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Falk Symposium 186
Challenges of Liver Cirrhosis and Tumors: Prevent it, Treat it, Manage Consequences
October 5 – 6, 2012
Congress Center Mainz
Mainz, Germany

Abstracts
Poster Abstracts
Falk Symposium 186

CHALLENGES OF LIVER CIRRHOSIS AND TUMORS: PREVENT IT, TREAT IT, MANAGE CONSEQUENCES

Mainz (Germany)
October 5 – 6, 2012

Scientific Organization:
P.-A. Clavien, Zurich (Switzerland)
P.R. Galle, Mainz (Germany)
G.J. Gores, Rochester (USA)
U. Protzer, Munich (Germany)
M. Schuchmann, Mainz (Germany)
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Session I

Hepatocellular Carcinoma (HCC)
The size of the problem – Clinical algorithms

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Hepatocellular carcinoma (HCC) is a major health problem with heterogeneous geographic incidence as a result of an heterogeneous prevalence of risk factors. These include infection with hepatitis B (HBV) or C viruses and alcohol intake. Hereditary hemochromatosis is less prevalent and non-alcoholic steatohepatitis has an increasing importance. Contamination with aflatoxin acts in combination with HBV infection. Mortality rate in each area almost equals incidence exposing the lack of effective therapy at diagnosis. More than 700,000 cases are diagnosed yearly.

In more than 90% of the cases HCC develops in chronic liver disease, namely cirrhosis. Thus, prevention is based in avoiding acquisition and maintenance of risk factors. Antiviral treatment has a positive impact, but if delayed until cirrhosis, its efficacy is controversial.

HCC is the main cause of death in cirrhotics. The sole option for long term survival relies in its detection at an early stage when curative treatment is feasible. Since the population at risk is identified and Ultrasound (US) is an effective screening test, all scientific associations recommend regular US in patients at enough risk for HCC. Screening should be initiated if effective treatment would be indicated upon diagnosis. Alpha-fetoprotein (AFP) and other markers do not have clinical value for screening and diagnosis. Tumor biopsy is negative 40% of the patients with HCC < 2 cm. This has primed diagnostic criteria based in imaging techniques. HCC diagnosis is established if intense arterial contrast uptake followed by contrast “washout” in delayed venous phase is observed at MR or CT in a nodule > 10 mm within a cirrhotic liver.

Upon HCC diagnosis the patients have to be staged and treated. The BCLC model is the recommended system for outcome prediction and treatment indication. As shown in the figure, it stratifies patients into 5 stages and each of them is linked to a specific treatment option.

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BCLC Staging and Treatment Strategy, 2012

The potential of surveillance – The Japanese experience

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Background: Beginning in 1965, the Liver Cancer Study Group of Japan (LCSGJ) started a nationwide prospective registry of all patients with hepatocellular carcinoma (HCC). To determine the effectiveness of surveillance and treatment methods longitudinally, we analyzed improvements over time in overall survival (OS) of 173,378 patients with HCC prospectively entered into the LCSGJ registry between 1978 and 2005.

Methods: All patients throughout Japan with HCC were entered into the LCSGJ registry. Patients were grouped by years of diagnosis, with OS and 5-year OS rates calculated. We also assessed OS and 5-year OS rates in patients who underwent resection, local ablation, transarterial chemoembolization (TACE), and hepatic arterial infusion chemotherapy (HAIC) and in those with baseline serum alpha-fetoprotein (AFP) ≥ 400 ng/ml.

Results: The overall 5- and 10-year OS rates in the cohort of 173,378 patients were 37.9% and 16.5%, respectively. Over time, however, mean maximum tumor size decreased significantly, whereas 5-year OS rates and median survival time increased significantly. Similar findings were observed separately in patients who underwent resection, local ablation, TACE, and HAIC, as well as in patients with AFP ≥ 400 ng/ml.

Conclusion: The establishment of a nationwide HCC surveillance program in Japan has contributed to longer median OS and increased OS rates in patients diagnosed with this disease. These findings suggest that the establishment of a surveillance program in other countries with patients at risk for HCC may provide significant survival benefits.
Molecular pathogenesis of human liver cancer

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The cardinal hallmark of cancer is a profound heterogeneity in cellular morphology, genetic landscape and response to therapeutic interventions. This heterogeneity is seen in tumors from the same and different organs. The relative contribution of the genetic and/or epigenetic mutations occurring within a specific cell type or different tumor subtypes developing from distinct cells in the tissue to the maintenance of tumor heterogeneity is still unresolved. It is however recognized that the activation of the same oncogenic process at different stages of cellular lineage can strongly affect both malignant potential and tumor morphology.

Hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) are the major primary adult human liver cancers (PLC). Both HCC and CC are morphologically, genomically and clinically very heterogeneous with dismal clinical outcome. In addition, a rare form of primary adult liver cancer, combined hepatocellular-cholangiocarcinoma (CHC), is recognized and has morphologic characteristics of both HCC and CC. Although the cell(s) of origin for PLC is not firmly established, hepatocytes, cholangiocytes and adult liver stem/progenitor have been proposed as the cells of origin for some or all the variants of primary human liver cancer. We have previously applied an integrative oncogenomic approach to address the clinical and functional implications of the overlapping phenotype between the HCC, CHC, and CC, and identified a novel HCC subtype, CC-like HCC (CLHCC), which expressed CC-like traits (CC signature). CLHCC showed, similar to CC and CHC, an aggressive phenotype with shorter recurrence-free and overall survival. In addition, CLHCC co-expressed embryonic stem cell-like expression traits (ES signature) suggesting its derivation from bi-potential hepatic progenitor cells (also referred to as hepatoblasts).

We have recently investigated the cellular origin of liver cancer by exploiting the hierarchical nature of liver development. This study is based on the ex vivo genetic manipulation of cells at specific stages of the hepatocytic lineage and transplantation of the genetically altered cells into immune-compromised mice. The results from this study will be discussed.
HCC – Systemic therapy and synergies by combination

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After years of therapeutic nihilism due to the inefficacy of conventional cytotoxic chemotherapy, the multikinase inhibitor sorafenib was the first agent to demonstrate a significant improvement in the overall survival for patients with advanced hepatocellular carcinoma (HCC). However, the overall survival prognosis on sorafenib treatment is still lower than 10 months in most cases in clinical practice, particularly for patients with negative prognostic indicators such impaired liver function or more advanced disease. Up to now, no other targeted agent has proven efficacy to prolong survival in patients with advanced HCC in a phase III trial in the first- or second-line setting, and no treatment option currently exists outside of clinical trials for patients with acquired resistance or intolerance to sorafenib. No oncogene addiction is yet known to be implicated in hepatocarcinogenesis and this may explain why no single agent will achieve sustained partial or complete response in the majority of patients. The identification of the key driver signalling pathways and the assessment of relevant targets for specific subclasses of patients will hopefully lead to a more personalized medicine. Several agents with mainly antiangiogenic properties are currently in the phase II and III development for the treatment of patients with advanced HCC including brivanib, ramucirumab, everolimus, tivantinib or resminostat. In addition, the role of targeted therapy in earlier stages of the disease in combination with TACE or in the adjuvant setting after potentially curative approaches is under investigation. This article will provide a concise overview on recent developments of systemic therapy in advanced HCC with a special focus on synergistic combinations and combined treatment modalities.
HCC: Surgical options

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Hepatocellular carcinoma (HCC) is a serious health problem worldwide because of its association with hepatitis B and C viruses. Liver transplantation (LT) and liver resection are the two best established curative treatment options.

LT, in selected cases is the best treatments since it removes both the tumor and the underlying liver disease. The prerequisite for long term success of LT for HCC depends on tumor load and strict selection criteria with regard to the size and number of tumor nodules. The need to obtain the optimal benefit from the limited number of organs available has prompted the maintenance of selection criteria in order to list only those patients with early HCC who have the better long term outcome after LT. In such conditions, LT in unresectable HCC patients achieves 5-year survival above 75%.

Since LT can only be proposed to less than a third of patients with HCC, liver resection, including the laparoscopic approaches, appears as one of the best alternative therapy. The decision making process for liver resection should integrate tumour stage, quality and function of the underlying liver parenchyma, volume of the future liver remnant and general condition of the patient. In patients with the best features (solitary tumour, compensated cirrhosis (Child A), no portal hypertension), the reported 5-year survival rates range from 50–70%. However, recurrence rate after liver resection for HCC is still high (> 50% at 5 year) being related to the underlying liver disease and the biological characteristics of HCC tumours. In specific cases, liver resection and LT may be combined in the same patient.
Hans Popper Award Lecture

Hepatocellular carcinoma: The BCLC approach to clinical and translational research

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Hepatocellular carcinoma (HCC) is a worldwide health problem with significant increase in Europe and Americas. Several advancements in the understanding of the molecular pathogenesis, epidemiology and management of the disease during the last 20 years have changed the approach to HCC. The major role of hepatitis C virus infection in the West has been fully established and recent data suggest the emerging role of metabolic syndrome leading to non-alcoholic fatty liver disease and steatohepatitis. Molecular biology of the disease is better understood, including the importance of subclasses such as proliferation, Wnt signalling and inflammation, the identification of drivers of oncogenesis as targets for therapies along with the relevance of the microenvironment in the initiation and progression of this neoplasm. The evidence of the pivotal role of key signal transduction pathways and the improvements in experimental models have allowed to refine the selection of drugs for testing, although no oncogenic addition loops are yet recognized. Imaging techniques have allowed HCC detection at early stage, confident non invasive diagnosis avoiding biopsy and accurate staging. Such capacity has facilitated a better understanding of the natural history of the disease, the proposal of novel staging systems and the definition of the 1st line treatment for any evolutionary stage at diagnosis. This is the major advantage of the BCLC staging and treatment strategy that links the evaluation of the patients with the optimal recommended therapy. This classification has been adopted by AASLD, WGO and EASL-EORTC guidelines for management of HCC and is the main tool used globally for patient treatment allocation and exchange of information among researchers. It now includes five effective treatments: surgical resection, ablation, liver transplantation, chemoembolization and sorafenib. Particularly, the advent of the multikinase inhibitor sorafenib as an effective molecular targeted therapy represents a breakthrough that has changed the landscape of treatment interventions. All these approaches have been shown to improve survival through robust investigations and currently, the diagnosis and management of patients with HCC can be applied according to evidence-based science.

The better understanding of the clinical pattern, natural history and treatment indication has paved the road for advanced clinical research in several areas: prevention, early diagnosis and adjuvant therapy both after potentially curative and palliative treatment. Further advancements in the field should come from the intense and generous collaboration between basic and clinical researchers.
Primary sclerosing cholangitis (PSC) is a chronic inflammatory and fibrosing disease of intra- and/or extrahepatic bile ducts. PSC mainly affects young to middle aged patients and leads to liver cirrhosis and end stage liver disease within 10–20 years. PSC is associated with a greatly increased risk to develop hepatobiliary malignancy, mainly cholangiocarcinoma (CCA), for which PSC is the main risk factor in northern countries.

Little is known about the pathogenesis of CCA in PSC. Although it may be assumed that CCA develops as a consequence of long standing biliary inflammation, most tumors are detected within the first year after PSC diagnosis. CCA incidence remains stable thereafter at around 0.5% per year. The association of biliary dysplasia and cancer within the same liver may point to a low grade to high grade dysplasia to carcinoma sequence in CCA pathogenesis. NFkB activation and IL-6 may be involved in inflammation induced biliary epithelial carcinogenesis. Mutations in genes controlling apoptosis and cell cycle, such as p53 and p16 tumor suppressor gene have been demonstrated in PSC-associated CCA. The transcriptional control of oncogenes by microRNAs may also be involved in CCA pathogenesis and their role in PSC associated carcinogenesis is under investigation.

The current guidelines do not recommend CCA surveillance strategies in patients with PSC. The early detection of these tumors is extremely difficult and it is challenging to differentiate benign dominant strictures from malignant stenoses using the currently available imaging techniques. The value of carbohydrate antigen 19-9 (CA19-9) for the screening or diagnosis of CCA is controversial. The low sensitivity of brush cytology can be increased by using fluorescence in situ hybridisation (FISH), detecting chromosomal aberrations. Recently, proteome analyses of bile fluid and even urine have shown promising results in the non-invasive detection of PSC-associated CCA. These results are exciting, but will have to be confirmed in larger studies and the diagnostic accuracy will have to be shown in early stage tumors.
Liver transplantation for perihilar cholangiocarcinoma

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Perihilar cholangiocarcinoma is a complex and devastating disease. Its complexity in part arises from the difficulty of establishing a diagnosis, especially in PSC patients. We have found fluorescent in situ hybridization of cytologic specimens obtained at the time of ERCP to be very helpful in establishing a diagnosis of cholangiocarcinoma. In particular, FISH polysomy, a marker for aneuploidy and chromosomal instability, is useful in establishing a diagnosis of this malignancy. This cancer is also difficult to stage. Endoscopic ultrasound with fine needle aspirates of regional lymph nodes has high utility in identifying patients who have advanced disease with lymph node metastases. Once we have established a diagnosis and staged the disease, patients who are resectable by conventional surgical techniques are referred for surgery. However, patients who are not resectable or who have primary sclerosing cholangitis (PSC) and meet highly selective criteria become eligible for liver transplantation. These patients must have a radial mass less than 3 cm, cannot have intra or extra hepatic metastases, and must otherwise be suitable for liver transplantation. The protocol employs external beam radiation therapy followed by brachy therapy, and then Capecitabine until a staging laparotomy is performed. There is a high dropout rate while patients await liver transplantation of approximately 30% by 12 months, due to tumor progression. Overall, survival rates are approximately 65–70% at five years. The disease recurrence rate is 20%. Patients who have masses greater than 3 cm or who do not meet the criteria identified above have worse outcomes. These survival rates are better than those following surgical resection. Vascular complications occur frequently after liver transplantation. Portal venous anastomotic strictures are very common and can be managed by stent placement. In summary, neoadjuvant chemoradiation plus liver transplantation achieves excellent survival for patients with early stage perihilar cholangiocarcinoma.
Liver adenoma

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Hepatocellular adenoma (HCA) are benign hepatocellular tumors developed mainly in female. Recently, major advances were performed in the identification of new molecular signaling pathways related to benign hepatocyte proliferations. Progressively, we have three major signaling pathways altered in benign hepatocyte proliferation: inactivation of HNF1A, activation of the WNT/β-catenin and IL6/JAK/STAT3 pathways. Analyses of HCA have revealed new oncogenes (CTNNB1, STAT3, IL6ST and GNAS) and tumor suppressor gene (HNF1A) altered by somatic mutations. Further genotype/phenotype analyses identified a molecular classification of HCA in 4 subgroups closely associated with clinical, histological and prognostic features. Recent international studies have reported the clinical impact of the molecular classification in HCA patients including: identification of new risk factors, improvement in diagnosis, refinement of prognosis evaluation and related treatments.

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Session III

Viral Hepatitis
New insights into the replication cycle of hepatitis C virus and its interaction with the host cell

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Hepatitis C viruses (HCV) comprise a group of positive-strand RNA viruses that together with the flaviviruses and the pestiviruses belong to the Flaviviridae family. As a major cause of acute and chronic liver disease, HCV has received much attention.

The HCV genome contains a single large open reading frame encoding for a polyprotein that is cleaved into 10 different products. To all of these proteins distinct functions could be ascribed and three of them, the NS3 protease, the NS5A replicase factor and the NS5B RNA-dependent RNA polymerase are currently exploited as targets for antiviral therapy. With the advent of adequate cell culture models new insights into the close interaction between HCV and the host cell have been gained. For instance, several molecules involved in viral entry have been characterized and a complex picture emerges how the virus productively infects a cell. Moreover, numerous host cell factors have been identified contributing to efficient HCV replication. Two prominent examples are cyclophilin A that seems to activate the viral replicase and micro RNA 122 that enhances stability and translation of the viral RNA genome. Importantly, both host cell factors are actively pursued for HCV-specific antiviral therapy. Finally, surprising discoveries have been made how HCV interferes with the activation of the interferon system, yet the virus is sensitive to the antiviral state induced by interferons, arguing that interferons may drive viral persistence. The common denominator of all these findings is that HCV usurps multiple cellular processes to achieve efficient virus propagation in the context of a long-lasting infection.
Viral Hepatitis, HCV: How to treat in 2012

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Recently, telaprevir and boceprevir, two protease inhibitors, have been approved by the Food and Drug Administration (FDA) and European Medicines Evaluation Agency for genotype 1 patients in combination with Peg-IFN and ribavirin. Nowadays, triple therapy of directly acting antivirals (DAA), namely protease inhibitors with Peg-IFN and ribavirin forms the basis of new standard-of-care treatment of naive and treatment-experienced genotype 1 patients.

Genome-wide association studies have identified several single nucleotide polymorphisms near the IL28B gene (encoding IFN-λ3) to be strongly associated with spontaneous and treatment-induced clearance of HCV infection in genotype 1 patients treated with Peg-IFN and ribavirin. Recent studies evaluating predictors of response in naïve patients treated with boceprevir and telaprevir combined with pegylated interferon and ribavirin have showed that CC polymorphism at IL-28B is associated with response and can identify candidates for shorter treatment durations. Conversely, polymorphisms at IL-28B are not predictive factors of response in treatment-experienced treated with triple therapy.

However, the genetic barrier to resistance of those first-generation NS3/4A protease inhibitors is low and cross-resistance is extensive. The use of inhibitors will generate a new population of non-responders disclosing resistant variants. As no therapeutic can be proposed for those non-responders to triple therapy with protease inhibitors, clinicians should include such patients in clinical trials testing new DAAAs, thereby offering them a better chance for a cure. Indeed, clinical trials are currently evaluated new DAAAs such as second generation of NS3/4A inhibitor, nucleoside analogue inhibitors of HCV polymerase, non-nucleoside inhibitors of HCV polymerase, NS5A inhibitors and molecules targeting host cell proteins.

For non-1 genotypes, Peg-IFN and ribavirin remain the standard therapy. A flat dose of 800 mg/day is recommended for genotypes 2-3 patients whereas weight-based dose of ribavirin need to be given to genotypes 1-4-5-6. In non-1 genotypes patients, new regimen including DAAs are currently tested in late-stage clinical trials and will be available in the near future.

In terms of disease progression, the impact of HCV eradication via antiviral therapy is well-known. In European countries, antiviral therapy will reduce morbidity and mortality related to Hepatitis C virus infection. This beneficial effect of antiviral therapy will be amplified by the use of protease inhibitors.
Insights into immunology of hepatitis B virus infection

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Human hepatitis B virus (HBV) infects the liver of humans or humanoid primates. In humans, HBV infection often causes an inflammatory liver disease – hepatitis B. Vertical transmission from mothers to their neonates, or infection during the first year of life, results in persistent, often life-long infection in > 90%. In contrast, infection during adulthood is cleared in > 95% of cases, and results in life-long protective immunity.

While a correlation between a strong and polyclonal HBV-specific T cell response and virus clearance has been well established, factors determining the strength of T cell responses as well as factors shifting the balance from immune tolerance in chronic infection to immune clearance of HBV are hardly understood. Immune recognition of HBV, the innate immune response, early adaptive B- and T-cell responses, regulatory T cells, the liver microenvironment as well as peculiar properties of hepatocytes and non-parenchymal liver cells to present antigen and to skew immune responses contribute to the outcome of infection.

Understanding this complex interplay requires systematic immune monitoring of well characterized human cohorts, but also experimental approaches using primary human cells and mouse models of HBV infection. Using these models we begin to understand the immune recognition of HBV and how it influences the outcome of HBV infection.
Perspectives of future therapy for hepatitis B and D

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Treatment of hepatitis B infections is well established. Over the last years, international and national guidelines were published defining distinct treatment algorithms for different patient populations [1–3]. Two different treatment concepts are available: One the one hand pegylated interferon alpha (PEG-IFNα) allowing finite treatment with the aim to induce sustained immune control of HBV infection, on the other hand inhibitors of the HBV polymerase which are the nucleoside analogues lamivudine, telbivudine and entecavir and the nucleotide analogues adefovir and tenofovir. Maintainance therapy with nuceloside or nucleotide analogues is required for most patients and life-long treatment is frequently recommended. The decision which form of therapy should be used depends on multiple factors, such as the level of liver transaminases, potential contra-indications to IFN-treatment, HBV viral load, any previous treatment, the HBV genotype and the stage of liver disease [1–3].

Importantly, successful treatment of hepatitis B reduces the risk to develop clinical endpoints. Chronic hepatitis B very rarely progress to hepatic decompensation if continued treatment is provided and thus very few patients with chronic hepatitis B are currently listed for liver transplantation. Still hepatocellular carcinoma may develop, but the HCC-risk is significantly reduced by treatment-induced HBV-DNA suppression [4]. However, treatment options are currently limited to approved drugs and no phase-III trial for alternative compounds is currently ongoing. Several open questions still need to be resolved: Which patients require long-term antiviral therapy? Is it possible to stop nucleoside or nucleotide treatment after several years? Is there still a role for combination therapies of PEG-IFNα plus HBV polymerase inhibitors? Can we define biomarkers allowing allocation of the best treatment concept to each individual patient (e.g. which patients should receive PEG-IFNα and which patients should be treated a priori with nucleoside or nucleotide analogues? Are there any safety concerns of long-term treatment with polymerase inhibitors? Will resistance be an issue when long-term monotherapies are applied in most patients?

Alternative treatment concepts, which are currently in early clinical development, include immunotherapies such as alternative interferons (e.g. lambda-Interferon), toll-like-receptor agonists or therapeutic vaccinations. It needs to be defined which patients benefit most from these approaches. In addition, different steps in the HBV life-cycle can be targeted by antiviral compounds. First phase I studies on an HBV-entry inhibitor developed by Stephan Urban and colleagues have started [5–7]. These new treatment concepts should aim to eliminate HBsAg from serum and thus would also be important for hepatitis D virus infection, the most severe form of chronic viral hepatitis [8, 9]. PEG-IFNα is effective in only one quarter of hepatitis delta patients [10] and thus alternative treatment concepts are urgently needed.

Future treatment of hepatitis B will likely be a personalized medicine approach considering individual host, viral and environmental factors. Both, clinical and basic research is needed to define the optimal individual therapy for each individual.
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Session IV

Clinical Hepatology
Serum markers or elastometry vs. liver biopsy? The clinician’s perspective

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The prognosis and management of chronic liver diseases greatly depend on the amount and progression of liver fibrosis with the risk of developing cirrhosis. Liver biopsy, traditionally considered as the reference standard for staging of fibrosis, has been challenged over the past decade by the development of novel non-invasive methodologies. These methods rely on two distinct but complementary approaches: i) a “biological” approach based on the dosage of serum biomarkers of fibrosis; ii) a “physical” approach based on the measurement of liver stiffness using transient elastography. Non-invasive methods have been initially studied and validated in chronic hepatitis C but are now increasingly used in other chronic liver diseases, resulting in a significant decrease in the need for liver biopsy. However, they will likely not completely abolish the need for liver biopsy and they should rather be employed as an integrated system with liver biopsy.
Serum markers or elastometry vs. liver biopsy? The pathologist’s perspective

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Liver biopsy is and will remain the gold standard for assessing type, activity and extent of liver disease. Since it is an invasive measure that carries a small, but not irrelevant risk of significant unwanted effects there is a continuous effort to replace liver biopsy by non invasive measures. In the context of non-neoplastic liver diseases these efforts have centered on the development of serum derived algorithms and on the application of elastometry. While the latter has made its way into routine application to the expense of liver biopsy, the numerous serum algorithms have failed to develop clinical relevance in daily routine. There are several relevant points to be addressed:

• While serum assays and elastometry solely aim for determining liver fibrosis, histopathological assessment of liver biopsy is a multiparametric test, that determines type (comorbidity!), activity and stage (fibrosis) of disease and allows for exact analyses of causes of unclassified liver disease or unexpected comorbidity or differential diagnosis. Liver biopsy can be used as the basis for consultation, discussion in interdisciplinary conferences, additional or comparative analyses even after years and may provide a status at diagnosis or initiation of therapy. Furthermore has a high negative predictive value. Thus liver biopsy by itself is highly superior in its extent of information compared to any non-invasive test.

• While liver biopsy is a direct test – fibrosis and all other morphological alterations are visualized – serum algorithms and elastometry are indirect test – they do not measure fibrosis, but surrogate parameters (e.g. liver stiffness in elastometry). Due to this constellation multiple parameters affect the validity of elastometry, such as inflammatory activity, congestion or cholestasis and may lead to misinterpretation and limits its applicability.

