imaging, especially in small metastases in liver, bone and lymph nodes. So nowadays, 68Ga-DOTA-labeled radiopeptides is the investigation of choice in managing of neuroendocrine tumors.