• Advantages of elastometry beside its non-invasiveness is its high reproducibility and that it can be repeated easily; therefore, follow-up analysis can be performed without problems.

In conclusion, any chronic and potentially progressive or even life-threatening liver disease should at least be assessed by liver biopsy if any relevant clinical consequences may arise from the histopathological analysis. Liver elastometry is complementary and especially useful for follow-up. Attempts to replace liver biopsy by elastometry threatens to establish a self-fulfilling closed circle leading to inferior diagnostic assessment and many missed therapeutic options.
Cholestatic liver disease

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Cholestasis is an impairment of bile formation and/or bile flow which may clinically present with fatigue, pruritus – partially mediated by the lysophospholipase autotaxin (1) – and, in its most overt form, jaundice (2). Early biochemical markers include increases in serum alkaline phosphatase (AP) and/or γ-GT activities, followed by conjugated hyperbilirubinemia at more advanced stages. Cholestasis may be classified as acute or chronic (> 6 months) and intrahepatic or extrahepatic. Intrahepatic cholestasis is caused by hepatocellular functional defects or obstructive lesions of the small intrahepatic bile ducts. Most chronic cholestatic diseases are purely intrahepatic, whereas primary and secondary sclerosing cholangitis (PSC/SSC) may affect both small and large intrahepatic and extrahepatic bile ducts.

Our ability to systematically investigate genetic risk of complex diseases in cohorts of well phenotyped patients has been enhanced considerably by recent genome-wide association studies (GWAS). To date, several studies across a number of cholestatic disorders have provided previously unrecognized insights into disease pathogenesis. GWAS in primary biliary cirrhosis (PBC) and PSC have confirmed major histocompatibility complex associations and revealed multiple novel susceptibility loci outside the major histocompatibility complex (MHC) region (3,4). Notably, most of the non-MHC risk loci have been found in other immune-mediated diseases as well. Novel insights have been derived with the potential for therapeutic intervention, such as the Interleukin (IL)-12 signalling cascade discovered in PBC and the role of the IL-2/IL-21 signalling axis uncovered in PSC. It is envisaged that the characterization of variants in disease models, the stratification of risk alleles by clinical course and the identification of interacting environmental factors will enhance the translation of these findings into personalized therapeutic prevention and intervention programs.

Hence, careful occupational, drug and family history are critical in the diagnostic algorithm. Abdominal ultrasound differentiates intra- and extrahepatic bile duct dilatation with high sensitivity. The next step is testing for serum antimitochondrial antibodies (AMA) and IgG4 levels. The diagnosis of PBC, which represents the major cause of small-duct biliary diseases, can be made with confidence in a patient with high-titer AMA (≥ 1/40) and elevated AP without liver biopsy (2). IgG4-related disease is a newly recognized fibroinflammatory disease characterized by tumefactive lesions, dense lymphoplasmacytic infiltrates rich in IgG4-positive plasma cells, storiform fibrosis, (often but not always) elevated serum IgG4 concentrations, and excellent response to steroid therapy (5,6). If IgG4 levels, AMA and PBC-specific antinuclear antibodies are negative, magnetic resonance cholangiopancreatography – or endoscopic ultrasound in the case of distal bile duct obstruction – are the imaging modalities of choice, as long as no endoscopic intervention is indicated (2). If the diagnosis in patients with intrahepatic cholestasis remains unclear, liver biopsy (≥ 10 portal fields) should be performed (2). The histopathological evaluation should include other bile duct diseases (ABCB4 deficiency, sarcoidosis, drug-induced liver injury [DILI]), disorders not involving bile ducts (storage or infiltrative liver diseases, nodular regenerative hyperplasia) and hepatocellular cholestasis (benign recurrent intrahepatic cholestasis [BRIC], hormone
therapy, paraneoplastic syndromes). Recently it has been suggested that patients with autoimmune cholestatic liver disease should be categorized as PBC, PSC/small duct-PSC and autoimmune hepatitis (i.e. according to the predominating features) and that overlapping syndromes (secondary autoimmune hepatitis) be considered as distinct diagnostic entities (7).

Three different forms of progressive familial intrahepatic cholestasis (PFIC types 1–3) are caused by severe homozygous mutations of the hepatobiliary transporters for phosphatidylserine (ATP8B1), bile salts (ABCB11) and phosphatidylcholine (ABCB4), respectively (8,9). Genetic testing for ABCB4 should be considered in patients with a negative AMA test and with biopsy findings that might be compatible with PBC or PSC (2,7). Of note, variations in severity of disease manifestation are observed with different genotypic variants in these transporters, which gives rise to a phenotypic spectrum – ranging from isolated elevations of AP and/or γ-GT levels (10) to BRIC, gallstones, DILI and intrahepatic cholestasis of pregnancy (ICP) in adults (11) as well as PFIC in children. Accordingly, genetic diagnosis is hampered by the genotype-to-phenotype challenge, in as much as a large number of gene variants await extensive functional studies, representing a difficulty for patient counseling (12). Recently, nuclear receptors and their variants have emerged as important regulators of hepatobiliary transporters. Receptor ligands such as obeticholic acid, which binds to the central bile salt sensor FXR, and other chemically modified bile salts such as nor-UDCA, which undergoes cholehepatic shunting and induces HCO3--rich choleresis (13), have now opened the door for therapeutic trials in cholestatic liver diseases (14).

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Hemochromatosis

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The term hemochromatosis (HC) or hereditary hemochromatosis refers to a unique clinicopathologic subset of iron-overload syndromes that are the result of a genetically determined failure to stop iron from entering the circulatory pool. The recognized basis for this metabolic abnormality is inadequate hepcidin synthesis or activity. The subset currently includes the classic disorder related to HFE C282Y homozygosity and the rare disorders more recently attributed to loss of transferrin receptor 2 (TfR2), hepcidin (HAMP), hemojuvelin (HJV) or to a specific subset of ferroportin (FPN) mutations.

HC associated with HFE, TfR2, HAMP, and HJV mutations are all characterized by inadequate hepcidin synthesis, and in fact, hepcidin deficiency, is the central pathogenic factor for all forms of hemochromatosis. Hepcidin is the physiologic inhibitor of ferroportin, the iron-transporter that pumps iron into the bloodstream from the enterocytes and macrophages. Lack of hepcidin in HC leads to progressive saturation of circulating transferrin, followed by iron accumulation in the parenchymal cells of key organs follows, creating a distinct risk for iron-mediated tissue damage. The time of onset and pattern of organ involvement vary depending on the rate and magnitude of plasma iron overloading, which are, in turn, related to the underlying mutation. This is the basis for the distinction between the milder adult-onset syndromes (HFE- and TfR2-related) and the more severe juvenile-onset forms (HJV- and HAMP-related).

The C282Y change in HFE, the most common disease-associated genetic polymorphism in Caucasians, predisposes to development of clinical HC, but concurrence of additional acquired (i.e. alcohol) or yet unidentified genetic factors are necessary for expressing a full blown disease. In conclusion, like diabetes, hemochromatosis results from the complex, nonlinear interaction between genetic and acquired factors involved in hepcidin synthesis/activity. Depending on the underlying mutation, the coinheretance of modifier genes, the presence of non-genetic hepcidin inhibitors, and other host-related factors, the clinical manifestation may vary from simple biochemical abnormalities to severe multiorgan disease. Recognition of the endocrine nature of hemochromatosis suggests intriguing possibilities for new and more effective approaches to diagnosis and treatment. The dissection of the pathogenic pathways involved in the disrupted hepcidin production and iron homeostasis will allow us to develop new and more effective tools for diagnosis and management of this disorder.

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Non-alcoholic fatty liver disease (NAFLD) is increasingly diagnosed worldwide and considered to be the commonest liver disorder in Western countries. It comprises a disease spectrum ranging from simple steatosis, through non-alcoholic steatohepatitis (NASH) to cirrhosis. Simple steatosis is largely benign and non-progressive, whereas NASH can lead to cirrhosis, liver failure and hepatocellular carcinoma (HCC). HCC can also occur in the absence of cirrhosis. The pathogenesis of NAFLD involves a complex interplay between obesity, insulin resistance and gut microbiota with increased hepatic free fatty acids probably the final common pathway. Genetic susceptibility to all forms of the disease is determined, at least in part, by variation in the PNPLA3 gene encoding adiponutrin although the mechanism for this association is currently unclear. Accurate disease staging and grading still requires liver biopsy but blood tests and imaging modalities are emerging that identify patients most likely to have NASH and advanced fibrosis. Therapeutic strategies can be divided into those directed at components of the metabolic syndrome with potential beneficial liver effects and those directed specifically at the liver. Recent data suggest that diet and exercise improves NASH, particular in those achieving > 7% weight loss. Bariatric surgery has been shown to improve steatosis in all studies and inflammation and fibrosis in some. With respect to anti-diabetic drugs, results for metformin have not been convincing and concerns over the safety of glitazones has reduced the initial enthusiasm for their use. Studies with the emerging GLP-1 analogues are ongoing. Metformin and statins may both reduce the risk of HCC. ACE inhibitors and angiotensin II receptor blockers hold most promise as anti-hypertensive agents for patients with NASH and hypertension. With respect to more specific liver-directed therapies, there have been promising studies of Vitamin E in adults and children although is associated with increased all cause mortality and an increased risk of prostate cancer. Liver transplantation is successful but disease recurrence rate is high in the absence of treatment of the underlying metabolic syndrome.
Autoimmune hepatitis

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Autoimmune hepatitis was the first chronic liver disease with a favourable response to drug therapy and a dismal prognosis when left untreated. A timely diagnosis before cirrhosis develops, the avoidance of immunosuppressant side effect, non-responders to standard induction therapy, and adherence to therapy are the greatest challenges. An established and recently simplified revised scoring system allows for a reproducible and standardized approach to diagnosing AIH in a scientific context and is often employed in clinical practice. The use and interpretation of sero-immunological and molecular biological tests discriminates AIH from other etiologies of chronic hepatitis, i.e. chronic viral infection as the most common cause of chronic hepatitis worldwide. The diagnosis relies on a combination of indicative features of AIH and the exclusion of other causes of chronic liver diseases. An initial liver biopsy specimen is required for diagnostic purposes and for grading and staging. A specific feature of AIH is the association of extrahepatic immune-mediated syndromes.

The indication for treatment is present in patients with established AIH, elevations of aminotransferase activities (ALT, AST), an elevation of serum immunoglobulin G and histological evidence of interface hepatitis or necroinflammatory activity. This is incorporated into 2010 guideline update of the American Association for the Study of the Liver (AASLD). Since its original description in 1950 and first treatment studies the basic therapeutic strategy of inducing remission with steroids and azathioprine has not been modified in principle. Alternative immunosuppressive drugs have been tested in small series and include transplant immunosuppressants. A recent large multicenter prospective treatment trial suggests that budesonide may offer an alternative in non-cirrhotic AIH patients capable of minimizing unwanted steroid effects. The ultimate treatment approach upon drug treatment failure is liver transplantation. Only 4% of transplant candidates are transplanted for AIH but the risk for graft loss because of recurrence has to be considered and recurrent AIH treated after transplantation.

Suggested readings:


TIPS for variceal hemorrhage and ascites

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Transjugular intrahepatic portosystemic shunts (TIPS) were developed as a way to decompress the hypertensive portal vein in subjects with cirrhosis who had complications related to portal hypertension. The two principal complications of portal hypertension that are treated with TIPS include variceal hemorrhage and ascites. Varices develop in a time-dependent manner in subjects with cirrhosis; however, only a third of subjects with varices experience bleeding. There is currently no role for TIPS in primary prophylaxis of variceal hemorrhage or pre-operative decompression of the portal vein for non-liver related abdominal surgery in subjects with cirrhosis. Once bleeding starts, esophageal variceal hemorrhage is initially controlled with a combination of endoscopic and pharmacological therapy. Portal pressures > 20 mm Hg identify a subset of patients with variceal hemorrhage who are at high risk of continued bleeding and failure of medical treatment. For patients who experience continued bleeding or early recurrent hemorrhage, TIPS can establish hemostasis in over 90% of cases. TIPS is also highly effective in establishing hemostasis in subjects with variceal bleeding from isolated gastric varices. Once initial hemostasis is established, TIPS has traditionally been reserved for those who fail first-line approaches for secondary prophylaxis of bleeding with endoscopic band ligation and non-selective beta blockers. Recently, early intervention with TIPS following initial hemostasis has been shown to be superior to this traditional approach. TIPS have also been studied as a treatment of refractory ascites. It is the best current treatment to maintain an ascites-free state in such cases but has not been convincingly shown to improve survival. It is also associated with an increased risk of encephalopathy. It is currently not known if performing TIPS earlier in the natural course of cirrhosis will improve survival. It is also controversial whether the risk of hepatocellular carcinoma is increased in long-term survivors after TIPS.
Liver transplantation

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Technical aspects of liver transplantation (LT) have been well established since several years. Technical variations include the conventional technique with replacement of the caval vein by the graft and the piggy-back technique. Graft retrieved from deceased donors may be transplanted with comparable results regardless if transplanted as a whole, split or reduced-size graft. Living donation is a procedure preferentially used in Asian countries where the brain death concept is not accepted in the population. Major concern may arise in grafts from non heart beating donors not only for ethical reasons but also due to the high rate of biliary complication after this form of retrieval.

Surgical aspects leading to complications following LT are mainly vascular thrombosis and biliary complications. Moreover, the recurrence of the initially underlying disease is of great concern which particularly true for hepatitis C reinfection. Among all indications, the rate of grafts which are going lost after transplantation is the highest in HCV patients. Studies are urgently needed to test the capacity of the new antiviral substances – protease- und polymerase inhibitors – in preventing and treating HCV reinfection. The long-term use of immunosuppressants remains another problem which deserves our attention. In particular the prevention of renal impairment and the development of malignancies – cutaneous as well as gastrointestinal and bronchial – need further studies.

The central issue in organ transplantation – so in LT – is organ shortage entailing an ongoing debate on organ allocation. In general, LT is indicated when the spontaneous prognosis of the disease is worse than the prognosis with transplantation. More than 10 years ago the Model of End-stage Liver Disease (MELD score) has been developed to identify the patient with the most urgent need for a LT. However, the clinical introduction of this score has contributed to a substantial deterioration of transplant results. The situation has been aggravated by the steadily increasing number of transplant centres which is not only true for countries such as Germany but also for the United States. Consequently, there is a strong demand for regulations in transplantation medicine and, in particular, in the field of organ allocation. A possible solution could ensue from a change of the principles of organ allocation. The presently used algorithms focus on urgency but a benefit-driven model would, probably, better meet the reasonable use of sparse organs.
Familial amyloid polyneuropathy (FAP) (syn.: Familial amyloidosis, hereditary amyloidosis) is an autosomal dominant inherited disease due to mutations of the transthyretin (TTR) gene coding for the corresponding protein, consisting of 127 amino acids. The gene is located on chromosome 18q. More than 100 different mutations are known. Other mutant precursor proteins produced in the liver such as apolipoprotein I and II, lysozyme and and fibrinogen Aα may be of etiological importance as well. Amyloidogenic mutations of the TTR gene lead to decreased stability of the corresponding protein and subsequently to extracellular deposition of amyloid in several tissues (peripheral and autonomic nerves, walls of gastrointestinal tract, heart etc). The Val30Met (V30M) mutation is the most prevalent cause of FAP world-wide. There are endemic regions in Portugal, Sweden and Japan. The onset of symptoms is usually between 25 and 35 years of age but late onset families are also known. The most common clinical symptoms are polyneuropathy of the lower limbs, rhythmological disturbances and diarrhea/obstipation. TTR amyloid is predominantly produced in the liver, only as few as 5 % is synthesized in the retina and choroid plexus. Therefore liver transplantation has become widely accepted as the ultimate curative treatment of this disease in order to prevent the ultimately fatal outcome and ameliorate disabling symptoms. Because of shortage of donor grafts, livers of FAP patients are used for Domino-liver transplantation. Since last year a new therapeutic option has been approved by the European Medical Authority (EMA) for therapy of early stage FAP. The first results of a multi-center controlled trial have been published and shown a benefit in patients with an early stage of disease regarding neurological symptoms but also modified body mass index (mBMI). There are several other pharmacologic approaches been reported within the last years which may lead to stabilization of TTR tetramer. Therefore, this might be the beginning of new therapeutic options with pharmacological therapies in patients with FAP.
Alcoholic hepatitis

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Alcoholic hepatitis (AH) is a clinical syndrome characterized by jaundice, anorexia and hepatomegaly involving extensive hepatocellular necrosis, inflammation and scarring. Mortality varies depending on the severity of the disease; 30-day mortality rates of less than 20% were observed in patients with mild to moderate disease, but exceeded 40% in individuals with severe liver injury. In the long-term, patients who survive an episode of severe AH have a 70 % probability of developing cirrhosis.

A common consequence of chronic alcohol consumption is the development of hepatic steatosis. The mechanisms by which steatosis develop into steatohepatitis – a more severe inflammatory condition – remain only partly understood. Increased cell death (by necrosis or apoptosis) sets in motion further pro-inflammatory responses in the liver by producing cytokines and chemokines that help mobilize neutrophils and other inflammatory cells that further enhance liver damage. Also, it appears that overproduction of ROS by the damaged mitochondria could play a salient role. There is evidence that acetaldehyde and malondialdehyde (a by-product of lipid peroxidation) can combine and react with lysine residues on proteins, giving rise to stable malondialdehyde-acetaldehyde (MAA)-protein adducts. These adducts are immunogenic and, thus, can contribute to immune-mediated liver damage. Also, MAA adducts have proinflammatory and profibrogenic properties.

Treatment strategies for patients with severe alcoholic hepatitis are often broad spectrum in approach and may not treat specific pathways responsible for the initiation or progression of disease. Current therapeutic approaches include abstinence from alcohol, the correction of malnutrition, and specific drug treatment. Behavior modification and pharmacotherapy to assist in achieving and maintaining abstinence have been shown to provide clear benefit in improved survival. The pharmacological options typically consist of corticosteroids, pentoxifylline, infliximab, etanercept, anabolic-androgenic steroids such as oxandrolone, various antioxidants (including Vitamin E, silymarin, N-acetylcysteine and betaine) and granulocytapheresis. In addition, liver transplantation can be considered in patients who failed to respond to medical treatment. Early trials of anti-oxidant therapy in combination with zinc and selenium were promising but have not been replicated. S-adenosylmethionine (SAMe) or a combination of antioxidant therapy need further trials in order to draw firm conclusions.

Thus, the much desired breakthroughs in the treatment of AH will require more rigorous and efficient translational research, not only to identify novel concepts relevant to human disease, but also to understand why a promising experimentally legitimate therapeutic candidate has failed in subsequent clinical trials. A comprehensive understanding of the complex, multi-factorial pathogenesis of AH is absolutely necessary to ensure that only most well-characterized and promising therapeutic candidates proceed to the clinical development stage.
Antifibrotic therapy – Ready for the clinic?

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With the advent of highly effective antiviral treatments, therapies that prevent progression or induce regression of liver fibrosis are an unmet clinical need. We have made striking progress in our understanding of the mechanisms that underly liver fibrosis and cirrhosis, including the development of strategies and agents to prevent and reverse fibrosis.

However, translation of this knowledge into clinical practice has been hampered by 1) the limitation or overinterpretation of in vitro and in vivo models to confirm mechanisms and to test antifibrotic agents, and 2) the lack of sensitive biomarkers and technologies to quantify the degree of liver fibrosis and the dynamics of fibrosis progression.

While cirrhosis and subsequent decompensation are accepted hard clinical end-points, fibrosis and fibrosis progression are at best plausible surrogates for future clinical deterioration, the development of primary liver cancer or death. Notably, the vascular changes that are tightly associated with advanced fibrosis, i.e., angiogenesis, are at least as important as the quantity of deposited scar tissue itself.

This talk will give an overview of 1) central mechanisms that underly liver fibrosis progression and reversal, 2) optimized strategies for preclinical antifibrotic drug development, 3) novel techniques to perimit an improved non-invasive assessment of liver fibrosis and fibrogenesis in the individual patient, and 4) antifibrotic agents that already entered phase I-II clinical studies, part of them in liver diseases. Examples of such antifibrotic agents that have entered clinical proof-of-concept studies with optimized surrogate readouts are the humanized monoclonal antibodies STX-100 (integrin αVβ6), GS6624 (Loxl2), Carlumab (MCP-1/CCL2), FG3019 (CTGF), SAR156597 (IL-4/IL-13) and Fresolimumab (TGFβ); the poly-tyrosine kinase inhibitor Nintendanib; the pan-caspase inhibitor IDN-6556; rec. Pentraxin-2 (RM-151). The ongoing development of improved non-invasive methodologies to assess fibrosis progression will speed up the clinical development and validation of potent antifibrotic agents.
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POSTER ABSTRACTS

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Diagnostic and predictive value of some tumor markers in the diagnosis and follow-up of patients with hepatocellular carcinoma

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Introduction: New serologic markers with sufficient sensitivity and specificity are required in hepatocellular carcinoma (HCC). In the present study, we aimed at evaluating the diagnostic role of α-fetoprotein (AFP), protein induce by vitamin K absence or antagonist (PIVKA-II), vascular endothelial growth factor (VEGF), alpha-L-fucosidase (AFU) and transforming growth factor-beta I (TGF-βI) and follow-up of Egyptian patients with HCC and monitoring patients after therapy.

Methods: The study was conducted on 3 selected groups of patients and a control group. Group I included 10 patients with liver cirrhosis. Group II included 10 HCC patients without distant metastasis and group III included 10 HCC patients presenting with metastasis. Ten apparently healthy age and sex matched subjects were also included and served as control group. AFP, alpha-L-fucosidase (AFU), VEGF, PIVKA-II and TGF-βI were determined in the blood of all groups. The sensitivity and specificity of the tumor markers were calculated and compared.

Results: Significant differences in the median blood level of AFP, PIVKA-II, VEGF, TGF-βI and alpha-L-fucosidase activity (AFU) were found on comparing the HCC groups (with and without metastasis) with the other groups. The median blood levels of PIVKA-II, AFP level and AFU activity were lower in the HCC group without metastasis compared to that with metastasis (P < 0.001). On the other hand, the median serum VEGF level was higher in the HCC group without metastasis compared to that of the HCC group with distant metastasis (P < 0.001). Serum TGF-βI level did not vary significantly between both groups (with and without metastasis) (P > 0.05).

Discussion/Conclusion: There were significant lower median blood levels of all parameters in HCC patients without metastasis after ablation therapy compared to pre-treatment levels. Combined determination of serological markers could be used as a highly valuable tool for screening, diagnosis and prognostic markers of HCC.
Nutritional status in various etiology cirrhosis

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Introduction: Malnutrition is an important complication of cirrhosis, which increases the morbidity and mortality of patients with cirrhosis. We analyzed nutritional status in patients with alcoholic and mixed (viral-related and alcohol) liver cirrhosis.

Methods: A total of 139 Belorussian adult patients with cirrhosis were evaluated for nutritional status with standard anthropometric and laboratory tests. Severity of disease was determined according to Child-Pugh score. Patients were divided into two groups: in the first (n = 115) were patients with alcoholic liver cirrhosis and in the second (n = 24) with mixed etiology (viral-related and alcohol) cirrhosis.

Results: Results showed that both groups had not significantly differences in nutritional status and severity of disease. The group 1 (Child-Pugh C – 35%) showed that 93% of patients were malnourished, while 91.7% of all patients were malnourished in the group 2 (Child-Pugh C – 30%). More than half patients in both groups had malnutrition degree 1. Differences in malnutrition degree between groups were not statistically significant. ($\chi^2 = 0.253, P = 0.615$).

Discussion/Conclusion: There are no differences in nutritional status in cirrhotic patients depending on the cause of the cirrhosis.
Hematologic and hepatic abnormality in HVC+ patients with B NHL

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Introduction: Hepatitis C virus infection, known to cause hepatitis, cirrhosis and liver cancer, but is also associated with lymphomas (NHL). Molecular mechanisms by which HCV infection promotes B-cell NHL development remain unclear, but indicate that HCV-associated lymphomas may be a distinct entity.

Methods: A total of 258 patients with B malignant lymphoproliferations were tested for HVC infection. It was also rated the transaminases, bilirubin, INR, serum protein electrophoresis and other haematological parameters.

Results: The frequency of HCV virus infection was detected in 13.56% of B NHL patients. The histologic distribution in our lot was: 8 (22.85%) lymphoplasmacytoid, 5 (14.28%) follicular, 2 (5.71%) mantle, 10 (28.56%) large B cell, 3 (8.57%) diffuse small cell, 1 (2.86%) Hodgkin lymphoma, 3 (8.57%) multiple myloma and 3 (8.57%) acute lymphoblastic leukemia. The age of patients with HCV infection and B NHL was between 18 and 84 years, with an average of 55 years, which is not significantly different from the general B NHL group. Sex distribution favors females 62.45% and 54% of patients was from urban areas (51.7%) presented at least 1 extrahepatic laboratory abnormality, including mixed cryoglobulinemia (37.1%), anemia (31.43%), thrombocytopenia (27.6%), thyroid autoimmunity (16.2%), dermatological disorders (4.1%) and type 2 diabetes (4.1%). The pathogeny of this abnormality will be discussed. The sicca syndrome, nephropathy and polyneuropathy were observed in single cases for each manifestation.

Discussion/Conclusion: The B NHL associated with HVC infections may be a distinct entity with frequent extrahepatic abnormality which can interfere with disease evolution and therapy.
HCV infections and B lymphoma

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**Introduction:** In the last decades, it has been demonstrated that patients infected by hepatitis C virus (HCV) are more likely to develop B-cell non-Hodgkin's lymphoma (NHL) than those uninfected.

**Methods:** A total of 258 patients with B malignant lymphoproliferative disorder were tested for HVC infection. It was also rated the transaminases, bilirubin, INR, serum protein electrophoresis and all these parameters were monitored during the disease evolution.

**Results:** The frequency of HCV virus infection was detected in 13.56% of B NHL patients. The histology distribution in our lot was: 8 (22.85%) lymphoplasmacytoid, 5 (14.28%) follicular, 2 (5.71%) mantle, 10 (28.56%) large B cell, 3 (8.57%) diffuse small cells, 1 Hodgkin lymphoma, 3 (8.57%) multiple myeloma and 3 (8.57%) acute lymphoblastic leukemia. The age of patients with HCV infection and B NHL was between 18 and 84 years, with an average of 55 years, which is not significantly different from the general B NHL group. Sex distribution favours females 62.45% and 54% of patients was from urban areas. 56.66% of these patients have extranodal lesions, compared with 19% for group of B NHL without HCV infection (Chi² p < 0.05). Extranodal involvement refers mainly to the liver, spleen, salivary gland and digestive tract.

**Discussion/Conclusion:** The absolute risk of developing lymphoma when infected with hepatitis C appears to be low. This group of NHL has more frequent extranodal involvement and viral reactivation with chemotherapy and immune reconstitution hepatitis can complicate antineoplastic treatment.
Assessing internet environment influence on hepatology understanding

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Introduction: The wide adoption of Social web, the spreading of personal blogs, and the resulting user-generated content production and/or annotation, leads to a huge amount of “uncontrolled, living knowledge”. In this contribution we are focusing on medical data, in particular regarding the following liver diseases: liver steatosis, non-alcoholic liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), fat liver and the same topics in Italian language.

The medical blogging/writing community consists of healthcare professionals (doctors, pharmaceutical industries, Hospitals/Clinic, Universities, etc.) writing about experience and about current medical issues, and of users (patients or simply people interested on the topic) asking or even providing information about health related issues (their personal experience on). Therefore, there is a great diversity in the particular content.

While sharing knowledge on a particular topic from different point of view is generally a positive factor, it may lead to dissemination of wrong information. Therefore there is the need for technology in dealing with the partly biased and opinionated content to deliver correct information.

Methods: We have considered the scenario in which a person is browsing internet looking for the following terms: steatosis, non-alcoholic liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), fat liver, being interested in the disease itself, in possible treatments, and in other people experiences on the same disease.

We have performed the same query on general purpose search engines and specific blogs as Medworm. We have measured some parameters concerning the concepts describing diagnoses, treatments or medications. More in details: i) concept frequency per post, ii) identification of relevant concepts related to the query, iii) distance of the posted concept with respect to the state of the art literature. The distance is measured in a 3 level scale (completely wrong, biased, neutral, correct). Additional data are the information type: personal experience vs. dissemination; the author background (e.g., physician vs. patient vs. medical industry).

Results: The experimental tests have been performed on a set of medical weblogs and web sites. The content has been crawled based on the particular query under test. A summarizing table with number of evaluated sites and the collected parameters statistics will be reported in the final paper.

Discussion/Conclusion: We have evaluated how a medical topic is perceived in the “living web”. The goal was to understand how the information can be modified to bias people’s opinion. Furthermore topic diversity in medical weblogs has been considered. The methodology applied allow to gather information about the quality of a web content and it can be used also for improving web-based retrieval frameworks for presenting the different aspects of a medical topic to the final user.
The value of echo-guided liver biopsy in the positive diagnosis of a rare primary liver tumour – Pathological approach

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Introduction: Hepatic angiomyolipoma is a rare mesenchymal hepatic tumour with imagistic and cytologic characteristics that can mimic a hepatocellular carcinoma, especially on a biopsy specimen.

Methods: We present two female cases (39 and 43 years old) admitted to Fundeni Clinical Institute, Bucharest. Patients were imagistic diagnosed with a 13 cm hepatic left lobe tumour, respectively a 10.5 cm hepatic right lobe tumour. The ultrasound guided biopsy specimens measured about 8 mm, respectively 20 mm. The tumours were surgical removed. The biopsy and resection specimens were analyzed in light microscopy, including immunohistochemistry.

Results: Initial diagnosis on HE stain biopsy specimen was suggestive for hepatocellular carcinoma with important steatosis (8 mm biopsy), respectively suspicious for angiomyolipoma in the second case. The tumoral tissue showed a fibro-vascular-adipose pattern with large polygonal cells, with finely vacuolated or granular cytoplasm, mild nuclear pleomorphism, with trabecular disposition, fusiform cells or rare epithelioid cells. Further immunohistochemical studies showed positive stain for Vimentin, HMB45, MELAN A, S100 and actin, and negative for OCH1E5, CK7, CK8/18, CEA, CD34, Ki67 and Factor VIII in both biopsy specimens, consistent with hepatic angiomyolipoma diagnosis, confirmed on surgical specimens too.

Discussion/Conclusion: Hepatic angiomyolipoma is a rare primary liver tumour not easily to diagnose histologically on a needle biopsy. The size of biopsy specimens and immunohistochemical analysis play a very important role in a correct diagnosis.
Endotoxemia associated with neutropenia during antiviral therapy of chronic hepatitis C virus infection with severe fibrosis

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Introduction: The aim of study was to examine the level of serum endotoxin in patients with chronic hepatitis C virus infection with severe fibrosis and neutropenia during antiviral therapy (AVT) and to determine the possibilities of pharmacological correction of endotoxemia.

Methods: The development of neutropenia was analyzed in 39 patients (23 men, 16 women) with HCV-related liver diseases treated with combination of pegylated IFN-α and ribavirin. 21 patients had severe fibrosis (F3) and 18 – liver cirrhosis (F4) in accordance with Metavir score. All patients with cirrhosis were compensated. Content of endotoxin in serum was determined by chromogenic method Hbt LAL. Level of granulocyte colony-stimulating factor (G-CSF) by ELISA was also measured in blood of patients.

Results: In patients with HCV before AVT, total white blood cell (WBC) count and absolute neutrophil count (ANC) were within normal limit. The initial content of endotoxin and G-CSF in blood did not differ from parameters of control group. During AVT neutropenia (< 1,500 mm$^3$) developed in 24 patients. The increase in endotoxin level in blood was registered in all patients with neutropenia from the 8th week. In patients with neutropenia the level of serum endotoxin was significantly higher than in patients without neutropenia. The decrease of the content of G-CSF was determined, reaching the lowest values at the 12th week in cases with neutropenia. An inverse correlation between level of endotoxin and ANC was found as well as a direct correlation between neutrophils and level of G-CSF. Filgrastim was used in 15 patients. Filgrastim treatment maintained ANC not below 1,000–1,500/mm$^3$ and, thus, prevented necessity to reduce dose of interferon.

Discussion/Conclusion: Neutrophils are the first endotoxin-neutralizing link. Administration of G-CSF allows to stabilize ANC, which leads to decrease of endotoxemia level.
Effect of pituitary tumor-transforming gene on progression of liver fibrosis

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Introduction: Pituitary tumor-transforming gene (PTTG) is involved in multiple cellular pathways, including proliferation, DNA repair, transformation, angiogenesis induction, etc. PTTG is highly expressed in various tumors, including liver. However, the involvement of PTTG in preneoplastic liver diseases, fibrosis and cirrhosis, is still unclear. We studied the development of liver fibrosis induced by thioacetamide (TAA) in PTTG knockout (PTTG−/−) mice.

Methods: Liver fibrosis in PTTG+/+ and PTTG−/− mice was induced by intraperitoneal TAA treatment three times per week for 12 w, gradually increasing the dose of TAA from 50 mg/kg b.w. to 400 mg/kg b.w. from the 3rd week of the experiment. The severity of liver fibrosis was assessed by morphometric evaluation of liver slides, stained with Azan-Mallory, and liver hydroxyproline (HYP) determination. Serum markers of fibrosis, including collagens III type, procollagen III-NT and hyaluronic acid, as well as serum TGFβ1 and TNFα contents, were evaluated by ELISA techniques.

Results: The surface of the liver from the PTTG+/+ plus TAA group was rough and formation of small nodules was observed in contrast to the PTTG−/− plus TAA group. Histological examination (staining with both hematoxylin/eosin and Asan-Mallori) confirmed the presence of micronodular cirrhosis in the both TAA-treated groups. The TAA-groups showed bridging and septal fibrosis connecting portal area and central veins and accompanied with inflammatory cells infiltration. All these fibrotic signs were significantly more pronounced in PTTG+/+ animals. Morphometric quantification of collagen deposition in hepatic parenchyma showed the significant increase of the connective tissue square in liver slides from PTTG+/+ and PTTG−/− animals treated with TAA (3.4- and 2.6-fold, respectively). An increase of liver HYP content was detected in the PTTG+/+ plus TAA group, whereas the liver level of HYP in PTTG−/− mice treated with TAA did not differ from the corresponding non-treated group. Serum collagen III and hyaluronate levels were significantly higher in the PTTG+/+ non-treated group as compared to PTTG−/− intact animals. All the detected serum fibrosis markers and cytokine contents were significantly elevated after the treatment with TAA in both groups. However, serum TNFα content was lower in the PTTG−/− TAA-treated group as compared to the corresponding PTTG+/+ group.

Discussion/Conclusion: The presented data showed that in the absence of PTTG the development of TAA-induced liver fibrosis in mice was significantly reduced. These findings suggest an important role of PTTG in liver fibrotic damage.
Comparison of chronic hepatitis B patients using tenofovir and entecavir in terms of viral kinetics, virologic response and side effects

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Background and aim: The aim of this study is to compare chronic hepatitis B patients using tenofovir or entecavir in terms of viral kinetics, side effects and virologic response.

Material and methods: Subjects who used tenofovir or entecavir for chronic hepatitis B infection for varying durations were included in this retrospective study. Subjects were divided into groups as the ones whose HBV DNA levels reduced or not 2, 4 and 6 log$_{10}$ unit at 3, 6 and 12 months of therapy and whether tenofovir or entecavir use affected HBV DNA reduction rates. Additionally, whether tenofovir or entecavir therapies were different in terms of side effects and virologic response was investigated.

Results: A total of 135 subjects (79 males, 58.5% and 56 females, 41.5%) aged between 43–79 years were included in the study. Tenofovir or entecavir use did not affect the reduction rates of HBV DNA at 3, 6 and 12 months of therapy. In multivariate survey analysis, virologic response was seen to be better in case of tenofovir use and serum HBV DNA level < 100,000 U/ml (for tenofovir use odds ratio 0.642 and p = 0.028; for serum HBV DNA level < 100,000 U/ml, odds ratio 0.430 and p = 0.01). While side effects developed in 7 subjects who used tenofovir and 3 subjects who used entecavir, there was not a difference between case groups in terms of side effect frequency.

Conclusions: Results of this study suggested that virologic response rates were better in chronic HBV infected subjects who used tenofovir compared to entecavir and there was not a difference between two groups in terms of side effect rates.
Treatment with UDCA and neuroendocrine tumor

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Introduction: UDCA is a nontoxic hydrophilic bile acid used to treat predominantly cholestatic liver disorder; it is of unproven efficacy in non-cholestatic disorder such as acute rejection after liver transplantation, non-alcoholic steatohepatitis, alcoholic liver disorder, chronic viral hepatitis, drug induced hepatitis, tumor prevention. Cholelithiasis is a very common adverse reaction reported during octreotide therapy.

Methods: A 69-year old women presented with asthenia, mild right upper quadrant complaints.

Results: Biological: transaminases, γ-GT and glycemia were slightly increased. Ultrasonography: criteria of severe non-alcoholic steatohepatitis, sludge in gall-bladder. Endoscopic examination reveal a one cm tumor in duodenum with normal mucosal surface; endoscopic ultrasonography showed hypochochogene structure which was thought to arise from the submucosal layer. Upon informed consent the tumor was removed by endoscope resection for diagnosis and treatment. Pathologic examination revealed neuroendocrine tumor with incert potential of malignancy. Immunohistochimy: neuroendocrine tumor CROMO positive, SYN positive, GAS positive, glucag negative, VIP negative KI 67 positive. The patient starts therapy with octreotide 20 mg im monthly and UDCA 15 mg/kg/body. Patient's progress was evaluated at three, six and twelve months and all laboratory test values falling within the normal range. There was no evidence of disease recurrence after one year of follow-up.

Discussion/Conclusion: Non-alcoholic steatohepatitis, cholelithiasis and endocrine system are closely related. The extent to which application of UDCA influence this process is only partly understood. In this case treatment with acidum urso-deoxicolicum was useful not only for treatment of NASH but also for prophylaxis of stone of gallbladder; another beneficial effect of UDCA is to prevent recurrence of duodenal tumor. This case emphasis the need of further researches for a better understanding of the NASH, cholelithiasis and gastrointestinal hormone secretion.
Prevalence and risk factors for liver involvement in individuals with PiZZ-related lung disease

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Introduction: Alpha-1-anti-trypsin deficiency is one of the commonest heritable human diseases, predisposing to liver and lung injury. Significant heterogeneity in phenotypic expression is well documented, but less is known of the prevalence, severity and correlates of chronic liver disease (CLD) among individuals presenting with lung disease.

Methods: A well-characterised cohort of 57 PiZZ adults attending a tertiary referral chest clinic was screened prospectively for clinical, biochemical, radiological and (when appropriate) histological evidence of CLD.

Results: 36 of 57 (63.2%) had one or more abnormality of liver function, liver ultrasound or risk factors for CLD and 24 of these underwent liver biopsy. Eight (16.3%) had evidence of advanced fibrosis or cirrhosis and were more likely to be male \((p = 0.05)\) with: increased liver echogenicity at ultrasound \((p = 0.002)\); splenomegaly \((p < 0.001)\); lower platelet count \((p = 0.004)\); higher body mass index \((p = 0.02)\); alanine transaminase \((p = 0.007)\), alkaline phosphatase \((p = 0.0009)\), prothrombin time \((p = 0.002)\) and maximal vital capacity \((V_{C_{max}}, p = 0.03)\). Screening with liver ultrasound provided a sensitivity and negative predictive value for CLD of 100% as were the specificity and positive predictive value for platelet count \(\leq 174 \times 10^9/L\), prothrombin time \(\geq 13.8\) seconds, bilirubin \(\geq 28\) \(\mu\)mol/L, serum albumin \(\leq 30\) g/L, alkaline phosphatase \(\geq 159\) U/L and splenomegaly. Among individuals undergoing liver biopsy, fibrosis stage correlated negatively with both absolute and predicted ratio of residual volume to total lung capacity \((p = 0.004\) and \(p = 0.02\), respectively), and correlated positively with both absolute and predicted forced expiratory volume in 1 second \((p = 0.03\) and \(p = 0.04\), respectively) and \(V_{C_{max}}\) \((p = 0.008\) and \(p = 0.02\), respectively).

Conclusion: Significant CLD is common in PiZZ individuals with lung disease and can be screened effectively by a combination of conventional tests of liver function, platelet count and liver ultrasound.
Diabetes mellitus-type 2 and chronic hepatitis B – Metabolic changes

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Pathogenesis of diabetes mellitus in the context of chronic hepatitis is controversial and involving: insulin resistance and decreased secretion of insulin deficiency, hepatic steatosis.

Introduction: The objective of this study was to analyze the phenotype of diabetes mellitus (DZ2) patients with chronic hepatitis B virus (HBV).

Methods: We selected 130 patients with HBV-group A and 60 patients with DZ2 and HBV, representing group B. Selection was followed by parameters: BMI, waist circumference, lipid profile and glucose profile. To assess liver fibrosis we used the ratio AST/platelet (ASPR), the ratio AST/ALT and Forns index.

Results: Obesity was present in 39.5% of patients in group A and 58.6% in group B – lipid profile suggesting the most likely atherogenic dyslipidemia in patients with type 2 diabetes association; 26.3% of patients with HBV without diabetes had hypertriglyceridemia, compared to 60.6% in patients with DZ2 and HBV. Report AST/ALT, rough values were higher in diabetic patients with metabolic imbalance in those treated with insulin. Changes glucose (fasting glucose, oral glucose tolerance test and diabetes) was present in 31.2% of patients with HBV.

Discussion/Conclusion: This study indicate that patients with HBV with type 2 diabetes have clinical features that are distinct from the classical type of diabetes (abdominal obesity and triglycerides hipoHDLcolesterolemia low).
Incidence of diabetes mellitus, obesity and cardiovascular changes in hepatic steatosis

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Hepatic steatosis in many circumstances, can be a way of onset of hepatic toxicity or metabolic, an important stage in the development of dyslipidemia.

Introduction: The objectives of this study were to determine the incidence of diabetes mellitus, obesity and cardiovascular changes in patients with hepatic steatosis.

Methods: We selected 96 patients, 56 men and 40 women aged between 45 and 65 years, with known hepatic steatosis and obesity grade II and III, selected based on BMI and Lorentz formula, and also investigated in terms of cardiology. 42 cases in men and 20 women admitted alcohol consumption.

Results: The incidence of diabetes mellitus in both sexes was 70% (42M/33F) aggravated by obesity and fatty liver disease with complications precipitation. Coronary hearth disease is common in both sexes (41M/23F) was precipitated in menopausal women. Arterial blood pressure was greatly increased in both sexes (36M/21F). Chronic obstructing obliteration of lower limb was more common in men than women (6M/4F) precipitated by smoking in both sexes. Gout was more common in men (9M/5F) and dyslipidemia approximately equal in both sexes (32M/19F).

Discussion/Conclusion: Our results indicate that obesity is associated with hepatic steatosis, more frequently in patients with primary hypertension, manifest stress, consumption of alcohol. Type II diabetes mellitus is associated in 70% of cases of obesity, hepatic steatosis and arterial blood pressure in both men and women.
A combined algorithm for non-invasive diagnosis of liver cirrhosis

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Introduction: The non-invasive staging of liver fibrosis in chronic liver diseases is a new challenging area. Different proposed algorithms associate either Fibroscan® and Fibrotest® or AST to platelet ratio index (APRI) and Fibrotest. For the large availability of Fibroscan in Italy we hypothesized an original algorithm for diagnosis of liver cirrhosis associating Transient Elastography and APRI, using Fibrotest in case of disagreement between these two tests.

Methods: We built an algorithm based on Fibroscan and APRI with cut off values for diagnosis of liver cirrhosis, respectively, of 12.5 and 2.0 derived from the fusion of the previously validated algorithms of Castera L and Sebastiani G (J Hepatol 2010;52:191–8). In case of disagreement between these tests we performed as third analysis Fibrotest, and just in case of doubtful diagnosis of cirrhosis a liver biopsy was done.

The study collected data of one hundred consecutive patients with a histological diagnosis of cirrhosis or non-cirrhotic chronic liver disease visited at our Unit in the last two years. All the patients underwent liver biopsy, Fibroscan, APRI and Fibrotest. After data analysis according to the proposed algorithm we calculated the performance of this considering as gold standard liver histology.

Results: Liver cirrhosis was present in 18% of patients. Concordance between TE and APRI was present in 70% of patients. Fibrotest was performed in 30%, while liver biopsy was done in only 8% of patients. Sensitivity and specificity of the combined algorithm was respectively 94.1% and 90% with a PPV and NPV of 88.9% and 94.7% and a likelihood ratio + and - respectively of 9.4 and 0.07.

Discussion/Conclusion: The new algorithm is effective for diagnosis of liver cirrhosis with a number of saved biopsies of 92/100, a percentage greater than that of the algorithms of Castera or Sebastiani. This new algorithm might be less expensive for the Liver Units having Fibroscan and the cost of fibrotest can be justified by the number of biopsies saved and the high accuracy of this algorithm.
The study of predictive factors concerning the risk of renal complications of chronic ascitis

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Introduction: Mortality in hepatic cirrhosis is influenced by complications development. The most frequent and serious complications in the course of hepatic cirrhosis are due to upper gastrointestinal bleeding, hepatorenal syndrome, refractory ascitis, hepatocellular carcinoma and spontaneous bacterial peritonitis.

Objectives: Our study intends to select specific predictive parameters for assessing the risk of renal dysfunction development.

Material and method: We studied a group of 292 patients with hepatic cirrhosis and refractory ascitis followed over a 4-years period. The exploration protocol consisted of complex clinical, biological and functional liver exploration and complete analyze of the ascitic fluid, haemodynamics and renal function. Global statistics evaluations showed a majority of male patients (70.5%) compared to the female patients (29.5%) and a mean age of 56.2 ± 6.14 years within the group.

Results and discussions: During the 4-years active follow-up, 32 patients presented hepatorenal syndrome, 38 refractory ascitis and 64 patients one or more episodes of upper gastrointestinal bleeding. Also, 22 patients developed hepatocellular carcinoma and 16 spontaneous bacterial peritonitis. Early diagnosis of refractory ascitis and hepatorenal syndrome can be accomplished firstly by analyzing the systemic haemodynamic parameters (Holter monitoring of blood pressure) and the parameters evaluating the renal function (creatinine clearance, diuresis testing, ascitic fluid albumin monitoring).

Conclusion: Hepatic cirrhosis evolution is marked by many various complications that can change the prognosis. Haemodynamic systemic parameters and those evaluating the renal function are the most efficient in assessing the risk of renal complications within the cirrhotic patients.
Can faecal calprotectin predict the spontaneous bacterial peritonitis in cirrhosis?

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Spontaneous bacterial peritonitis can be precipitated by the bacterial translocation through the inflamed colonic mucosa. The presence of faecal calprotectin is directly proportional with the migration of neutrophils, and can be considered a marker of intestinal inflammation.

**The aim** of the study was to determine the role of semi quantitative dosage of calprotectin in the screening of patients with spontaneous bacterial peritonitis.

**Methods:** 31 patients with hepatic cirrhosis and 21 healthy subjects (the control group), were included in a prospective study. Patients with inflammatory bowel disease and other conditions that might determine an abnormal level of faecal calprotectin were excluded. Cirrhosis complications (vascular decompensation/ascites) with spontaneous bacterial peritonitis were diagnosed using the diagnostic paracentesis procedure. Stool samples were taken for the semi quantitative determination of the faecal calprotectin.

**Results:** The faecal calprotectin level was higher in the cirrhosis group compared to the control group (78.5\% vs. 20.3\%, \(p < 0.001\)). Also a high level of calprotectin was correlated with the presence of spontaneous bacterial peritonitis (85.3\% in patients with spontaneous bacterial peritonitis vs. 37.2\% in patients with ascites, without spontaneous bacterial peritonitis, \(p < 0.02\)).

**Conclusions:** Faecal calprotectin could serve as a screening tool in patients with cirrhosis complicated with spontaneous bacterial peritonitis.
Patterns of decompensation in patients with non-alcoholic cirrhosis vs. alcoholic cirrhosis

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In the progression of hepatic cirrhosis many episodes of decompensation and complications can appear. They can be divided in two main types as it follows: vascular decompensation (ascites and variceal hemorrhage) and parenchymal decompensation (jaundice, hepatopetal encephalopathy). Also, taking into account the etiology of the cirrhosis, the level of fibrosis varies from one person to another.

The aim of this study was to evaluate the patterns of decompensation of hepatic cirrhosis considering its etiology.

Methods: A retrospective analysis using the observation charts of 440 people hospitalized in our Gastroenterology Center, over a three year period, was done. The patients suffered from hepatic cirrhosis, had a certain etiology (toxic or viral: B, C) and presented decompensation elements: ascites, encephalopathy, variceal hemorrhage, jaundice, hepatorenal syndrome, spontaneous bacterial peritonitis and hepatocellular carcinoma.

Results: The patients with viral etiology of the cirrhosis had an increased incidence of hepatocarcinoma (30.2% vs. 15.7%) and the patients with alcoholic etiology had more hospitalizations for frequent decompensations like ascites and hepatopetal encephalopathy (78.5% vs. 61.3% for ascites and 27% vs. 13.4% for hepatopetal encephalopathy). There were no considerable differences concerning other types of decompensation (jaundice, variceal hemorrhage, hepatorenal syndrome and spontaneous bacterial peritonitis).

Conclusions: The ascites and the hepatopetal encephalopathy are the two main ways of decompensation in patients with hepatic cirrhosis toxic induced whilst the patients with hepatic cirrhosis with viral involvement, had a larger prevalence of hepatocellular carcinoma.
Liver fibrosis may reduce the efficacy of budesonide in the treatment of autoimmune hepatitis and overlap syndrome

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Conflicts of interest: none

Background and aim: The aim of the present study was to assess the efficacy and tolerability of budesonide as an alternative first line treatment option for autoimmune hepatitis (AIH) and the overlap syndrome.

Methods: A total of 18 AIH or overlap syndrome patients were evaluated. Outcomes of treatment by the end of the study were defined as treatment failure, partial response, complete response and remission.

Results: Complete response and remission were achieved in 61.1% (11/18) of patients, while 38.9% (7/18) of patients were considered treatment failures. Liver fibrosis was observed in 55.5% of patients' biopsies. More patients with liver fibrosis failed to respond to treatment compared to patients without fibrosis, a difference bordering on statistical significance (60% vs. 12.5%; p = 0.066). Although statistically insignificant, the presence of at least one side effect was observed more frequently in patients with fibrosis compared to those without fibrosis (80% vs. 37.5%; p = 0.145). Overall, side effects occurred significantly more commonly in non responders than responders (100% vs. 36%; p = 0.013).

Conclusions: Budesonide is an effective treatment option for the management of AIH, with a low incidence of side effects in patients without findings of advanced liver disease. The presence of liver fibrosis may increase the likelihood of treatment failure as well as the risk of developing side effects. Our study findings suggest that budesonide may be effective in a select group of AIH patients. Further studies are needed to determine its exact place for the treatment of AIH and overlap syndrome.

Keywords: autoimmune hepatitis, primary biliary cirrhosis, overlap syndrome, liver fibrosis, steroid side effects, budesonide, prednisone
Diagnosis of hepatomegaly always a surprise

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Introduction: We present a series of 10 patients hospitalized in internal medicine service for different symptoms, constantly accompanied by important hepatomegaly previously unknown.

Methods: In particular, all patients had spontaneous alteration of clotting and there were elevated cholestasis enzymes (GGT and ALP), in addition to no other changes in liver function. Patients didn’t have portal hypertension (excluded clinically, by ultrasound, upper gastrointestinal endoscopy) and 4 of them associated heart failure, with marked impairment of cardiac diastolic function on echocardiography. Although INR was 1.4 to 2.2, liver biopsy was performed in all patients (in one case was recorded severe bleeding, which needed surgical hemostasis).

Results: Pathological diagnoses were: 4 sarcoidosis, 3 tuberculosis and 3 amyloidosis.

Discussion/Conclusion: Hepatomegaly associating elevation of cholestasis enzymes and alteration of coagulation without other liver test disturbances may suggest granulomatous and infiltrating disease of the liver, associated or not with other organ damage.
Portal vein thrombosis pour prognostic factor in cirrhotic patients

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Introduction: Portal vein thrombosis (PVT) complicates most often cirrhosis without having any clear predictors.

Methods: We followed 20 patients with PVT diagnosed in the last two years in patients with cirrhosis of different etiologies. 12 of them had significant thrombocytopenia or spontaneous impaired clotting and were excluded from oral anticoagulants, applicable to the other 8 patients, to prevent thrombosis extension.

Results: After two years, none of the patients died, but there were repeated episodes of portal encephalopathy, hardly reducible ascitic decompensations, digestive bleeding with a higher rate than up to portal vein thrombosis diagnosis. No significant differences were recorded between the evolution of patients anticoagulated spontaneously either oral. 9 patients developed portal cavernoma.

Discussion/Conclusion: Portal vein thrombosis is a complication of liver cirrhosis, which increases the rate of episodes of decompensation of the disease, significantly altering the quality of life, with limited therapeutic resources.
Correlation between Hamaguchi score, insulin resistance and fatty liver indexes in adult patients affected by non-alcoholic fatty liver disease

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Introduction: Non-alcoholic fatty liver disease (NAFLD) is a common finding in the general Italian population ranging from 20–30% of adult. The non-invasive diagnosis of NAFLD is usually made by Liver US examination, but an easy diagnostic algorithm is still lacking.

Aim of this study was to assess the correlation between semi-quantitative severity of steatosis at US scan of the liver and the degree of obesity, presence of insulin resistance or serum biochemical abnormalities. We also evaluated the possible correlation with some validated indexes of liver steatosis/fibrosis (fatty liver index, FLI; NAFLD fibrosis score; AST to platelet ratio index, APRI).

Methods: We perform a cross-sectional study on a sample of 100 consecutive adult patients undergoing US scan at our Liver Unit. All patients were enrolled after the finding of steatosis at liver US scan. Exclusion criteria were: i) HBV, HCV or HIV infection; ii) alcohol intake > 30 g/day; iii) diagnosis of autoimmune hepatitis, CBP, CSP, HCC or other liver malignancies.

All subjects underwent physical examination, anthropometric assessment (BMI, waist circumference) and ultrasonographic (US) liver examination. Fasting blood samples were collected for the assessment of common liver function, hepatitis status, levels of serum glucose, insulin and lipid profile. Degree of fatty infiltration of the liver was graded in six levels according to Hamaguchi score (Am J Gastroenterol 2007;102:2708–15) and evaluating: i) bright liver and hepatorenal contrast; ii) deep attenuation of ultrasounds; iii) vessel blurring. We calculated homeostasis model assessment (HOMA 1/HOMA 2), QUICKI and McAuley as indexes of insulin resistance.

Correlation analysis was performed by Pearson or Spearman test. Stepwise multiple regression analysis was also performed. A p < 0.05 was considered statistically significant.

Results: One hundred patients were enrolled in the study, 50 males and 50 females, median age was years 52.2 (range 18–79). The severity of fatty liver was positively related to anthropometric measurements (BMI and waist circumference), insulin resistance index (HOMA), ALT and GGTL levels. The Hamaguchi score was also related to FLI, but not to NAFLD fibrosis score or APRI.
Discussion/Conclusion: The severity of US steatosis was positively correlated with obesity indicators such as BMI and waist circumference, insulin resistance (HOMA), ALT and GGT levels. Furthermore, US score of fatty liver showed a good correlation with FLI (Bedogni G) another accurate predictor of hepatic steatosis. Ultrasonography is a non-invasive and readily available technique that might be used for diagnosing and monitoring of hepatic steatosis and insulin resistance. The application of Hamaguchi score for fatty liver is advisable in this setting, both for the good correlation with several parameters that are characteristic of metabolic syndrome and the most reliable clinical index of fatty liver probability: FLI.
Liver cancer in HBV cirrhosis and prolonged antiviral treatment – 20 year observation – A clinical case

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Introduction: Hepatocellular carcinoma (HCC) is the most common type of liver cancer. Most cases with HCC are secondary to either viral hepatitis infection (HBV or HCV) or cirrhosis. Chronic infection with hepatitis B virus may be associated with chronic inflammation of the liver, leading to cirrhosis over a period of several years. This infection dramatically increases the incidence of HCC.

Case report
We present a 56-year-old man, in whom HBV infection (HBsAg positive) was discovered in 1983. Ten years later, in 1992, laboratory investigations performed due to general weakness, showed elevated aminotransferases. Liver biopsy was performed and showed chronic active hepatitis, initial portal cirrhosis and lots of hepatocytes’ nuclei strongly positive for HBcAg. From 1992 to 1997 the patient was treated with hepatoprotectors. The second liver biopsy in 1997 confirmed the cirrhosis. Antiviral treatment with conventional interferon was conducted from 1997 to 2000, with biochemical and virologic response and relapse after discontinuation. Lamivudine treatment was performed from 2000 to 2003 (33 months). Because of severe biochemical flare and virological breakthrough we assumed of a viral mutant and drug resistance. Lamivudine was stopped and another course of interferon therapy was initiated. Active hepatoprotective treatment and hyperbaric oxygenation were performed. From November 2006 to May 2008 (18 months) cyclic therapy with peginterferon was performed.

In June 2009 a hypoechoic lesion in the right liver lobe by abdominal ultrasonography (US) and slightly elevated alpha-fetoprotein were found. The contrast-enhanced US, computed tomography (CT) and MRI confirmed the diagnosis HCC. Because of the presence of virologic relapse, treatment with telbivudine was started before the operation. Resection of the tumor was performed successfully in July 2009, with morphological data of moderately differentiated HCC. Due to resistance to telbivudine, tenofovir therapy was started in August 2010.

During the 3-year postoperative follow-up normal alpha-fetoprotein, biochemical tests and negative HBV-DNA were observed. There were no US, CT and MRI signs for local tumor recurrence. The patient is still on tenofovir therapy.

Discussion/Conclusion: This case is an example for the evolution of HBV infection from chronic hepatitis to cirrhosis and HCC during 20-year period of observation. The active follow-up allows early diagnosis and radical surgical treatment. Nucleotide analogues substantially suppress viral replication, reduce hepatitis activity and could delay disease progression.
Combined therapy for primary biliary cirrhosis after suboptimal response to UDCA monotherapy

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Introduction: Aim was to evaluate the effect on histological evolution of primary biliary cirrhosis (PBC) of two years combined therapy (UDCA-budesonide) in patients with incomplete response to UDCA monotherapy.

Methods: We studied 22 patients with PBC (stages I–III) with suboptimal response to UDCA monotherapy (13–15 mg/kg/day, 12 months). Due to incomplete response of this therapy, 13 patients (A group) were treated with combined therapy (UDCA 13–15 mg/kg/day and budesonide 9 mg daily divided in 3 doses) and 9 patients (B group) received increased dose of UDCA (15–20 mg/kg/day). In this comparative study we evaluated serum levels of aminotransferase, Bb, AP, liver histology, activity and fibrosis scoring (METAVIR criteria) at 6, 12 and 24 months.

Results: In both groups, clinical symptoms significant improved after 6 month (in 23% of cases in A group and 33% of cases in B group), in 60.7% after 12 months and 89.28% after 24 months. In B group the mean value of serum bilirubin concentration was reduced from 6.7 ± 2.5 mg%, at baseline, to 2.8 ± 1.3 mg% at 6 months and to 1.7 ± 0.7 mg% at 12 months. Aminotransferase values were reduced more quickly comparative with bilirubin and AP levels: with 44.6% at 6 months and 63.2% at 12 months. In A group, aminotransferase values reduced more slowly, but significant decrease AP after one year (p = 0.001). Inflammatory activity was significantly reduced in the combined therapy (6 cases, 46.15%) and in 2 cases (22.22%) with monotherapy. Fibrosis decreased in group A in 5 cases, but in B group only in one case. After 24 months, histological stage of disease improved only in A group (3 cases). In A group two patients presented hyperglycemia, 2 mild hirsutism and 4 osteoporosis, but in B group we observed side-effect in only one patient (diarrhea). Most of the side-effects appeared in patients with stage III PBC and only in two patients we reduced the budesonide dose.

Discussion/Conclusion: UDCA combined with budesonide improved liver histology and liver enzymes, where as the effect of UDCA monotherapy was mainly on liver function tests. The daily dose of UDCA 15–20 mg may be sufficient to achieve a good biochemical response.
Contribution of non-viral risk factors to development of hepatocellular carcinoma

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Introduction: The aim of this study was to assess the role of non-viral causes, as independent risk factors, in development of hepatocellular carcinoma (HCC).

Methods: We studied retrospectively 188 patients which developed HCC in the last four years (53.17 ± 3.24 years). The diagnosis was established by clinical picture, laboratory parameters, imagistic examinations and was histological confirmed. The disease evolution was evaluated, according CLIP score and Okuda staging system.

Results: The viral aetiology of HCC was predominant (75.53%): virus C (88 cases), virus B (36 cases), B + C virus (18 cases). Also, in a significantly percent of whole group, HCC has a non-viral aetiology (46 cases, 24.4%): alcohol-induced liver disease (20 cases), primary biliary cirrhosis (3 cases), diabetes mellitus (9 cases), obesity associated with NASH (8 cases) and other aetiology (6 cases). Alcohol abuse increased likelihood to develop HCC in 85 cases: in 65 cases in association with viral aetiology (45.77%) and in 20 cases (43.4% of non-viral aetiology) as non-viral risk factor. Diabetes mellitus was present in 34 cases, but in 25 cases was associated with virus infection. The presence of diabetes remained an independent risk factor for HCC after exclusion viral hepatitis, alcohol use, PBC or other causes. HCC was developed in cirrhotic patients in 118 cases: 81 cases with HBV or HCV infection and 37 cases with non-viral aetiology. Cirrhotic patients were classed as Child-Pugh A (60 cases), Child-Pugh B (38 cases) and Child-Pugh C (20 cases). The type of HCC was: solitary (82 cases), paucifocal (2–3 nodules) in 60 cases, multifocal (> 3 nodules) in 33 cases and diffuse (13 cases). The distribution of solitary HCC was: < 2 cm (12 cases), 2–5 cm (51 cases) and > 5 cm (19 cases). Partial or complete portal vein thrombosis was present in 43 cases: 29 patients with C virus, 13 with B virus and only in one case without virus. Association of C virus infection and alcohol abuse was correlated with tumour dimensions (r = 0.308, p = 0.001). The values of glycated hemoglobin and BMI were not correlated with tumour dimensions.

Discussion/Conclusion: The main risk factor for development of HCC remains virus C infection. Obesity and diabetes increase the risk of non-viral HCC and operate as independent risk factors.
Effect of alcohol consumption on the progression of hepatitis C virus infection and risk to develop hepatocellular carcinoma

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Introduction: The aim of this comparative study was to evaluate the effect of association between chronic alcohol consumption and hepatitis C virus (HCV) infection and risk of development hepatocellular carcinoma (HCC).

Methods: We studied 88 patients with chronic HCV infection: A group consists of 37 heavy alcohol drinkers (intake over 80 g ethanol/day for more than 10 years) and B group consists of 51 non-alcoholic patients. We monitored and evaluated the clinical manifestation, alcohol consumption, biochemical parameters, liver function tests and histological aspects of liver biopsy (HAI score) after 12, 24 and 36 months.

Results: At baseline, the mean value of alcohol consumption in A group was 116.25 g/day. In B group, all patients were non-alcoholic in the last five years, but 9 patients are history of medium or low alcohol consumption. After 6 and 12 months, the mean value of AST/ALT ratio was < 1 in A group and between 1 and 1.3 in B group. This level of AST/ALT ratio was maintained for whole period. Sub-unitary AST/ALT ratio was correlated with the presence of histological active hepatitis and exclusively with the presence of the C viral infection. After 12 months, the steatosis was present in both groups, but most frequent in A group (89.19%), comparative with B group (68.62%). At 24 and 36 months, the steatosis grade was significantly higher in A group. The score of fibrosis was more severe in patients with HCV chronic infection and alcohol intake.

The incidence of cirrhosis after three years was significantly increased in alcoholic patients: 37.83% in A group and 15.68% in B group. HCC developed in 9 cases (10.22%): 6 cases in A group and 3 in B group.

Discussion/Conclusion: Association of HCV infection with alcohol abuse was correlated with high steatosis grade and severe fibrosis. The risk of quickly development of HCC was higher in alcoholics patients.
Anticoagulation therapy in cirrhotic patients with nonmalignant portal vein thrombosis

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Background and aims: Portal vein thrombosis (PVT) is a common complication in patients with cirrhosis especially in advanced disease cases. Increasing evidence supports the relative benefit of oral anticoagulant treatment, but there are still limited data regarding safety and efficacy of this approach. We evaluated this therapy in a series of patients with cirrhosis and non-neoplastic PVT.

Methods: We analyzed data from 24 patients with cirrhosis and PVT, diagnosed from January 2009 to December 2011, who received anticoagulant therapy for acute (n = 2) and subacute thrombosis (n = 3) or progression of previously known PVT (n = 19). Patients with cavernomatous transformation were excluded. Thrombosis was diagnosed, and recanalization was evaluated by using Doppler ultrasound, angio-computed tomography, and/or angio-magnetic resonance imaging analyses.

Results: Partial or complete recanalization was achieved in 13 patients (52%; complete in 3 patients). Early initiation of anticoagulation was the only factor significantly associated with recanalization. Patients who achieved recanalization were maintained indefinitely on anticoagulant treatment and developed less frequent portal hypertension-related events during follow-up, but this difference was not statistically significant (p = 0.9). Four patients developed bleeding complications and there was one death related to anticoagulation. There were three more deaths during follow up all related to liver disease progression and two patients received a liver transplant. Rethrombosis was reported in one patient with partial recanalization after anticoagulation therapy was stopped. Advanced liver disease (MELD score > 15 at the start of therapy) and a platelet count < 50 x 10⁹/L, were significantly associated with higher risk for experiencing a bleeding complication (p < 0.05). In patients with lack of recanalization after 6 months anticoagulation therapy was stopped.

Conclusions: Anticoagulation is a relatively safe treatment that can lead to partial or complete recanalization in about 50% of patients with cirrhosis and PVT. Patients should be maintained indefinitely on treatment to prevent rethrombosis.
Efficacy and safety of triple therapy in clinical practice

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Background: In real life, efficacy and safety profile of triple therapy often differs from therapeutic trials.

Aim: To evaluate safety profile and effectiv eness of triple therapy in patients with chronic hepatitis C (CHC) in a real-life setting, in a prospective ongoing study.

Patients and method: We are treating 46 patients with CHC, all with severe fibrosis (F3/F4 METAVIR-evaluated histological or by a non-invasive method) using triple therapy (peginterferon alpha2a or2b [P] + ribavirin [R] + telaprevir [T] or boceprevir [B], [PRT/PRB]). 38 patients passed 12 weeks of therapy (28 PRT, 10 PRB) and their registered data were considered. Anaemia was considered severe when < 9 g/dl. The viral load was determined at start and after 4/8 and 12 weeks of therapy (real-time PCR, Abbott, LoQ 12 Ul/ml).

Results: There were 2 naïve patients, 4 null responders, 4 partial responders and 28 relapers. Median age was 57 years (31–70), median HCV RNA 1,559,968 Ul/ml. Weight loose occurred in 24 patients (16 PRB, 8 PRT). Viral load at 4, (respectively 8 weeks in PRB) was undetectable in 28 patients (73.68%), at 12 weeks in 30. Anaemia was present in 78.94% cases, it was severe in 10 cases (26.31%). 15 patients with PRT presented hyperuricemia, 1 in PRB group. Platelet decreased < 90000/mmc in 92% of patients. Rash was present in 8 patients but not severe. 6 patients developed hypercreatininemia, 6 hypocalcemia and 36.8% hypertri-glycerideridemia. Therapy was stopped in one patient due to adverse reactions

Conclusions: Both regimens of triple therapy for CHC are relatively well tolerated with good virologic response in motivated patients. They need a careful follow-up and a prompt intervention with corrective measures for adverse events.
Hepatocellular carcinoma: Aspects of management at two tertiary centers in Romania

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²Department of Gastroenterology and Hepatology, University of Medicine and Pharmacy, Timișoara, Romania
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Introduction: The incidence of hepatocellular carcinoma (HCC) in Romania has been tremendously increasing over the past two decades due to the increasing number of hepatitis B/D/C infected individuals. The aim of this observational study was to document the real-life experience of patients with HCC from diagnosis to death or cure, following the national guidelines of diagnosis and management of HCC.

Methods: This longitudinal study includes 198 patients with newly diagnosed HCC at two tertiary centers of gastroenterology in Romania between 01.07.2010 and 30.04.2012, capturing demographic and clinical characteristics, treatments performed and outcome. Demographic, clinical and tumoral characteristics were examined as potential determinants associated with the type of therapy in univariate and multivariate analyses.

Results: The median age at diagnosis was 58.7 ± 10.5 years and 71.7% of patients were males. Seventy four (37.4%) patients received potentially curative therapy (10.1% transplant, resection 14.6%, local ablation 12.6%). Combined therapy was applied in 10.6% of patients. TACE was performed in 19.1% of patients, 11.1% received sorafenib or chemotherapy, and 32.8% received no specific therapy. Patients with HCC that underwent curative therapy were in BCLC classification A and B (p = 0.009), had no ascites (p = 0.03), had a nodule size < 5 cm (p = 0.03) and diagnosis was established by screening (p = 0.005). The single independent factor associated with curative therapy was HCC diagnosis during routine screening (p = 0.004).

Conclusion: This interim analysis in two tertiary centers of gastroenterology documents that HCC curative therapy is suitable in about one third of patients; it is related to site-specific practices, tumor and underlying disease characteristics.
Does IL28 genotype variability influence the EVR in HCV patients?

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Introduction: The aim of our study is to evaluate IL28 genotype variability in our patients and their influence on the early viral response rates.

Methods: We evaluated 168 patients recording the following parameters: patient demographics, early virologic response and IL28B.

Results: We had 100 females and 68 males in our study group, with a mean age of 48.75 ± 10.6 years with the following IL28 genetic profile: 46 cases with C/C genotype (27.3%), 37 patients (84%) with EVR, 8 (18.1%) without EVR, 2 naive patients who did not reach 12 weeks of treatment yet. 102 patients with C/T (61.3%), 51 cases (52%) with EVR, 47 (47.9) without EVR, 4 naive. 20 cases with T/T genotypes (11.9 %), 9 (45%) with EVR, 11 (55%) without EVR. Comparing the EVR rates according to genetic host profile we observe a statistic significant difference between the three batches regarding early viral response (P = 0.0173). Comparing the C/C versus C/T genotype batches we observe there is also a statistic significant difference (P = 0.0095). Comparing the C/T versus T/T genotype groups the difference does not reach the significance threshold (P = NS).

Discussion/Conclusion: In our study group, from 168 patients 97 had EVR (59.8%). 27% of cases had favorable C/C IL28 genotype, the most frequent genotype being C/T (61%) The EVR rate was directly related to the IL28B genotype: 77% in C/C IL28B genotype vs. 52% in C/T and 45% in T/T genotype.
Upper gastrointestinal bleeding in liver cirrhosis – Prognostic factors

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Introduction: Acute upper gastrointestinal bleeding (UGIB) continues to be a common cause of hospital admission and morbidity and mortality. The identification of patients at a high risk could contribute to improved management of patients with gastrointestinal bleeding, including early therapeutic intervention.

Methods: We divided the batch into two groups: Group I – 647 patients were diagnosed with liver cirrhosis and group II – 1326 noncirrhotic patients. In each group we evaluated possible prognostic factors for mortality.

Results: In group I (352 males [54.4%] and 204 females [45.5%]). Mortality rate: in variceal hemorrhage – 77 (17%) significantly higher than the one in the other groups, 18 cases (9.9%) in nonvariceal hemorrhage in cirrhosis and 49 cases (3.7%) in nonvariceal bleeding (p < 0.00001). Prognostic factors in variceal bleeding: serum albumin (p = 0.000139), rebleeding (p = 0.005095), MELD score (p < 0.0001), severe encephalopathy (p < 0.0001). Nonvariceal bleeding in cirrhosis: anemia (p = 0.0024), Child-Pugh (p = 0.0092), hypovolemic shock (p = 0.0006). Group II: Baylor score (p < 0.0001), Rockall score (p < 0.0001), number of blood units (p = 0.013), aspirin consumption (p = 0.005).

Discussion/Conclusion: Mortality rates were: 17% in variceal bleeding, 10% in nonvariceal hemorrhage in cirrhotic patients and 3.7% in nonvariceal bleeding in noncirrhotic patients. The degree of hepatic insufficiency (MELD score, serum albumin) is the most important prognostic factor for cirrhotic patients. Also severe encephalopathy, anemia and the rebleeding rate are increasing the risk of mortality. In noncirrhotic patients Baylor and Rockall scores and hypovolemic shock are the most important but also aspirin consumption and number of blood units administered may predict the mortality risk.
Extremely low vitamin D levels are associated with increased mortality in patients with liver cirrhosis

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Background: Vitamin D serves an important role in regulating immune response mechanisms, and vitamin D deficiency has been associated with unfavourable outcomes in patients infected with chronic hepatitis C. Patients with advanced liver disease frequently suffer from vitamin D deficiency. However, it remains unknown whether vitamin D deficiency has an influence on mortality in these patients. Thus, we prospectively studied a cohort of patients with advanced liver disease to assess the influence of vitamin D deficiency on survival.

Patients and methods: Ninety-two patients with liver cirrhosis (mean age, 55 years; range, 19–76 years; 66% males; CTP stage C, 41%) were included in our prospective single-centre survival study. Serum vitamin D levels were determined using a chemiluminescence immunoassay (N = 61). AUC analysis, chi-square statistics and multivariate binary regression analysis were used to determine the optimal cut-off.

Results: The median vitamin D level was 8.2 ng/ml (range < 4.0–95.8 ng/ml) Overall, 51% of patients (31/61) died during follow-up of at least 24 months. AUC analysis determined a vitamin D level of 6.0 ng/ml as optimal cut-off for discriminating survivors from non-survivors. Kaplan-Meier analysis of survival confirmed low vitamin D levels as significant predictor of death (p = 0.004). Of note, multivariate analysis identified low vitamin D levels (OR = 6.3; 95% CI: 1.2–31.2; p = 0.024) and MELD scores (OR = 1.4; 95% CI: 1.2–1.7; p < 0.001) as independent predictors of survival. Patients with low vitamin D levels died more often from septic complications (43%) than patients with vitamin D levels > 6.0 ng/ml (20%).

Conclusions: Extremely low serum levels of vitamin D levels are associated with increased mortality in patients with advanced liver disease. Infectious complications are more frequent in these patients. We speculate that impaired immune function due to vitamin D deficiency might explain this observation. Further studies in larger cohorts are warranted to replicate our findings.
### Tab. 1: Patient characteristics

<table>
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<tbody>
<tr>
<td>Males (%)</td>
<td>66%</td>
</tr>
<tr>
<td>Age (median, range)</td>
<td>58 (19–76)</td>
</tr>
<tr>
<td>MELD (median, range)</td>
<td>14.2 (6.4–35.4)</td>
</tr>
<tr>
<td>Vitamin D serum levels (ng/ml, median, range)</td>
<td>8.2 (&lt; 4.0–95.8)</td>
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#### Aetiology of liver cirrhosis

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<table>
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<tbody>
<tr>
<td>Alcoholic</td>
<td>43 (66%)</td>
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<tr>
<td>Chronic viral hepatitis</td>
<td>7 (11%)</td>
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<tr>
<td>Others</td>
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#### Child-Pugh Stage (N, %)

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<tr>
<td>A</td>
<td>12 (18.4%)</td>
</tr>
<tr>
<td>B</td>
<td>23 (35.4%)</td>
</tr>
<tr>
<td>C</td>
<td>30 (46.2%)</td>
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### Univariate Analysis

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<th>Exp (B)</th>
<th>95% CI</th>
<th>p</th>
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<tr>
<td>Age</td>
<td>0.998</td>
<td>0.956–1.033</td>
<td>0.94</td>
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<tr>
<td>Gender (male vs. female)</td>
<td>1.283</td>
<td>0.439–3.752</td>
<td>0.65</td>
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<tr>
<td>Etiology (alcoholic vs. non-alcoholic)</td>
<td>1.891</td>
<td>0.540–6.622</td>
<td>0.32</td>
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<tr>
<td>Vitamin (≤ vs. &gt; 6.0 ng/ml)</td>
<td>5.333</td>
<td>1.621–17.546</td>
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<tr>
<td>MELD</td>
<td>1.378</td>
<td>1.170–1.622</td>
<td>&lt; 0.001</td>
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### Multivariate Analysis

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<th>95% CI</th>
<th>p</th>
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<tr>
<td>Vitamin (≤ vs. &gt; 6.0 ng/ml)</td>
<td>6.318</td>
<td>1.280–31.179</td>
<td>0.012</td>
</tr>
<tr>
<td>MELD</td>
<td>1.411</td>
<td>1.172–1.699</td>
<td>&lt; 0.001</td>
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Increased numbers of CD4⁺, CD8⁺ and Foxp3⁺ immune cells in malignant and benign liver tumors

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Introduction: The role of Tregs which inhibit activation and differentiation of CD4⁺CD25⁻ or CD8⁺ T cells and the function of NK cells have been investigated in several diseases including autoimmune and malignant tumors. We investigated the liver distribution of cells in different liver compartments in benign and malignant liver tumors and tied to assess the role of infiltrate in the antitumor response.

Methods: We investigated immunohistochemically paraffin specimens from 18 hepatocellular carcinomas (HCC), 5 haemangiomas and healthy controls for CD3, CD4, CD8, CD56, CD57 and Foxp3 and flow cytometry for Foxp3.

Results: The peritumoral and intratumoral infiltrate in HCC consisted mainly in CD8⁺ and CD4⁺ cells, moderately Foxp3⁺ cells and less CD56⁺/CD57⁺ cells (NK and NKT). In haemangioma patients the inflammatory infiltrate in the same areas was significantly lower. In liver sinusoids and portal tract CD4⁺ and CD8⁺ cells were significantly more in HCC as compared to controls. Foxp3 cells were missing in controls and present in HCC stroma. Flow cytometry demonstrated a dominance of CD8⁺ lymphocytes with a lower number of CD4⁺ lymphocytes in HCC livers. The proportion of intrahepatic Treg was significantly higher in HCC liver than in control livers (p < 0.01). 30% from haemangiomas had low CD4⁺ and CD8⁺ infiltration while 66.7% from HCC had high CD4⁺ and CD8⁺ infiltration in the tumor (χ² = 4.44, p = 0.035).

Discussion/Conclusion: Our data suggest that the increased Treg number in the liver in HCC might responsible for the suppression of innate immune system and of the failure of the innate anti-tumor response.
Accuracy of ARFI to predict stage of liver fibrosis in patients with liver diseases

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Introduction: Acoustic radiation force impulse (ARFI) is a noninvasive technology to evaluate liver stiffness and to predict stage of liver fibrosis. ARFI is integrated into conventional B-mode ultrasonography probe and results are expressed as shear wave velocity in m/s. Our aim was to establish clinical applicability of ARFI method to predict stage of liver fibrosis.

Methods: We enrolled 100 consecutive patients, who underwent liver biopsy in our department. We compared results of liver histology (Metavir) with results of ARFI examination performed until 9 months from liver biopsy and determined correlation with other markers of liver disease. For this purposes we created different groups according to F-stage. ARFI results were calculated as an average value from 10 measures in different parts of the liver.

Results: Diagnosis presented in 100 patients was following: 31 pts. with AIH, 10 pts. with PBC, 10 pts. with EtOH, 12 pts. with HBV and 37 pts. with HCV. ARFI shear wave velocity cut-off value was 1.17 m/s for F0 + F1, 1.9 m/s for F2 + F3 and 2.69 m/s for F4. AROC for F0 + F01 vs. F2 + F3 + F4 was 0.95 (95% confidence interval 0.84–0.99) with cut-off 1.32 m/s, sensitivity (SE) 90.2% and specificity (SP) 76.2%. AROC for F0 + F1 + F2 vs. F3 + F4 was 0.94 (CI 0.88–0.97) with cut-off 2.05 m/s with SE 94.2% and SP 78.6%. AROC for F0 + F1 + F2 + F3 vs. F4 was 0.95 (CI 0.92–1.00) with cutoff 2.42 m/s and SE 96.3% and SP 84.2%. ARFI results statistically correlated (p < 0.001) with trombocytes, INR, albumin and AST.

Discussion/Conclusion: Ultrasonography associated ARFI method seems feasible and valuable for noninvasive assessment liver fibrosis. Optimal cut-off value for liver fibrosis (F > 2) is 1.32 m/s and 2.05 m/s for significant liver fibrosis (F3 + F4). ARFI can precisely determine advanced stages of liver fibrosis (F3 + F4). It can be repeated in every routine ultrasonographic examination.
Quantitative gene expression of liver enriched transcription factors in curatively treated hepatocellular carcinoma

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Background: Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, and has a good prognosis only when is treated curatively. The development of new systems that can predict the likelihood of recurrence after curative treatment, including molecular prognostic factors, is much needed. The liver enriched transcription factors (LETFs) are critical in inducing and maintaining hepatic phenotype during liver organogenesis and their expression level in HCC could have prognostic implications.

The aim of our work was to investigate the expression profile of liver enriched transcription factors FoxA2, HNF6 (ONE CUT1) and C/Ebp alpha in hepatocellular carcinoma specimens from liver resections or liver explants after liver transplantations, in comparison to non-tumoral liver tissue from the same patients.

Methods: The study group included 22 patients, 12 with liver resection and 10 with liver transplantation for HCC. Total RNA was isolated from tumoral and non-tumoral tissue fragments and gene expression has been quantified by qRT-PCR, using beta-actin as reference gene. A higher than 5-fold change in relative gene expression has been considered significant.

Results: In 9 patients (40.9%) a higher than 5-fold change in relative gene expression has been detected. A significant up-regulation of the studied liver enriched transcription factors has been found in 4 patients (18.1%). A significant down regulation has been identified in 5 patients (22.7%) out of which HNF6 down regulation was detected in 4 patients. Only in one patient (4.5%) dramatical changes in LETFs expression has been detected – FoxA2 and HNF6 were not detectable and C/Ebp alpha expression had a 100-fold decrease. The patient had a tumor recurrence in 4 months after the treatment.

Conclusions: A significant change in LETF gene expression has been identified in 40.9% of patients curatively treated for hepatocellular carcinoma. HNF6 was the most frequently down regulated LETF in our study.
Follow-up and predictors of graft outcome in recurrent hepatitis C post-liver transplantation

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Introduction: HCV associated allograft injury is incriminated as the most common cause of both death and graft failure among HCV infected recipients. Current antiviral therapy is still far from optimal. The aim of our study was to evaluate the predictive factors of patient and graft survival in the cohort of Romanian patients transplanted for HCV cirrhosis.

Methods: Medical records of 78 patients who underwent LT for HCV liver cirrhosis between April 2000 and November 2011 were reviewed. To identify potential predictors of graft and patient survival, univariate and multivariate Cox’s proportional hazards regression model was used.

Results: The overall patient and graft survival rate at 1 year post LT was 84.1\% and respectively 82.5\%; at 5 years was 65.5\% and respectively 58.5\%. As predictors of both graft failure and patient death were identified: presence of hepatocellular carcinoma (HCC), lack of post-LT antiviral therapy, de novo post-LT diabetes mellitus. Other factors identified as negative predictors of graft failure were: severe recurrent hepatitis C (F $\geq 2$) (p = 0.01) and time to HCV histologic recurrence $< 12$ months (p = 0.03). Independent predictors of graft failure were: advanced fibrosis following LT (F $\geq 2$); lack of antiviral therapy; presence of HCC and de novo diabetes mellitus. 65.4\% of patients underwent liver biopsies and 38 patients underwent antiviral therapy. Sustained virological response (SVR) was obtained in 29.03\% and early virological response (EVR) in 63.2\% of patients.

Discussion/Conclusion: Early diagnosis and antiviral therapy of recurrent hepatitis C can improve patient and graft survival following liver transplantation.
Cardiovascular risk in patients with nonalcoholic fatty liver disease with and without newly diagnosed diabetes mellitus type 2

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Introduction: The relationship between the diabetes mellitus type 2 (DM) and increased cardiovascular risk (CVR) is well known. In patients with nonalcoholic fatty liver disease (NAFLD) an increased cardiovascular risk is also present. The role of different biomarkers is discussed, but the influence of diabetes in these cases is not yet clear.

Methods: In this study we evaluated and compared the frequency and the degree of deviations of some factors, related with increased CVR in 250 patients with NAFLD with and without newly diagnosed DM.

Results: In comparison of the groups with and without DM, there was no difference regarding the weight status categories and BMI, waist circumference, the frequency and the type of dyslipidemia, the triglycerides/HDL-cholesterol ratio, uric acid levels, fasting insulin and insulin levels at 120 min during OGTT (but significantly higher insulin levels at 60 min of OGTT in DM, \( p = 0.029 \)); the of NAFLD (simple steatosis/steatohepatitis) with or without fibrosis, the degree of activity and stage of fibrosis, AST and ALT levels. The patients with NAFLD and newly diagnosed DM were older compared to those without DM (\( p = 0.001 \)). In this group of cases, the frequency (\( p = 0.0001 \)), and severity of metabolic syndrome (\( p = 0.001 \)), the serum levels of blood glucose (\( p = 0.0001 \)), glucose/insulin ratio at 60 min during OGTT (\( p = 0.0001 \)), HOMA-IR (\( p = 0.022 \)), HbA1c (\( p = 0.0001 \)), GGT (\( p = 0.007 \)) and ferritin (\( p = 0.024 \)) were significantly higher and the values of platelets (\( p = 0.01 \)), QICKI (\( p = 0.002 \)), and insulin/glucose ratio at 60 min during OGTT (\( p = 0.0001 \)) significantly lower. The calculated Framingham Risk Score and SCORE were also higher in cases with DM (\( p = 0.05 \)).

Discussion/Conclusion: There are many metabolic and other factors, related to NAFLD, but independent of DM, which are associated with increase cardiovascular risk. On the other hand, in NAFLD and newly diagnosed DM the impaired glucose metabolism is related with additional increase of CVR.
Natural fluctuations of serum HBsAg level in HBeAg-negative chronic hepatitis B

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Medical University – Sofia

Introduction: Quantification of HBsAg was proposed to guide Peg-IFN therapy for chronic hepatitis B (CHB). The decrease of qHBsAg ≥ 10% at 3rd month of therapy was identified as a predictor of sustained virological response in HBeAg-negative CHB. Short-term fluctuations of qHBsAg during natural course of CHB are not studied.

Methods: We tested HBsAg within 3-month interval without therapy in 10 HBeAg-negative patients with chronic HBV infection. All of them were viremic with HBV DNA level > 2,000 IU/ml. CHB was histologically proven in 8/10 of subjects. HBV DNA and HBsAg levels were measured initially and 3 months thereafter by real-time PCR assay (LightCycler, Roche Diagnostics) and Elecsys HBsAg quant immunoassay (Roche Diagnostics), respectively. We have re-evaluated coefficient of variation for qHBsAg and the SD was 1–1.5% in low and high level ranges.

Results: During the observation period HBsAg level:
1. Remained relatively unchanged only in 1/10 of patients.
2. Spontaneously decreased (at least 10%) in 4 subjects, while HBV DNA levels in all of them remained relatively unchanged.
3. Elevation of HBsAg level (> 10%) was found in the rest 5 patients, although HBV DNA level in all of them spontaneously decreased with at least 0.5 log cp/ml.

Discussion/Conclusion: HBsAg titer might fluctuate significantly and separately from viral load even within short (3-month) period of natural course of HBeAg-negative CHB. Further studies are needed to elucidate which decline of HBsAg titer during therapy is clinically relevant.
Radical or conservative surgery for hydatidosis of the liver and effects of the residual liver parenchyma: 30 years multicentric experience

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Department of General and Pediatric Surgery, University Hospital Stara Zagora¹, University Hospital Plovdiv², Bulgaria

Aim of the study: To compare the efficacy and safety of radical and conservative surgical interventions for liver hydatid disease in childhood.

Material and methods: Patients who underwent any type of surgical treatment between December 1981 and May 2012 due to liver cyst hydatid were retrospectively evaluated in 254 patients. Preoperative diagnostic tools, medical treatments, demographic, immunology and clinical characteristics, surgical procedures, morbidity and mortality rates, postoperative follow-up and recurrence were compared in the groups.

Results: The 254 patients were divided into two groups with respect to the treatment modality: Group A (n = 98, mean age: 42.1 ± 16.5 years, 69 male, 29 female) – radical surgical treatment and Group B (n = 156; mean age: 51.6 ± 3.9 years, 98 male, 58 female) – conservative surgery. The preoperative evaluation of the patients included liver function tests, a complete blood count, immunological tests: hemagglutination antibody (IHA) and ELISA; abdominal ultrasonography (USG), abdominal computed tomography (CT). The cysts were classified according to the five categories described by Gharbi. The follow-up period ranged from 3 to 5 years. Associated with risk of dissemination of infection or anaphylaxis although operative time was significantly shorter in the conservative group (P < 0.001), recurrence was significantly reduced in the radical group (P = 0.045). No statistically significant differences were found in terms of hospitalization duration, cyst count and size, location, postoperative complications or follow-up between the two groups.

Discussions: The morbidity rate of the patients who underwent radical surgical modalities was also significantly lower. The mean age of the patients was 35.8 years (6–68 years). The diagnostic methods primarily included abdominal ultrasonography and computed tomography with a rate of 81.8% and magnetic resonance imaging in 11% of the patients. 30% of patients have an eosinophilia. Surgery is the only effective treatment for hepatic hydatid disease and is recommended for both symptomatic and asymptomatic cases. Most surgeons agree that proper management must include sterilization of the cysts, avoidance of spillage, and evacuation of the cyst and removal of the germinal layer. Numerous solutions have been used as scolicidal agents; however, some of these, such as formalin and silver nitrate, are toxic. We use 10% povidone-Jodine and no complication for sanation of the cysts with this medicament and hypertonic solution of NaCl or H2N2. In histopathological investigation we find intrahepatic cholestasis before treatment. Has is reason for use pericystectomy for III and IV Stage cysts by Gharbi’s scale. Aspiration should not be performed if hydatid disease is suspected. The drugs of choice are albendazole, mebendazole and praziquantel.
Conclusions: Conservative surgical procedures in liver surgery are considered simpler and safer to perform, the rate of postoperative complications such as biliary fistula, residual cavity and recurrence, and cavity suppuration has been reported to be about 28%. On the other hand, radical surgery can be performed with low risk of recurrence (3.2%). We believe radical surgical procedures present a lower rate of recurrence and less morbidity, and thus should be the surgical treatment of choice for hepatic hydatid disease and show better postoperative results.
Alternative treatment of hepatitis B and C by phosphogliv when interferon cannot be used

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The paper demonstrates efficacy of alternative treatment of chronic hepatitis B and C with signs of liver cirrhosis. A specific case is reviewed.

A 46 year-old patient complained about dyspepsia, meteorism, general weakness, sensation of heaviness in the right under the ribs, and hair loss, in particular in lower limbs. Five years before, the patient had been diagnosed with hepatitis B and C with no pronounced signs of the disease. The duration of the disease was unknown. At that time, the patient refused interferon treatment because of possible side effects.

At the moment of seeing the doctor blood biochemistry revealed transaminase level three times the norm. PCR analysis for HCV-RNA was performed. 1b genotype virus was found along with high virus intensity. Echoscopy showed fine grain liver tissue structure, increased liver echogenicity and slightly increased liver size. A fiber test showed stage F2–F3 liver damage. Interferon treatment of the virus was found challenging due to combined hepatitis B and C. High virus intensity also impeded successful treatment outcome. The patient received, along with diet, replacement phosphogliv treatment, a hepatoprotective anti-inflammatory nanotechnology drug. The course included a 21 day intravenous drug transfusion twice a day and 30 day capsule intake. The treatment produced overall improvement in the general condition with hair regain and normalized transaminase level. Currently, the patient is on Ursofalk®.

The case is of interest due to the efficacy of replacement phosphogliv treatment if interferon cannot be used.
Manifestations and complications of liver cirrhosis: Role of mediators of intercellular interactions

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The aim of study is to evaluate relationship between intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) serum levels and manifestations and complications of viral liver cirrhosis (LC).

Material and methods: 42 patients with LC (27 men, 17 women) were examined. Patients were divided into classes A (24 patients), B and C (18 patients) depending on Child-Pugh criteria. Control group included 16 healthy volunteers comparable on sex and age. Blood concentration of ICAM-1 and VCAM-1 was carried out by means of ELISA. Statistical analysis was used to fit the nonparametric statistics.

Results: ICAM-1 and VCAM-1 serum levels were increased in LC. Adhesion molecules levels in blood were not connected with disease etiology, genotype and degree of viral load of HCV. Severe cases of LC (classes B and C according Child-Pugh, decompensated portal hypertension and hypersplenism) were characterized by higher parameters of ICAM-1 and VCAM-1 in blood.

ICAM-1 and VCAM-1 levels increased from 0–1 degree to 2–3 degree of esophageal varices (EV). Parameters of VCAM-1 ≥ 7525 ng/ml were associated with increased risk of presence of 2–3 degree of EV in LC. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of VCAM-1 ≥ 7525 ng/ml for detection of 2–3 degree of EV were 100.0, 44.4, 70.6, 100.0, 76.2 accordingly.

Conclusions: The obtained data show elevation of ICAM-1 and VCAM-1 levels in liver cirrhosis. Maximal elevation is revealed in severe variants of disease. Association of increased VCAM-1 levels and esophageal varices degree in liver cirrhosis is a useful noninvasive marker of the esophageal varices.
Hyaluronic acid – Age-related liver fibrotic marker

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Introduction: Hyaluronic acid (HA) forms constituent of extracellular matrix in all connective tissues. It is mainly produced by mesenchymal cells including synoviocites and cleared by hepatic sinusoidal endothelial cells. HA is one of the most used non-invasive markers for evaluation of liver fibrosis – alone or as a part of different fibrotic scores – Hepascore, ELF, Fibrospect, Fibrometer.

Aim: The aim of this study was to evaluate influence of age on HA levels.

Methods: HA (ELISA, Corgenix, UK) was measured in 61 patients with chronic hepatitis B and liver biopsy done the same day, and 10 healthy controls. The mean age of healthy subjects was 48 ± 16 years and for hepatitis B patients 38 ± 11 years. Liver biopsies were assessed by Metavir.

Results: We found positive correlation between age and HA in healthy controls \( r = 0.762 \), but also in HBV patients \( r = 0.528 \). Furthermore, we observed that levels of HA in patients \( \leq 40 \) years with advanced fibrotic liver changes (F3 and cirrhosis) and healthy adults \( \geq 50 \) years did not differ.

Discussion/Conclusion: Use of HA as surrogate marker of liver fibrosis – alone or as a part of recently published combined non-invasive scores, should be age-adjusted. For evaluation of liver fibrosis different cut off values should be used for age group below 40 and over 50 years, because serious overestimation of hepatic changes in elderly could be done.
Autoimmune hepatitis (AIH) and celiac disease in two-year-old child: Diagnosis and therapy

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Introduction: As a result of specific clinical picture absence in children with AIH, timely diagnostics and therapy are found difficult.

Methods: The article presents clinical example of early debut diagnosis and treatment of two autoimmune gastrointestinal diseases in 2-year-old child.

Results: A hereditary tainted girl: her father has celiac disease. The girl had a rapid onset at 1.5 years: decreased appetite, body weight loss from 11.0 to 7.5 kg, skin itch, leg swelling, abdominal circumference increasing, liver +2.0 cm, tightly-elastic edge, and mushy stool up to 300 grams per day. Examination: ESR 53 mm per hour, Le 13.3 x 10^9/l, crude protein 43 g/l, ALT 14 norm (N), AST 12 N, Gamma-GT 4 N, total bilirubin 61.1 mkmol/l, increased IgG, M, A, antimitochondrial autoantibodies (AMA-M2) 4 times, and transglutaminase IgA 3 times. Morphological study of jejunum mucosa: signs of celiac disease. Treatment: gluten-free diet, prednisolone 1.5–1.0 mg/kg, ursodeoxycholic acid (UDCA) 125 mg per day, Creon (pancreas-lipase), symptomatic therapy. Appetite increased, no itching, ALT 5 N, AST 5 N, Gamma-GT 2 N. Within two years of taking prednisolone steroid-related reactions were formed; ALT, AST 1.5–5 N, autoantibodies to lysosomal antigen of liver and kidney (LKM-1) is two times greater, serum cortisol is decreased. At 4 years prednisolone was canceled, budesonide, UDCA were prescribed. Treatment is well tolerated and side effects of glucocorticosteroid therapy are stopped. The girl grew up during the year by 11 cm, ALT, AST 1.5–3 N, Gamma-GT N, autoantibodies number is not increased.

Discussion/Conclusion: The application of a new generation of corticosteroids in combination with UDHA is promising in the treatment of AIH in children; in order to better the disease prognosis and improve the quality of life.
Long-term outcomes following drug-eluting bead transarterial chemoembolisation (DEB-TACE) as part of multimodality treatment for hepatocellular carcinoma

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Introduction: Treatment protocols for hepatocellular carcinoma (HCC) are evolving rapidly. We sought to determine long-term outcomes in patients with HCC treated with DEB-TACE as stand alone or part of multimodality treatment at a single centre.

Methods: Our departmental database of HCC, diagnosed using EASL radiological criteria, was reviewed retrospectively. From August 2006 to January 2011, 80 patients (60 males and 20 females) underwent DEB-TACE some of which also had surgery and/or percutaneous ablation. A total of 186 episodes of DEB-TACE treatment were performed in 80 patients (minimum 1 episode and maximum 8 episodes). 37.5% of patients presented with multifocal disease with a further 7.5% presenting with tumour plus satellites. The mean MELD (Model for End-stage Liver Disease) in this cohort was 9.53 (range 6–22). Demographics, procedural details, clinical measures and outcomes were studied. Median age was 69 years (range 33–87). All patients were included in the survival analysis. Overall survival was described using Kaplan-Meier methods.

Results: 53 patients with a median tumour size of 49 mm (range 12–163 mm) were treated with DEB-TACE alone with a mean number of procedures of 2.1. The median survival in this group was 28.5 months (798 days). The 1- and 3- year survival rates in this group where 66% and 38% respectively. 27 patients with a median tumour size of 40 mm (range 12–100 mm) were treated with a combination of therapies and at 55 months (1540 days) the median survival had not yet been reached. Survival in this group was 51.1% at time data collection. In this group the 1- and 3- year survival rates were 86% and 64% respectively. In our cohort of patients with HCC, DEB-TACE, both with or without combination therapies, resulted in median survival of 44 months. Overall survival rates at 1- and 3-years were 74.5% and 50.3% respectively.

Discussion/Conclusion: In our centre this procedure is safe and well tolerated with multimodality treatment showing an improved survival outcome. Our results highlight the importance of a multidisciplinary approach with the application of multimodal therapy in the management of HCC with an improved survival for appropriately selected patients.
Fetal hemoglobin in liver cirrhosis with pulmonary hypertension

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Objective: To study changes in the level of fetal hemoglobin (HbF) in patients with liver cirrhosis (LC), depending on the presence of pulmonary hypertension (PH).

Methods: The concentration of HbF in the blood was studied in 98 patients with LC (56 men and 42 women aged 35 to 60 years). Application Control Group (CG) – 30 donors. For quantitative analysis of HbF developed and patented a way to rocket electrophoresis in agar gel. All patients underwent determination of the diameter of the pulmonary artery (PAD) and mean pulmonary artery pressure (PAP) using an ultrasonic scanner «ALOKA-5500 Prosound» (Japan).

Results: The content of HbF levels in patients with LC averaged 2.98 ± 0.07% of total Hb (p < 0.001 compared to control), and the excess of the normal concentration of HbF had in 72 patients. In 49 patients with LC reported signs of PH, and an increase in PAD above 25 mmHg PAP, of which 12 cases – within 30 to 35 mmHg in this subindex of HbF averaged 3.02 ± 0.03%. In 49 patients PAP was ≤ 25 mmHg, and the level of HbF – an average of 2.86 ± 0.01% of total Hb.

Conclusion: Increased level of HbF in the blood as a marker of tissue hypoxia in adults with LC is associated with the presence of PH. Increased PAP is a consequence of hemodynamic changes in the pulmonary circulation in LC. PH can lead to a breach of the oxygenation of blood and the development of tissue hypoxia. HbF promotes a better adaptation than adult Hb to chronic hypoxia, which develops with LC.
The lipopolysaccharide-binding protein plasma concentration in liver cirrhosis

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Objective: To examine changes of the lipopolysaccharide-binding protein (LPB) in the blood plasma of patients with liver cirrhosis (LC).

Methods: LPB concentration in blood plasma was studied in 120 patients with LC (66 men and 54 women aged 30 to 60 years). The control group (CG) – 15 healthy donors. The level of LPB was determined by Elise test using the test-systems company Hycult Biotech.

Results: LPB concentration in LC was significantly higher than in CG (mean 43.0 ± 1.4 mcg/L vs. 13.5 ± 0.9 mcg/L, p = 0.001). Variability in the values of LPB in LC was in the range of 10.4 mcg/L to 58.3 mcg/L. LPB concentration was associated with the activity of inflammation and severity of LC class on the Child-Pugh. Mean values for LPB in LC class "A" were 37.9 ± 2.1 mcg/L, class "B" – 43.8 ± 2.5 mcg/L, class “C” – 48.9 ± 2.3 mcg/L (λ² = 5.61, p = 0.048). In LC patients with concentration of LPB > 50 mcg/L compared with LPB < 30 mcg/L, ascites was found on 29% more often, varicose veins of the esophagus – by 17.4%, cytolytic syndrome – 23%. Statistical significance of differences in the two groups of patients with LC was higher (p = 0.0001).

Conclusion: In patients with LC showed an average of 4–5-fold increase compared with the normal blood concentrations of markers of nonspecific immunity – LPB. The growth of LPB shows the severity of endotoxemia, stress antiendotoxin immunity. It is associated with the activity of the pathological process in the liver, the severity of clinical manifestations of LC and of hepatocellular insufficiency.
Mitochondrial abnormalities in nonalcoholic steatohepatitis in pediatric patients

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Introduction: In the last decade, there has been a growing incidence of nonalcoholic steatohepatitis (NASH) in children, being a major cause of serious liver dysfunction that could lead to cryptogenic cirrhosis. Although this pathology has become a common disease worldwide, its morphogenesis remains unexplained. Despite increasing interest in NASH, there are only few reports on the hepatocyte ultrastructure in this pathology. The current study is a continuation of our submicroscopic research on liver biopsy in children with NASH.

Aim and methods: The study objective was electron microscopic analysis of the image of abnormal hepatocyte mitochondria, including their zonal distribution in biopsy material collected from 10 children (6 boys and 4 girls), aged 2–14 years (mean 5 years) with clinicopathologically diagnosed NASH. Histopathological investigations of liver biopates from these patients showed evidence of NASH, i.e. steatosis, inflammation, ballooned hepatocytes, Mallory’s hyaline bodies, focal necrosis and varying degree of fibrosis in the absence of clinical, serological or histological findings of infectious liver diseases, autoimmune hepatitis, metabolic liver disease and celiac disease.

Fresh small tissue blocks (1 mm3 in size) from the liver biopates were fixed with solution containing 2% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M cacodylate buffer (pH 7.4) and routinely processed for ultrastructural analysis. Ultrathin sections were double stained with uranyl acetate and lead citrate, and examined using an Opton EM 900 transmission electron microscope.

Results: The electron microscopic analysis of the biopsy material obtained from children with NASH revealed characteristic mitochondrial structural defects within hepatocytes, mainly mitochondrial polymorphism, especially megamitochondria, loss of mitochondrial cristae and the presence of linear crystalline inclusions within the mitochondrial matrix of moderate electron-increased density. The cristalline inclusions were particularly evident within megamitochondria. The megamitochondria with characteristic inclusions seemed to be distributed randomly, both within the cell and in the hepatic zones, without special variation in abundance.

Discussion/Conclusion: These data indicate that NASH in children is associated with marked abnormalities in hepatocyte mitochondria, especially their polymorphism in the form of megamitochondria, loss of mitochondrial cristae and the presence of crystalline inclusions within the matrix.
Prophylactic therapy with nor-ursodeoxycholic acid in experimental thioacetamide-induced liver fibrosis

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Introduction: Recently we demonstrated a high therapeutic efficacy of nor-ursodeoxycholic acid (nor-UDCA), the C23 homologue of ursodeoxycholic acid (UDCA) in rat thioacetamide (TAA)-induced liver fibrosis reversal. Now we studied whether nor-UDCA is able to prevent TAA-fibrosis. The aim of this study was to compare the preventive antifibrotic effects of nor-UDCA and UDCA in a rat model of TAA-induced liver fibrosis.

Methods: Liver fibrosis was induced by TAA treatment (200 mg/kg, i.p.) twice a week for 12 w. During 8 last weeks of the trial, fibrotic rats were daily administered with UDCA (40 and 80 mg/kg) and nor-UDCA (corresponds to 40 and 80 mg/kg of UDCA) by oral gavage. The severity of liver fibrosis was assessed by morphometric evaluation of liver slides, stained with Azan-Mallory, and hydroxyproline (Hyp) determination. Serum markers of fibrosis, including tissue-inhibitor of metalloproteinases (TIMP), collagens I, III, IV types, procollagen III-NT, hyaluronic acid and laminin, as well as serum cytokine (TGFβ1, TNFα and IL-6) contents, were evaluated by ELISA techniques.

Results: The TAA treatment resulted in advanced fibrosis/cirrhosis with complete fibrous septa formation and dramatic increase in liver Hyp content. All the studied serum fibrosis markers were significantly elevated in rats treated with TAA for 3 m. Neither UDCA nor nor-UDCA changed liver Hyp content. However, both doses of nor-UDCA significantly decreased the square of connective tissue in the liver (21% and 43%, respectively). All the tested compounds did not change serum cytokines (TGFβ1, TNFα and IL-6) contents. Serum TIMP-1 level was lowered by the highest doses of both UDCA and nor-UDCA, whereas hyaluronic acid content was diminished under the influence of both doses of nor-UDCA. Only nor-UDCA (80 mg/kg) decreased serum laminin content. Serum collagens I, IV types and procollagen III-NT contents were decreased in rats treated with both doses of UDCA and nor-UDCA, whereas only the highest dose of nor-UDCA diminished collagen III type level in serum.

Discussion/Conclusion: Our data suggests that the preventive antifibrotic action of nor-UDCA applied at a high dose (corresponds to 80 mg/kg of UDCA) was more efficacious than UDCA one in the model of TAA-induced liver fibrosis.
Hepatocellular carcinoma: Risk factors of carcinogenesis, carcinogenesis rate

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**Introduction:** Hepatocellular carcinoma represents 80–90% of the primitive liver cancer, with worldwide increasing incidence. Liver cirrhosis regardless of etiology is an important risk factor in development of HCC. Chronic HBV and HCV infection contribute to HCC in more than 80% of cases. Chemicals, aflatoxin B1, smoking and alcohol consumption are each independent risk factors, and also NASH associated with diabetes or obesity.

**Methods:** 483 patients with liver cirrhosis, included during 2001–2007, evaluated every 3–4 months by clinical evaluation, biochemical and serological tests, imaging exploration. The fallow of the entire group was done over a period of approximately 7 years. Parameters: dimensions and number of tumors, distribution according to sex, age, therapeutic methods, survival rate.

**Results and Conclusions:**
1. Prospective cohort study that included a total of 483 patients, followed for an average of 85 months, revealed hepatocellular carcinoma as the first complication (15%), followed by ascites, SDH, hepatic encephalopathy.
2. The annual rate of carcinogenesis was 2.4% for HCV and 4% for HBV, data that overlap the literature.
3. Risk factors involved in carcinogenesis evolution is represented by:
   – Age > 60 years
   – Liver cirrhosis evolution > 5 years
   – For male HBV etiology
4. Biochemical parameters like low platelet count and elevated ALT or fluctuations in this parameter correlated with increased risk of developing hepatocellular carcinoma.
The efficacy of mesalazine therapy (Salofalk® tablets) in spondylarthropathies

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Introduction: There are case reports suggesting a possible favorable effect of mesalazine in patients with spondylarthropathies. Ankylosing spondylitis are inflammatory disorders of unknown etiology. Many different exogenous and endogenous factors appear to play a role in their development. Both the colon and ileum are frequently affected in patients with ankylosing spondylitis and subclinical lesions in the terminal ileum have been described.

Aim of study: We established the efficacy of mesalazine in the management of ankylosing spondylitis with or without affected colon and ileum.

Material and methods: Controlled clinical study involving a total of 118 patients with confirmed ankylosing spondylitis, 31 patients are endoscopical lesions in the colon and/or ileum. All patients received 2 g of mesalazine per day for 24 weeks. 91 of 118 patients were positive for HLA-B 27 antigen.

Results and discussions: The development of clinical, biological and endoscopical parameters has been analyzed after 24 weeks of therapy. The evolution of clinical parameters (joint pain, functional impotence, sleep disorders), biological parameters (C protein reactive) and endoscopical parameters under mesalazine therapy was favourable in 72.8% of cases (86 patients). The patients with colon and ileum lesions had the most favourable evolution in 83.8% (26 patients).

Conclusions: The efficacy of mesalazine in the management of ankylosing spondylitis is increased. The best results have been obtained with patients with colon and ileum lesions.
The role of HLA complex genes in non-alcoholic fatty liver disease

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Introduction: HLA complex is a genetic factor that may be involved in the pathogenesis of non-alcoholic liver fatty disease (NAFLD) or may contribute to disease susceptibility. The aim of our study was to evaluate the relationship between HLA complex and NAFLD and, for the first time in Romania, to compare HLA frequencies in NAFLD group with healthy population.

Methods: In NAFLD group we included 46 patients with high level of aminotransferases and a bright liver at abdominal ultrasound and we excluded the patients with other conditions known to be associated with hepatic steatosis. In control group we included 300 healthy candidates. In both groups we performed HLA class I – A, B and HLA class II – DR-, DQ- using ARROW BLOOD DNA method and molecular technique SSO-HISTO-SPOT. In 36 patients from NAFLD group we determinated alleles with molecular technique PCR-SSP.

Results: We compared the antigen frequencies of NAFLD group with control group and we found that HLA A24 (31.12% in NAFLD group vs. 19.5% in controls), A31 (11.12% vs. 3.6%), A32 (13.3% vs. 8.4%), B18 (26.6% vs. 9.2%), B49 (8.89% vs. 3.6%) and B53 (6.67% vs. 0.08%) were significantly high expressed in NAFLD group than in controls. We found HLA-B8 and B44 in very few patients and HLA-B17, B65 were no detected. Class II antigens DR15, DR16 and DR8 had a higher incidence in study group than in controls. The prevalence of HLA-A1, A3, DR1, DR3, DR4 and DR7 were less frequent in NAFLD group than in controls. Moreover, HLA DQB1*03:01 and DQB1*05:02 were high statistical in NAFLD group. There is no relationship between HLA complex and anthropometric measures, aminotransferases levels, presence or not of diabetes mellitus in both groups.

Discussion/Conclusion: Our study demonstrate that some HLA complex genes (A24, A31, A32, B18, B49, B53) are related with the disease and others (DR1, DR3, DR4 and DR7) seems to be protective for development of NAFLD.
The relationship between bone mineral density and liver cirrhosis in postmenopausal women

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Introduction: The pathogenesis of osteoporosis in patients with chronic hepatic diseases is unclear but it is observed that osteoporosis affects especially trabecular bones. Aim of our study was to compare the prevalence of osteopenia and osteoporosis in two groups: group A – women in postmenopausal period with liver cirrhosis and group B – healthy women in postmenopausal period.

Methods: We included 48 women with liver cirrhosis (25 with alcoholic and 23 with viral etiology), mean age 56.3 years and 65 healthy women in postmenopausal period, mean age 57.4 years. In all patients we measured calcium level, ionized calcium, serum albumin, body mass index. The severity of cirrhosis according to Child classification was class B for every patient. None patient had any bone fracture due to osteoporosis before the study. The bone mineral density (BMD) was determined by DEXA at the lumbar spine and hip. BMD was defined by a T-score (between -1 and -2.5 for osteopenia and a T-score inferior to -2.5 for osteoporosis).

Results: The mean T-score in alcoholic group at lumbar spine was -2.99 ± -0.3 and at hip was -1.34 ± 0.80. In viral group the mean T-score at lumbar spine was -2.98 ± 0.4 and at hip was -1.15 ± 0.64 and in healthy women at lumbar spine was -0.63 ± 0.7 and at hip was -0.50 ± 0.34. We did not find any statistical differences according to the alcoholic or viral etiology of cirrhosis, both for lumbar spine and hip determination, but statistical significant for lumbar spine in cirrhotic group versus healthy group (p = 0.005). The mean total calcium (p = 0.001) and ionized calcium (p = NS) were lower in both groups but the significant decrease of total calcium in group A was probably related with the significant low level of serum albumin in group A compared with group B. There were no differences between study and control group, according to BMI.

Discussion/Conclusion: Osteopenia and osteoporosis in patients with liver cirrhosis had no relationship with etiology but were significant more frequent in study group than in healthy women.
RVR in chronic hepatitis C patients on standard bi-therapy

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Introduction: Patients with chronic HCV infection who achieve rapid viral response (RVR) during Peg-IFN/RBV therapy have 90% chance for sustained viral response. The aim of our study was to evaluate the predictive factors of RVR to bi-therapy in chronic hepatitis C (CHC).

Methods: 41 patients (22 males) with chronic HCV infection (genotype 1 or 3) were studied. The median age was 34 (19–62) years. Nine were with advanced fibrosis F ≥ 3 and 30 were genotype-1. The baseline HCV RNA level was 242,000 (8640–6,600,000) IU/ml. IL28B genotype was tested in 34 subjects. All patients received standard bi-therapy with Peg-IFN-α2a/RBV. HCV RNA was measured initially and at treatment week-4 by real-time PCR assay (LightCycler, Roche Diagnostics).

Results: RVR was observed in 68% of studied patients: 57% for genotype-1 and 100% for genotype-3. The lack of RVR was associated with higher baseline HCV RNA level, stage of fibrosis 3–4 and higher age (median 51 vs. 32.5 years). RVR was also found among patients with IL28B genotype-TT as well as in the half of subjects with genotype-1 and IL28B-CT.

Discussion/Conclusion: RVR can be achieved with standard bi-therapy in the majority of patients with CHC even in genotype-1 under 60 years old, mostly without advanced fibrosis, independently of IL28B genotype.
Natural course of HCV RNA. The paradigm of 5 logs?

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Introduction: Fluctuations of HCV RNA during the natural course of chronic HCV-infection may affect the assessment of treatment response. The aim of our study was to evaluate spontaneous changes of viremia for 6–12 months and to analyze the influence of different factors.

Methods: 56 patients (19 of them non-responders/relapsers to Peg-IFN/RBV) with chronic HCV infection were studied. HCV RNA was tested 6 and/or 12 months before therapy. Change of viremia with at least 0.5 logs was accepted to be relevant.

Results: A relevant spontaneous change of viremia was found in 34% of patients: an increase in 6 subjects and decrease in 13. Higher variation rate (45%) was observed after 12-month compared to 6-month period (28%), more frequent among naïve than in treated-subjects: 40.5% vs. 21%.
Elevation was observed in cases with initial viremia < 5 log IU/ml and reduction if it was > 5 log/ml and irrespective of treatment, IL28B-genotype or liver fibrosis.
Viral reduction was found in 3/8 of patients with IL28B-CC and no variations in IL28B-TT. Both elevation and decline were observed in 9/24 of patients with IL28B-CT.
In 54.5% of subjects with F ≤ 2 HCV RNA varied with both elevation and reduction.

Discussion/Conclusion: Viral load fluctuates spontaneously with more than 0.5 logs in a significant proportion of patients within 1 year. Relevant variations are less-frequent after Peg-IFN/RBV therapy. One can speculate that fluctuation of viremia is a result of heterogeneous viral-host interactions and level of 5 logs IU/ml represent a “balance” between these complex and not well defined yet host-viral factors.
Hepatitis C-associated hepatocellular carcinoma in an African woman with non-cirrhotic liver

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**Introduction:** Hepatocellular carcinoma (HCC), on the rise in many countries, is of multifactorial etiology: Cirrhosis from any cause is one of the strongest known risk factors for HCC. Despite this fact, HCC may develop in non-cirrhotic livers in some individuals: In particular, liver cirrhosis in HBV-infected patients is not a prerequisite for hepatocarcinogenesis. In contrast, it is generally believed that the presence of cirrhosis determines the increased risk for HCC in individuals with chronic HCV infection. To date there is very little data on HCC arising in HCV infected, but non-cirrhotic, livers.

**Methods:** A 67-year old Ethiopian women previously treated successfully for chronic hepatitis C in 2007 with a 48-week course of peginterferon-alpha-2a combined with ribavirin, and who achieved a sustained virological response, showed a nodule of 5 cm in diameter in the right liver lobe at a liver ultrasonography done in September 2009. The patient had no significant history of alcohol use, cigarette smoking and iron overload, and was negative for serological evidence of HBV co-infection.

**Results:** A CT scan confirmed the presence of the lesion, and after a biopsy a pathological diagnosis of HCC in non-cirrhotic liver (stage 1 fibrosis with Ishak score) was made. A transarterial chemoembolization of the nodule followed by portal embolization of the right liver lobe was performed in order to induce left lobe hypertrophy with the aim of allowing a further surgical resection of the tumor. Intrahepatic HBV-DNA was negative.

**Discussion/Conclusion:** This case shows that HCC can arise in livers with chronic hepatitis C infection without cirrhosis and without evidence of other risk factors (HBV infection, alcohol intake, iron overload, smoking habits). These findings highlight a previously under-recognized risk for HCC in HCV-infected individuals who do not have cirrhosis.
Treatment of chronic viral hepatitis B and C in patients with inflammatory bowel disease

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Medical University – Sofia

Introduction: Immunosuppressive therapy is usually required in patients with inflammatory bowel disease (IBD). Some patients with IBD also have chronic HBV or HCV infection. The risk of exacerbation of liver disease during immunosuppressive therapy is real. The therapy with interferon alpha in IBD patients is challenging because the risk of disease activation.

Aim: To investigate the rate of worsening of IBD during interferon therapy and reappearance of HBV infection in IBD patients, carriers of anti-HBcor antibody, during immunosuppressive therapy.

Methods: Six patients with ulcerative colitis (UC) and 5 with Crohn’s disease (CD) were included. Three of them had HBV infection, another 3 had HCV infection and 5 were HBsAg negative but carriers of anti-HBcor antibody. In all patients stable remission of IBD was achieved with immunosuppression (azathioprine or adalimumab).

Results: In 1 patient with IBD and HBV infection during peginterferon treatment exacerbation of disease was met. The other 2 patients with IBD and HBV infection received lamivudine therapy. No worsening of IBD was found. In IBD patients, carriers of anti-HBcor antibody, no HBsAg re-appearance was observed. In all patients with IBD and HCV infection no exacerbation of disease was observed during peginterferon and ribavirin therapy.

Discussion/Conclusion: The therapy with peginterferon and ribavirin is relative safer than peginterferon monotherapy in patients with IBD and chronic viral hepatitis. Nucleos(t)ide analogues allow immunosuppressive treatment of IBD patients infected with HBV. The immunosuppression caused by azathioprine or adalimumab is not enough to cause HBV re-appearance in IBD patients, carriers of anti-HBcor antibody.
Liver steatosis and iron overload

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Introduction: Results of recent studies have been demonstrated high prevalence of iron overload in some chronic liver diseases. However, the characteristic of this syndrome is not well established yet. The aim of this study was to evaluate the relationship between liver steatosis and syndrome of iron overload in patients with chronic liver diseases and healthy controls.

Methods: A total of 220 subjects were included in 7 groups: i) nonalcoholic fatty liver disease (NAFLD, n = 35), ii) alcoholic liver disease (ALD, n = 35), iii) chronic hepatitis C (CHC, n = 35), iv) chronic hepatitis B (CHB, n = 35), v) chronic hepatitis B and D (CHB + CHD, n = 10), vi) autoimmune liver disease (primary biliary cirrhosis [PBC] and chronic autoimmune hepatitis [CAH], n = 10), and vii) healthy controls (HC, n = 60).

Results: The prevalence of iron overload, serum levels of iron, ferritin, transferrin saturation, as well as hepatic siderosis were significantly higher (serum hepcidin – lower) in patients with NAFLD (p = 0.05–0.001), ALD (p = 0.005–0.001) and CHC (p = 0.05–0.001) compared to other CLD and HC. The changes in these parameters were the most intensive in steatohepatitis (NASH and ASH, p = 0.004–0.0001), than all other groups and cases with steatosis only, without differences between alcoholic and nonalcoholic etiology. The parameters of iron overload were more intensive and correlated with BMI (cases with steatosis) and alcohol consumption (p = 0.036–0.019); liver enzymes and some liver function tests (p = 0.001–0.0001), as well as hepatic siderosis, steatosis/steatohepatitis, and liver fibrosis (p = 0.019–0.0001).

Discussion/Conclusion: In conclusion, the prevalence and intensity of iron overload exists predominantly in patients with ALD, NAFLD and CHC, especially in cases with steatosis and steatohepatitis.
Analysis of the Notch signaling pathway in cholangiocarcinoma cell lines

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Introduction: Cholangiocarcinoma (CCC) worldwide is the most common biliary malignancy. CCCs are adenocarcinomas arising from epithelial cells alining the intrahepatic and extrahepatic biliary system of the bile duct. The Notch pathway is an evolutionarily conserved signaling module which is important for normal bile duct development. It has been reported to be involved in many chronic liver diseases. This suggests that analyzing the Notch signaling pathway in CCC might open new insights that help improve diagnosis and treatment of this deadly disease. Given the important role of the Notc h signaling in bile duct development, we are currently investigating the role of Notch signaling components in different human CCC cell lines (TFK-1, EGI-1, SZ-1).

Methods: The effect of a gamma secretase inhibitor (DAPT), on CCC’s growth, migration and in vitro metastasis was analyzed using WST-1 assay, wound healing assay and invasion assay respectively.

Results: Notch inhibition by DAPT and siRNAs lead to a decrease in the proliferation and colony forming abilities in a dose dependent manner. We were also able to attenuate EMT by inhibiting Notch. We showed that upon Notch inhibition there was a decrease in Slug and Snail, E-cadherin repressors, and as a consequence, an increase in E-cadherin expression. Notch application also inhibited migration and invasion of CCC cell lines.

Discussion/Conclusion: Blocking the Notch signaling pathway can successfully decrease the in vitro carcinogenesis of CCC. Notch signaling might be a new approach for targeting this deadly disease.
Serum TWEAK levels: To explain the mechanisms of development of nonalcoholic fatty liver disease

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Department of Gastroenterology of the Gülhane School of Medicine in Ankara, Turkey

Background and aim: Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) has recently been introduced as a potential mediator of cardiovascular disease. We aimed to evaluate the associations between TWEAK, chemerin and adipokines in patients with NAFLD.

Subjects and methods: TWEAK which was measured by ELISA and chemerin serum levels were measured prospectively in 60 patients with NAFLD. Twenty healthy controls were selected from the participants without NAFLD. BMI, waist circumference, plasma lipids, glucose, aminotransferases and adipokines were all evaluated for each patient. The relationship between TWEAK, chemerin and IFN, IL-6, MCP-1 and adiponectin was examined.

Statistical analysis: chi-square, t-test, Mann-Whitney U test, and logistic regression analysis were used.

Results: TWEAK levels were significantly higher 504.56 (76.47–1098.20) pg/ml vs. 308.64 (92.12–274.11) pg/ml (p < 0.001) in patients with NAFLD than controls as there was no difference for chemerin between the healthy and patients. IL-6 and MCP-1 levels were significantly higher in patients with NAFLD than controls as follows: 2.92 (1.18–25.60) vs. 1.68 (1–4.05), p < 0.001; and 190.73 (91–471) vs. 165.75 (126–267), p: 0.026. Adiponectin levels in patients with NAFLD were significantly lesser than controls as follows: 4443 (1035–10791) vs. 5934 (3266–11757) p: 0.006. Logistic regression analysis showed that TWEAK was an independent predictor in patients with NAFLD. Mean serum TWEAK level was lesser in subjects with fibrosis than without fibrosis in patients with NAFLD, p < 0.05.

Conclusion: Increased serum TWEAK concentration was significantly and independently associated with the development of NAFLD. TWEAK appeared to be robustly and negatively associated with fibrosis.
Tab. 1: The mean BMI were significantly higher in the subjects with NAFLD than the controls as shown.

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls (n = 20)</th>
<th>NAFLD (n = 60)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>24.8 (22–27)</td>
<td>27.35 (21.2–38.3)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>91 (80–107)</td>
<td>96 (86–126)</td>
<td>0.001†</td>
</tr>
<tr>
<td>Plasma glucose (mg/dl)</td>
<td>78 (69–88)</td>
<td>93 (60–121)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>178 (137–202)</td>
<td>197 (83–281)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>187 (83–255)</td>
<td>156.5 (26–534)</td>
<td>0.512†</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>104 (55–132)</td>
<td>120.5 (28–187)</td>
<td>0.027†</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>41 (31–54)</td>
<td>41.5 (29–54)</td>
<td>0.996†</td>
</tr>
<tr>
<td>AST (IU/ml)</td>
<td>22 (16–28)</td>
<td>42 (20–100)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>ALT (IU/ml)</td>
<td>22 (17–31)</td>
<td>91 (35–251)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>GGT (IU/ml)</td>
<td>31 (21–40)</td>
<td>56 (10–154)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Uric acid</td>
<td>4.6 (3.6–7)</td>
<td>6.195 (4.4–10.3)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Chemerin</td>
<td>172.16 (93.27–311.81)</td>
<td>176.40 (62.26–439.44)</td>
<td>0.657†</td>
</tr>
<tr>
<td>TWEAK</td>
<td>308.64 (92.12–274.11)</td>
<td>504.56 (76.47–1098.20)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>IFN</td>
<td>4.80 (2–9)</td>
<td>5.97 (3–15)</td>
<td>0.105†</td>
</tr>
<tr>
<td>IL-6</td>
<td>1.68 (1–4.05)</td>
<td>2.92 (1.18–25.60)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>MCP-1</td>
<td>165.75 (126–267)</td>
<td>190.73 (91–471)</td>
<td>0.026†</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>5934 (3266–11757)</td>
<td>4443 (1035–10791)</td>
<td>0.006*</td>
</tr>
</tbody>
</table>

Tab. 2: Mean serum glucose, GGT, TWEAK and MCP-1 levels were significantly lesser in subjects with fibrosis than subjects without fibrosis in patients with NAFLD.

<table>
<thead>
<tr>
<th></th>
<th>Without fibrosis (n = 30)</th>
<th>With fibrosis (n = 30) F1 in 29 and F2 in 1 pts</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>33 (21–44)</td>
<td>23 (23–43)</td>
<td>0.314*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.3 (21.2–33.6)</td>
<td>28.25 (23.2–38.3)</td>
<td>0.144*</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>94 (86–108)</td>
<td>98 (86–126)</td>
<td>0.043†</td>
</tr>
<tr>
<td>Plasma glucose (mg/dl)</td>
<td>95 (60–121)</td>
<td>91 (75–119)</td>
<td>0.018†</td>
</tr>
<tr>
<td>Insulin (µU/L)</td>
<td>10.08 (2.12–23.20)</td>
<td>11.45 (2.57–29.72)</td>
<td>0.271†</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.31 (0.33–5.40)</td>
<td>2.49 (0.58–6.54)</td>
<td>0.163*</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>204 (133–281)</td>
<td>192.5 (83–260)</td>
<td>0.329*</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>166.5 (52–525)</td>
<td>151.5 (26–534)</td>
<td>0.679†</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>121 (60–187)</td>
<td>119 (28–177)</td>
<td>0.706†</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>42 (29–54)</td>
<td>41 (31–54)</td>
<td>0.708*</td>
</tr>
<tr>
<td>AST (IU/ml)</td>
<td>39 (20–61)</td>
<td>48 (23–100)</td>
<td>0.011*</td>
</tr>
<tr>
<td>ALT (IU/ml)</td>
<td>84 (46–164)</td>
<td>111 (35–251)</td>
<td>0.004*</td>
</tr>
<tr>
<td>GGT (IU/ml)</td>
<td>68.5 (30–154)</td>
<td>54.5 (10–101)</td>
<td>0.013*</td>
</tr>
<tr>
<td>Uric acid</td>
<td>6.0 (4.4–8.1)</td>
<td>6.68 (4.5–10.3)</td>
<td>0.472†</td>
</tr>
<tr>
<td>Chemerin</td>
<td>177.59 (67.14–307.84)</td>
<td>176.17 (62.26–439.44)</td>
<td>0.267†</td>
</tr>
<tr>
<td>TWEAK</td>
<td>609.89 (76.47–1098.20)</td>
<td>467.87 (300.63–1005.51)</td>
<td>0.049†</td>
</tr>
<tr>
<td>IFN</td>
<td>6.05 (3–12)</td>
<td>5.97 (3–15)</td>
<td>0.813†</td>
</tr>
<tr>
<td>IL-6</td>
<td>2.59 (1.31–25.60)</td>
<td>3.47 (1.18–7.83)</td>
<td>0.162†</td>
</tr>
<tr>
<td>MCP-1</td>
<td>244.10 (91–471)</td>
<td>172.45 (101–385)</td>
<td>0.035†</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>3964 (1035–10077)</td>
<td>4476 (1394–10791)</td>
<td>0.446*</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, GGT = gamma-glutamyl transpeptidase, HDL = high-density lipoprotein, HOMA-IR = homeostasis model assessment for insulin resistance, LDL = low-density lipoprotein
* ≥ 88 cm for females, and ≥ 102 cm for males.
**Tab. 3:** Logistic regression analysis showed that TWEAK was an independent predictor in patients with NAFLD.

<table>
<thead>
<tr>
<th></th>
<th>TWEAK</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R (95% CI)</td>
</tr>
<tr>
<td>AST</td>
<td>-0.257</td>
</tr>
<tr>
<td>Uric acid</td>
<td>-0.383</td>
</tr>
<tr>
<td>IFN</td>
<td>-0.303</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>-0.270</td>
</tr>
</tbody>
</table>

**Tab. 4:** Serum TWEAK and chemerin levels in patients with and without insulin resistance (HOMA-IR).

<table>
<thead>
<tr>
<th></th>
<th>HOMA-IR &lt; 2.0 (n = 19)</th>
<th>HOMA-IR ≥ 2.0 (n = 41)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemerin*</td>
<td>184.01 (67.14–439.44)</td>
<td>175.93 (62.26–404.44)</td>
<td>0.781</td>
</tr>
<tr>
<td>TWEAK*</td>
<td>545.43 (307.66–1098.20)</td>
<td>486.13 (76.47–1005.51)</td>
<td>0.298</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>HOMA-IR &lt; 2.4 (n = 30)</th>
<th>HOMA-IR ≥ 2.4 (n = 30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemerin*</td>
<td>187.62 (67.14–439.44)</td>
<td>172.88 (62.26–301.07)</td>
<td>0.337</td>
</tr>
<tr>
<td>TWEAK*</td>
<td>519.97 (76.47–1098.20)</td>
<td>487.18 (314.03–1005.51)</td>
<td>0.807</td>
</tr>
</tbody>
</table>
Terlipressin infusion harmonize the hepatic and renal blood flow assessed by Doppler ultrasonography

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Introduction: Glypressin is discussed in the treatment of ascites.

Aim: To evaluate the effect of glypressin infusion of the hepatic and renal blood flow.

Methods: Portal and arterial hemodynamic of the liver and intrarenal arteries was assessed by Doppler ultrasonography in 7 patients with liver cirrhosis Child B and C (5 with hepatitis B or C and 2 ethylics) aged from 46 to 64 years. 34 parallel examinations were made during a 24-h infusion of terlipressin (Ferring) 0.2 mg/h at the first hour and 0.03 mg/h later (total 1 mg). Five parallel US examinations were done – the first four for one hour and fifth at the end.

Results: The portal vein mean velocity decrease from 14.70 to 13.20 cm/sec at 24th hour. The hepatic artery minimal diastolic velocity rise from 22.6 to 25.3 cm/sec at the end of the infusion. The resistance index of the hepatic artery decreased from mean 0.69 to 0.65. We observed a decrease since the start to the end of the infusion of the initial levels over 0.70 and an increase of the levels 0.7 below. In the kidneys the minimal diastolic velocity of the intrarenal artery increase from 22.05 to 23.80 cm/sec (60 min) and later decreased to 20.1 cm/sec. The resistance index decreased from 0.69 to 0.65. During the infusion the mean sodium excretion increase from 91 to 220 mmol/d.

Discussion/Conclusion: These observation confirm the natriuretic effect of the infusion of glypressin due to the harmonization of the hepatic and renal blood flow.
Effect of hypochromic anemia on the course of chronic liver injuries in children

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Aims: The goal of our research was to study the effect of a premorbid state, such as hypochromic anemia, on the course of chronic liver injuries in children.

Results: We observed 85 patients with chronic B hepatitis (CBH) aged from 1 to 14 years. The number of boys was 48 (56.4%) and that of girls – 37 (43.6%). Townsmen amounted to 72 patients (84.7%). In 41 patients (48.2%), CBH developed after acute B hepatitis, 20 (23.5%) patients had no evidence of acute hepatitis. Injections and hemotransfusions were detected in 24 patients (28.2%). CBH developed after 2 years following acute B hepatitis in 16.5% of the patients. The group of CBH patients with high activity incorporated 18 children, 29 patients had medium CBH and 39 children had mild CBH activity. CBH was of a wave-like character with exacerbations in 65.8% of the patients. On admission to hospital anemia was detected in 29 (34.1%) of the CBH patients. Alterations in erythrocyte and hemoglobin contents depended on the age of the patients. The most evident anemia was noticed in children of the first years of life. Concomitant hypochromic anemia elongated the periods of hospitalization. On discharge from hospital, children with lowered indices of blood erythrocytes, hemoglobin and oxygen capacity demonstrated more frequent hyperenzymemia and hepatomegaly (p < 0.05). A more complete recovery was more frequently observed in children without the syndrome of anemia.

Discussion/Conclusion: Thus, development of anemia in children with liver pathology can contribute to formation of prolonged convalescence and justifies therapy with incorporation of folic acid at early stages of the disease.
Studies on hepatoprotective activities of calcium folinate and betaine in rats with chronic alcohol intoxication

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²Grodno State Medical University, 230015 Grodno, Belarus

Introduction: It is suggested that folate deficiency contributes to the pathogenesis of alcoholic liver injury. This pathology is followed by an increased blood plasma homocysteine level, a decreased liver S-adenosylmethionine concentration and activation of lipid peroxidation. In case of the impaired folate cycle participation of betaine in conversion of homocysteine to methionine acquires a great significance.

Methods: We studied the effect of calcium folinate, betaine and their composition on the ethanol hepatotoxicity in experiment. For a month, male Wistar rats were intragastrically administered with a 25% ethanol solution at a dose of 4.0 g/kg 2 times a day. Along with ethanol, for 10 days the animals were treated with either calcium folinate (2 mg/kg), or betaine (100 mg/kg), or a combination of both these substances.

Results: Treatment with betaine or the betaine combination with calcium folinate prevented development of oxidative stress in the liver and an alcohol intoxication-provoked increase in the rat blood malondialdehyde level. The chronic alcoholization of rats revealed the morphological signs of liver injury: centrolobular diffuse lymphocytosis, balloon dystrophy on the lobular periphery and signs of microvesicular steatosis in the periportal zone. After 10-day administration of calcium folinate to the alcohol-intoxicated animals, the majority of them demonstrated a partial normalization of the liver picture: the severity of microvesicular steatosis reduced and the relative square of the sudanophilic area was 2-fold decreased. The combined administration of calcium folinate with betaine was more effective: a normal liver picture was observed in 2/3 of the cases and development of signs of fatty dystrophy was prevented. The relative squares of their sudanophilic areas did not differ from the intact controls.

Discussion/Conclusion: These data support the pharmacological potential of calcium folinate and betaine in the management of alcoholic liver injury.
HBV and alcohol consume

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²Polisano Medical Centre, Sibiu, Romania
³Transilvania University, Brasov, Romania

Introduction: In Romania, the prevalence of chronic viral B hepatitis has declined in the last decades because of the newborn vaccination, starting from 1995. Alcohol consumption continues to remain an important health problem, together with chronic viral hepatitis. These two factors, alcohol and virus, potent themselves. Our aim was to study the prevalence of chronic viral B infection in Transylvania and the consequences of alcohol consumption among patients chronically infected with HBV.

Methods: We have considered all the patients who were hospitalized in the medical departments of the County Hospitals from three major cities from Transylvania during ten weeks, and who were ultrasonographically examined. We have studied the prevalence of HBV infection and the association of this disease with alcohol consumption.

Results: From a total of 1377 patients who were examined, 25 patients were chronically infected with hepatitis B virus, the prevalence being of 1.81%. The medium age of the patients with HBV was 48.44 ± 12.63 years. The gender distribution was: 40% women and 60% men. 16% of the patients chronically infected with hepatitis B virus admitted an occasionally alcohol consumption. There were analyzed the patients with chronic viral B hepatitis who did not consume alcohol, as compared with those who are also consuming alcohol. At the last ones, there were found significantly higher values of the next parameters: the degree of liver steatosis (p = 0.009), the triglycerides level (p = 0.06), the glycemic level (p = 0.046), the level of GGT (p = 0.042). Also, the Forns index of liver fibrosis was higher in patients chronically infected with HBV who were also alcohol consumers, as compared with those with chronic B hepatitis who do not consume alcohol (6.953, as compared with 6.11, p = 0.295).

Discussion/Conclusion: In our study, the chronic infection with HBV was found with a prevalence of 1.81% among the hospitalized patients. The data is in accordance with the literature, where Eastern Europe is considered to be situated in the intermediary segment of prevalence. The alcohol consumption among patients chronically infected with HBV is pretty high.
Comparation with Maddrey discriminant function, model for end-stage liver disease and Child-Turcotte-Pugh scores for predicting mortality in patients with alcoholic hepatitis

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Clinic of Gastroenterology and Hepatology Clinical Center Nis, Serbia

Introduction: Alcoholic hepatitis is an acute or subacute inflammatory syndrome associated with significant morbidity and mortality. Maddrey discriminant function (DF) score and Child-Turcott-Pugh (CTP) score have been used for stratifying the prognosis of alcoholic hepatitis. The model for end-stage liver disease (MELD) score has been applied to alcoholic hepatitis and some investigators consider MELD score as a better prognostic indicator for severe alcoholic hepatitis. This analysis was aimed to compare MELD score with DF and CTP scores for predicting the short-term mortality in patients with alcoholic hepatitis.

Methods: The medical records of patients hospitalized with alcoholic hepatitis between 2007 and 2010 were analyzed retrospectively.

Results: Of the 26 medical records reviewed, 14 cases fulfilled the inclusion criteria (11 males and 3 females; mean age 42.1 years). Univariate analysis demonstrated that variables such as ascites, hepatic encephalopathy, splenomegaly, CTP, and DF scores were significantly correlated with increased 30-day mortality while MELD score was not. According to the multivariate analysis, only CTP score was statistically significant (p = 0.011) while DF and MELD scores were not significant for predicting 30-day mortality. The survival analysis with Cox regression test showed higher CTP and DF scores, but not MELD score, significantly increased the risk of in-hospital mortality.

Conclusions: This study demonstrates that DF and CTP scores are independent predictors of mortality in patients with alcoholic hepatitis.
Treating hyponatremia in hepatic cirrhosis: Are we forgetting something very important?

Ivan Rankovic¹, Dragan Popovic¹,², Djordje Culafic¹,², Milica Stojkovic¹, Miodrag Krstic¹,², Zoran Rajic⁴, Predrag Pesko²,³, Tomica Milosavljevic¹,²
¹Clinical Center of Serbia, Clinic for Gastroenterology, Belgrade, Serbia
² School of Medicine, University of Belgrade, Serbia
³Clinical Center of Serbia, First Surgical Clinic
⁴Clinical Center of Serbia, Clinic for Haematology

Introduction: Hyponatremia is very common among the population of cirrhotic patients but poorly understood by physicians and not clearly enough discussed in hepatology medical textbooks. On the basis of that we found that hyponatremia in cirrhotics is underdiagnosed, clinically not taken seriously and poorly managed. We want to emphasize the importance of distinguishing distributional and real hyponatremia advocating combining normal saline and Hartman solution infusions. Hyponatremia may not be just an readily predicted cirrhosis complication but an important contributing pathological factor which can seriously affect the survival and complication rates of these patients.

Methods: Retrospective comparative cohort study of patients who were monitored for electrolyte imbalance and properly corrected with combined crystalloid solutions. The comparison was made and interpreted with the Fisher statistical test of significance.

Results: The Fisher statistical test showed significantly better survival rates and less complications in the cohort treated with combined crystalloid infusions.

Discussion/Conclusion: The modern day gastroenterologist must recognize the indications for treating hyponatremia in hepatic cirrhosis. This clinical chapter has been many times forgotten in up to date hepatology practice. Hyponatremia must be interpreted by measuring serum osmolality and urine sodium concentration. Only then we can differ distributional and real hyponatremia in cirrhotics. We showed that proper use of normal saline and Hartman solution in these patients showed better survival rates and less complications. The use of saline and composite crystalloid solutions should be started in cirrhotic patient admitted in the hospital department because of their always present hyponatremia due to the secondary hyperparathyreoidism and use of diuretics. We are advocating a new approach in infusion treatment which comprises of distinguishing real hyponatremia and thus starting the treatment with combined crystalloid infusions targeting the physiological sodium range of 135–145 mmol/l.
Study regarding alcohol consumption in patients with chronic viral C hepatitis

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Introduction: Viral infections favour the development of alcoholic liver diseases; these two factors, alcohol and viruses, potent themselves. Ethanol intake is an independent predictor of liver cirrhosis in subjects with chronic HCV infection. Our aim was to study the prevalence and some consequences of alcohol consumption among patients chronically infected with HCV.

Methods: We have considered all the patients who were hospitalized in the medical departments of the County Hospitals from three major cities from Transylvania during ten weeks, and who were ultrasonographically examined. We have studied the prevalence of HCV infection and the association of these diseases with alcohol consumption. Liver fibrosis was non-invasively assessed by using the Forns index.

Results: A total number of 1377 patients were examined. The prevalence of the infection with HCV was of 7.5% (104 patients). 13.88% of them were also alcohol consumers. There were analyzed the patients with HCV who did not consume alcohol, as compared with those who are also consuming alcohol. At the last ones, there were found significantly higher values of the next parameters: the degree of liver steatosis (p = 0.02), the spleen diameter (p = 0.05), TGO (p = 0.00037), TGP (p = 0.0062), GGT (p = 0.00016), total bilirubin level (p = 0.027). The patients with viral C hepatitis who are also alcohol consumers, are, generally younger than those with viral C hepatitis who do not consume alcohol (54.42 years, compared with 57 years, p = 0.02). Also, the Forns index of liver fibrosis was higher in patients with HCV who were also alcohol consumers, as compared with those with HCV who do not consume alcohol (5.56, as compared with 5.11, p = 0.22).

Discussion/Conclusion: The alcohol consumption among patients chronically infected with HCV is pretty high, this fact being also involved in the response to the antiviral treatment. The patients who are infected with HCV and also consume alcohol have a higher steatosis grade and a higher degree of cytolysis and cholestasis.
Distribution of hepatitis C virus genotypes in Georgia and treatment of peginterferon alfa-2 (40KD) and ribavirin

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Background: Interferon + ribavirin is standard therapy for HCV infection. The genotype and viral load are important predictive factors for the treatment success. HCV has different genotypic distribution in various geographic regions.

Aims: Investigation of HCV is our region and to study results of combinations therapy with peginterferon alfa 2a + ribavirin.

Methods: We included 34 patients (7 females and 27 males) with chronic hepatitis C (CHC), mean age 35 years. CHC was diagnosed by clinical and laboratory tests (serological test, detection of HCV RNA [qualitative and quantitative]). Patients were treated with peginterferon + ribavirin for 6 or 12 months.

Results: 19 patients were infected with genotype 1b, 10 patients had genotype 3a and 4 genotype 2a. In one case genotype was undetectable, viral load (VL) was 86330 IU/ml. VL was between 8639–1,000,000 IU/ml and was monitored every three months, ALAT every two weeks. After 3 months of treatment HCV RNA undetectable in all patients and remained undetectable at the end of treatment (EOT). Normalization of ALAT increased in the beginning of treatment. All registered side effect were relevant to IFN toxicity. Further follow-up is required to assess sustained viral response after 6 months from treatment.

Conclusion: 1b is most prevalent genotype in Georgia (56%). EOT response was achieved in all patients treated with peginterferon alfa-2a and ribavirin, which is prevention of hepatocellular carcinoma.
Risk factors for recurrence of hepatocellular carcinoma (HCC) after radiofrequency ablation (RFA) in a cohort of Egyptian patients with HCV-induced cirrhosis: A multi-center analysis

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Hepatocellular carcinoma is one of the major complications of liver cirrhosis. Radiofrequency ablation is the treatment of choice for patients with an early stage HCC who are no candidates for surgical management; however, it is associated with a recurrence rate as high as 15–30% after one year. We aim to analyze the risk factors for HCC recurrence in Egyptian patients after radiofrequency ablation.

**Methods:** This study was carried out on a cohort of HCC patients presented to 2 large referral centers for management of HCC in Egypt. Only patients with an early stage HCC (BCLC stage A), eligible for RFA ablation were included in the analysis.

A total of 45 patients were recruited, evaluated and followed up for one year and classified into 2 groups: Group I: Patients who developed recurrence (n = 30, 66.6%), Group II: Patients who did not show any recurrence (n = 15, 33.3%).

Patient and tumor-related risk factors associated with recurrence were studied. Statistical analysis was done using SPSS software.

**Results:** The risk factors associated with recurrence included, smoking (70% in group I versus 40% in group II, \( p = 0.015 \)), hepatolomegaly (50% in group I versus 40% in group II, \( p = 0.001 \)) splenomegaly (90% in group II versus 53.3% in group II \( p = 0.001 \)), heterogenous liver (30% in group I versus 6.66% in group II, \( p = 0.001 \)), bilobar involvement (20% in group I versus 6.66% in group II, \( p = 0.001 \)) and tumors in contact with hepatic capsule (20% in group I versus 6.66% in group II, \( p = 0.017 \)).

**Conclusion:** Among various patient factors, only smoking, hepatomegaly, liver heterogeneity, and splenomegaly (a sign of portal hypertension) together with the tumor factors; bilobar involvement and proximity to liver capsule were the factors that showed a significant association with tumor recurrence in this study.
Hepatic encephalopathy in alcoholic hepatitis

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Introduction: Hepatic encephalopathy (HE) – serious and potentially fatal complication of cirrhotic patients (CP) with severe alcoholic hepatitis (AH). We analysed features of HE at CP with AH.

Methods: 43 CP with AH (7 had Maddrey's score > 32), 30 – Child-Pugh class B, 13 – C were compared with 241 CP without AH.

Results: Mean age of patients with AH – 44.6 ± 9.3 years (without AH – 52.0 ± 11.8, P < 0.001). Men with short anamnesis of cirrhosis (P25 = 0, P75 = 3 months) prevailed (χ² = 15.070, P < 0.001). 41 CP with AH (95%) and 208 CP without AH (86.3%) had HE (χ² = 1.987, P = 0.159). Higher degree of HE was observed at CP with AH (1.21 ± 0.78 vs. 0.83 ± 0.81, P = 0.004), without any significant in level of ammonia (P = 0.775) and psychometric test (NCT) (P = 0.184). HE at CP with AH was associated with levels of potassium (r = -0.664, P = 0.003; P < 0.0001), hemoglobin (r_s = -0.373, P = 0.018), malnutrition (r_s = 0.579, P = 0.007; P = 0.0072), hemorrhagic syndrome (r_s = 0.649, P = 0.031; P = 0.0187), (r = 0.362, P = 0.020; P = 0.0081).

Discussion/Conclusion: HE can be first manifestation of severe AH in young CP (Child-Pugh class A, B) with malnutrition, hemorrhagic syndrome, low level of potassium.
Introduction: Matrix metalloproteinases (MMPs) are responsible for the degradation of extracellular matrix. MMPs and their specific inhibitors (TIMPs) play an important role in the hepatic lesions. Matrix metalloproteinase-9 (MMP9), which represents the largest and most complex member of this family has been a subject of growing interest in human pathology. Metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) show a regulated and coordinated pattern of activity which allows tissue degradation and remodeling but at the same time it prevents tissue damage.

Purpose: To evaluate if measurements of MMP-9 and TIMP-1 have clinical applicability as markers of liver pathology.

Methods: 24 patients with chronic hepatitis C (CHC) and 20 healthy subjects as controls were enrolled in the study. The patients divided into two groups: 18 chronic hepatitis C and 6 liver cirrhosis. None of the patients was treated with antiviral and immunomodulating drugs during the 10-month period before inclusion into the study. The analysis of serum concentrations of total MMP9 (active and pro-MMP9) and TIMP1 was based on a quantitative sandwich ELISA using Quantikine kit manufactured by R&D Systems, Minneapolis, USA.

Results: Serum concentrations of TIMP-1 levels were significantly higher in patients with chronic hepatitis C compared to controls. Mean serum TIMP-1 levels were significantly higher in group with liver cirrhosis (640 ng/ml) compared to chronic hepatitis (480.3 ng/mL) and controls (210 ng/ml) (p < 0.05). Serum TIMP1 levels were correlated positively (r = 0.5240) with the degree of hepatic fibrosis. The circulating levels of MMP-9 decreased during progression of chronic hepatitis to cirrhosis showing the least level in the cirrhotic group. The present results suggest that increased TIMP-1 activity and altered MMP expression may play a part in fibroproliferation in liver disease.

Discussion/Conclusion: The present results suggest that the altered balance between circulating MMP-9 and TIMP-1 during HCV infection may play an important role in hepatic injury progression.
The diagnostic and prognostic value of associated autoantibodies to primary biliary cirrhosis

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Introduction: Primary biliary cirrhosis (PBC) is a chronic autoimmune cholestatic liver disorder which has the potential to progress to cirrhosis and eventually hepatic failure. The disease progression of patients with PBC in fact varies significantly among patients, including a relatively long asymptomatic phase in some patients while some have a more fulminate onset that progress to severe disease. The objective of this study was to identify autoantibody markers that may be used for diagnosis, to predict PBC outcome and for therapeutic evaluation.

Methods: We studied 30 patients with biopsy proved PBC (90% women, 10% men), and 30 systemically healthy subjects. Serum levels of autoantibodies (AMAs, antinuclear-ANAs, anti-double stranded-dsDNA, anti-SSA, anti-SSB, anti-centromere, anti-pANCA, anti-Scl 70) were measured using enzyme immunoassay EIA-INOVA USA kits.

Results: Anti-dsDNA, anti-SSB, anti-Sc70 and anticentromere autoantibodies missed in control group. The incidences of several types of autoantibodies were significantly higher in the sera of PBC patients than in healthy. Twenty seven of the patients had AMAs. Our study confirmed that individuals, who are repeatedly AMAs positive with no symptoms and normal liver enzyme levels, tend to have very early PBC. The incidence of ANAs was 40% in PBC patients and 3.3% in controls. The time to liver failure was shorter in ANA-positive, compared with ANA-negative, patients (p = 0.02). The prevalences for anti-SSA/Ro and anti-centromere were 6,6% and 10% of the patients, respectively and both autoantibodies were significantly higher in females than in males (p < 0.05). The presence of anti-centromere antibodies was associated with the portal inflammation. Anti-dsDNA and p-ANCA were found in 3 patients who have AIH-PBC overlap syndrome. Prevalences of anti-SSB/La or anti-dsDNA between males and females did not significantly differ. None of patients sample were positive for anti-Scl 70.

Discussion/Conclusion: Several ANA specificities had additional diagnostic or prognostic value: anticentromere enhances the risk for developing portal hypertension and anti-dsDNA and p-ANCA were found in patients who have AIH-PBC overlap syndrome.
Influence of triple therapy on nutritional status of patients with chronic hepatitis C

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Background: Loss of appetite, disgeusia and weight loss are frequent adverse events of therapy for chronic hepatitis C (CHC).

Aim: To evaluate variations of nutritional status in CHC patients treated with triple therapy compared with those treated with bitherapy.

Patients and method: We included patients receiving triple therapy (PegIFN + ribavirin + boceprevir/telaprevir [PRB/PRT]) in our unit in a prospective ongoing study. The nutritional status was appreciated by BMI, waist circumference, right arm circumference and tricipital cutaneous fold, measured at start, at 4, 8, and 12 weeks of therapy. Data were compared with those of a group of patients receiving bitherapy with PegIFN and ribavirin.

Results: We are treating 46 patients with CHC (14 males), median age 57 years (31–70) all with severe fibrosis (F3/F4 METAVIR) using triple therapy. 38 patients passed 12 weeks of therapy (28 PRT, 10 PRB), having a median height of 172.087 cm, weight 90 kg and a median BMI of 28.39. The mean values for waist, arm circumference and tricipital fold were respectively 101 cm, 32 cm and 28. At 8 weeks BMI decreased in 24 patients (with 1.02 ± 0.86), remain unchanged in 11 and 3 patients gained weight, and at 12 weeks only 16 patients continued to loose weight (-3.23 ± 1.88 kg). By comparison, all 40 patients in the bitherapy group experienced weight loss (BMI decreased with 2.86 ± 1.14 at 8 weeks and with 3.12 ± 1.26 at 12 weeks) (p = 0.05). The other nutritional indices varied accordingly.

Conclusion: Patients receiving triple therapy are better nourished than those treated by bitherapy, probably due do need to take the pills with eat (± fat) at regular times.
Clinicopathological features and outcome of autoimmune hepatitis/primary sclerosing cholangitis overlap syndrome

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Background: Overlap syndrome (OS) autoimmune hepatitis (AIH)/primary sclerosing cholangitis (PSC) is not well characterised in adults, being a relatively rare disease.

Aim: To evaluate the natural history of patients OS, compared with “classical” PSC.

Patients and method: We included 55 PSC patients followed > 3 years, with > 3 admissions, 8 diagnosed with AIH/PSC OS (4 simultaneous, 4 successive OS, in 2 AIH was first featured and in 2 PSC). Patients with OS received immunosuppressive (IS) treatment and UDCA, PSC patients only UDCA.

Results: The OS group significantly differed from PSC in: percent of female gender (p = 0.011), mean AST (p = 0.0005), ALT (p = 0.0002), mean IgG (p = 0.005) and IgM (p = 0.001), cholesterolemia (p = 0.05), plasmocytes on histology (p = 0.02), ANA+ > 1:80 (p = 0.002) and percent of patients with “definite AIH” according IAHG score (p = 0.001). There were not statistically significant differences between our groups in: patients’ age at diagnosis (p = 0.412), IBD association (p = 0.07), “onion-skin” fibrosis (p = 0.208), ASMA+ (p = 0.06), pANCA+ (p = 0.617). Mayo risk score for PSC was initially higher in OS (p = 0.174); it decreased in OS, while it increased in PSC in follow-up (p = 0.434). The major events: liver transplantation (3 OS, 1 PSC group), malignancies (8 PSC, 0 OS), death (5 PSC, 0 OS). Kaplan-Meyer survival curves showed no significant differences between groups, but it was longer in OS.

Conclusions: AIH/PSC OLS in not very rare in clinical practice. We have to think in AIH patients who became unresponsive to IS or in a CSP patient with flares of aminotransferases. OS prognosis seems to be better that in PSC.

Keywords: overlap syndrome, autoimmune hepatitis, primary sclerosing cholangitis, ANA, ASMA, pANCA, IBD, Mayo risk score, IAHG score for autoimmune hepatitis
The decreasing of the liver detoxic function in chronic hepatitis and liver cirrhosis patients and the ways of its pharmacological correction

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The determination of argynase blood activity (ABA) is an important index, reflecting the liver detoxic function. The aim of this investigation is to study ABA before and after the treatment of chronic hepatitis of toxic (alcohol, chemical, drug-induced, radiation) etiology and liver cirrhosis (LC) pts.

52 chronic toxic hepatitis (ChTH) and 33 LC pts have been examined, they having had ABA tests together with the common liver tests. All the pts have been separated into 5 groups, they receiving: I – 16 ChTH pts – ursodeoxycholic acid (UDCA) – Ursofalk®; II – 18 ChTH pts – silymarin; III – 18 ChTH pts – UDCA + lactulose; IV – 18 LC pts – basic therapy (diuretics and glucose-insulin-kalii mixture) + UDCA; V – 15 LC pts (basic therapy + UDCA + lactulose).

Before treatment the ChTH pts of groups I–III (0.58 ± 0.11 mmol/l/h; 0.53 ± 0.09 mmol/l/h and 0.59 ± 0.1 mmol/l/h respectively) and especially in LC pts groups IV–V (0.33 ± 0.08 mmol/l/h and 0.39 ± 0.1 mmol/l/h) an evident decrease of ABA in comparison with healthy people was noted (1.33 ± 0.08 mmol/l/h). After medication ChTH pts of groups I–II ABA evidently increased (1.11 ± 0.1 and 0.81 ± 0.08 mmol/h/l), it proving the improvement of the liver detoxic function. In pts of group III ABA got to normal data (1.29 ± 0.07 mmol/h/l). In LC pts of group V getting lactulose against the background of its therapy, a reliable increase of enzyme activity was noted (0.89 ± 0.12 mmol/h/l), it being compared with the effect of the basic therapy (0.58 ± 0.13 mmol/h/l). After the treatment in all ChTH pts the concentration of malon dialdehyde (MDA) decreased in blood, reflecting the intensity of lipid peroxydation of the cell membranes. So, the blood concentration MDA in groups I–III was 0.82 ± 0.09 mkmol/l, before the treatment it being 3.4 ± 0.11 mkmol/l, 0.33 ± 0.07 mkmol/l being normal.

In ChTH and LC pts an evident oppression of liver detoxic function takes place, it can be compensated by prescribing hepatoprotectors-antioxidants in ChTH, while for its considerable improvement the prescription of lactulose is necessary. Lactulose has an antiendotoxemic effect and with the help of it decreases the prooxidant endotoxin action and its stimulating effect upon fibrogenesis in liver due decreasing the activity of Kupffer’s cells, lipocytes and their ability to collagen III formation.
Adult living donor liver transplantation – 8 year donor safety experience

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Background: Adult to adult living donor (right lobe) liver transplantation (LDLT) is a modality to decrease the mortality rate on the waiting list (WL). Living donors represent a large pool of organs and seem to be the only immediately alternative. Selection for the ideal donor for LDLT is a complex process with no more than one-third of potential donors accepted as candidates for this procedure.

Aim and methods: We reviewed all LDLT performed in our center between January 2004 and April 2012. Potential donors were matched by age, sex, body mass index (BMI), history of smoking, relationship with the recipient, area of living, marital status, income distribution

Results: A total number of 138 subjects were evaluated as potential donors with the mean age at the time of surgery 34.9 years old, 58.14% of whom were women. Only 21.01% were unrelated with the recipient.
All donors had pre-operative imaging to define vascular and biliary anatomy and liver biopsy.
The non-exclusive reasons for rejection were: insufficient hepatic volume determined by CT volumetry (38.71%), positive hepatitis B serology (8.6%), severe dyslipidemia (8.6%), abnormal anatomy (4.3%), access to cadaveric hepatic graft (3.23%), socioeconomic reasons in 14.2%, recipient contraindication (3.23%), pregnancy during evaluation (1.08%); one patient was identified with focal nodular hyperplasia and another one patient was find with tumoral hepatomegaly.
Liver biopsy was done in all potential donors with good right lobe hepatic volume and 4.3% were excluded due to abnormal histopathology (> 20% steatosis).
Finally, 44 underwent surgery. Donor survival was 100% with seven days hospitalization rate in post-operative period.

Conclusion: The main objective of the donor evaluation process is to assure the safety of the donor with the least morbidity and no mortality. The donor evaluation process remains to be a large burden on the resources of our program.
Morphological exponents of fibroductular reaction in the model of experimental secondary biliary fibrosis induced by bile duct ligation in young rats. A preliminary report

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Introduction: It is assumed that chronic biliary obstruction provokes fibroductular reaction that leads to biliary fibrosis and cirrhosis due to cholangiocyte proliferation and accumulation of immature ductular cells. The model of secondary fibrosis caused by common bile duct ligation (CBDL) in rats, widely accepted in literature, resembles human primary sclerosing cholangitis. However, morphogenesis of this pathology has not been fully elucidated yet.

Aim: The major aim of the study was morphological analysis of the dynamics of biliary fibrosis in an experimental rat model, especially ductule proliferation and the degree of fibrosis.

Methods: Young Wistar Crl:WI(Han) rats were submitted to CBDL in inhalation anesthesia with a mixture of isoflurane and oxygen. After surgery, the rats were randomly divided into three groups (10 animals in each group) and killed after 1, 6 and 8 weeks following surgical induction of cholestasis. The comparative group consisted of 6 animals that were submitted to the same anesthetic procedures. Liver samples were obtained and fixed in buffered formalin solution; at the same time, for better intercellular interactions, material was secured for ultrastructural analysis by fixing the samples with fixative solution of paraformaldehyde and glutaraldehyde in cacodylate buffer. The bile ductule proliferation and inflammatory infiltrate were studied by HE stain. Fibrosis was determined by Sirius red, Masson’s trichrome, Masson’s-Goldner, Azan and reticulin stains. Fibrosis stage and inflammation grade were assessed by Batts and Ludwig numerical scoring system.

Results: On day 7 after CBDL, dilatation of the common biliary duct was observed. After week 6 the liver got darker, its surface became rough and consistency increased, becoming hardened. Seven days after CBDL, all the animals showed differently pronounced, mainly mild and/or moderate, ductule proliferation. After six and eight weeks, ductule proliferation was very intense. Many a time, the ductule proliferation occurred in a radiated form towards the parenchyma, forming thinner and thicker septa. The architecture of the liver parenchyma was prominently altered due to disorderly infiltrative growth of the proliferated biliary ductules. Seven days after CBDL, an increase was noted in the collagen fibers around the neoformed ductules, which got intensified throughout the weeks after the ligation, until the end of the study. Deposition of collagen fibers was
found also around the centrilobular vein, interface and inside the liver lobules, which underwent disarray of their architecture. In week 6 and 8, there was an intense disorganization of the lobule with the formation of regeneration nodules and cirrhosis, especially after eight weeks.

**Discussion/Conclusion:** Our study showed spontaneous and progressive character of fibroductular reaction induced by CBDL in young Wistar Crl:WI(Han) rats.
Transarterial chemoembolization and sorafenib combined therapy in patient with advanced hepatocellular carcinoma

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Introduction: Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and the eight most common in women; it ranks third in annual cancer mortality rates. It has been proven that sorafenib therapy and transarterial chemoembolization (TACE), applied separately, slower the cancer progression and prolong life in patients with HCC.

Methods: In 74-years old male with viral hepatitis B positive liver cirrhosis, was proven with HCC in March 2011, with four liver lesions, maximum size 73/89 mm. The patients was staged as BCLC Intermediate B and as Okuda I–II.

Results: The patient was considered inoperable and sorafenib therapy was started in April 2011. Due to enlargement of the tumor mass in June 2011 TACE was started. Until the present moment three chemoembolizations have been done, using Lipiodol and Gelaspond. In every three months the patient undergoes CT-scan for re-evaluation of tumor progression (enlargement, neovascularization) and if progression is recorded new TACE is done. The patient tolerates this combined therapy well; he is in excellent clinical condition with no apparent illness.

Discussion/Conclusion: Combined treatment with sorafenib and TACE can cease tumor progression and maintain patient in good clinical condition. Investigations are needed to prove whether this therapy is more effective compared to monotherapy of HCC.
Some parameters of iron and copper metabolism in patients with hereditary haemochromatosis

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Introduction: Haemochromatosis is an inherited metabolic disorder, characterized by the accumulation of iron mainly in liver. One of the main mechanisms which participate in the pathogenesis of liver damage in these patients is increased production of reactive oxygen radicals which are responsible for damage of hepatocytes. Divalent iron ions play important role in formation of oxygen radicals. One of the important antioxidative factors in organism is also Cu-protein ceruloplasmin. Ceruloplasmin with its ferroxidase activity oxidize Fe2+ to Fe3+ and blocks the effect of Fe2+ on the production of reactive oxygen species.

Methods: Examined group was formed of 16 patients with hereditary haemochromatosis and 14 healthy individuals. In patients were determined serum levels of copper and iron, levels of transferrin, apoceruloplasmin, prealbumin and ferroxidase activity of ceruloplasmin.

Results: Levels of iron were in patients with haemochromatosis significantly increased. Levels of copper were on the contrary decreased in comparison with healthy controls. In patients with haemochromatosis were decreased also levels of transferrin (2333 mg/l vs. 2775 mg/l) and ferroxidase activity (9.1 vs. 12.6 ucat/l).

Discussion/Conclusion: Very important is finding of decreased activities of ferroxidase in patients with haemochromatosis in which increased levels of Fe2+ are important source of the production of reactive oxygen radicals. There is also needed to mention finding of decreased levels of Fe-transport protein – transferrin. Decrease of ferroxidase activity in these patients could support the production of reactive oxygen radicals and thus increased oxidative stress. Decrease of transferrin level is supposed to be probably the consequence of damaged proteosynthetic function of the liver.
Markers of oxidative stress in patients with Wilson’s disease

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Introduction: Wilson’s disease (WD) is hereditary autosomal recessive disorder of copper metabolism. The main defect is disorder of copper excretion into the bile and its excessive storage in some organs. Disorder is caused by mutation of the gene encoding specific copper transport protein – ATP7B. Inhibition of copper excretion leads to increased free radicals production. Decreased synthesis of functional ceruloplasmin increases iron toxicity and thus oxidative stress become further increased.

The aim of our study was to find out how are selected parameters of oxidative stress affected by WD.

Methods: The studied group consisted of 18 patients with WD (10 women and 8 men). We determined total antioxidant capacity of blood plasma (TEAC), activity of superoxide dismutase in erythrocytes (SOD), plasma levels of malondialdehyde (marker of lipid peroxidation) and 3-nitrotyrosine (marker of damage of proteins by free radicals).

Results: TEAC as well as SOD activity were higher in patients with WD than in control group (2.51 mmol/l vs. 1.22 mmol/l, 11.7 U/g Hb vs. 9.2 U/g Hb). We found no significant difference in levels of nitrotyrosine between patients with WD and healthy controls (54.7 nmol/l vs. 53.2 nmol/l). The levels of MDA were lower in patients with WD than in healthy controls.

Discussion/Conclusion: The increase of TEAC and SOD in patients with WD may be a compensatory response to the decline of ferroxidase activity of ceruloplasmin in serum as well as a response to increased oxidative stress in liver.
Some parameters of oxidative stress in patients with hereditary haemochromatosis

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Introduction: Hereditary haemochromatosis is an autosomal recessive disorder, conditioned mainly by mutation of HFE gene, by increased absorption of iron and its loading into organs and tissues. In pathogenesis of liver parenchyma damage in this disease is supposed that important role plays increase of oxidative stress with release of products of lipoperoxidation which stimulate the activation of stellate cells with following increase of fibrogenesis.

Aim of the work: In our work we paid attention to follow some parameters in connection with oxidative stress and antioxidative capacity in blood of patients with inherited haemochromatosis.

Methods: Studied group was formed by 20 patients with inherited haemochromatosis and 16 healthy controls. In these we determined total plasma antioxidative capacity, activity of superoxide dismutase (SOD) and level of ceruloplasmin as antioxidative factors. Except of this we determined level of malondialdehyde (marker of lipid peroxidation) and 3-nitrotyrosine (marker of oxidative damage of proteins).

Results: As showed results of our study, total antioxidative capacity was in the patients with haemochromatosis significantly higher as in group of healthy individuals (2.47 vs. 1.37 mmol/l). Slightly increased was also the activity of SOD in erythrocytes of the patients with haemochromatosis (10.72 vs. 9.57 U/g Hb). Levels of malondialdehyde in patients with haemochromatosis are not significantly different from values in control group. The level of nitrotyrosine was in patients with haemochromatosis significantly higher than in controls (90.29 vs. 71.41 nmol/l).

Discussion/Conclusion: Increased antioxidative capacity in serum of patients with haemochromatosis could represent the answer on increased oxidative stress in tissues.
Ceruloplasmin and its enzymatic activity in patients with Wilson’s disease

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Introduction: Wilson’s disease (WD) is inherited autosomal recessive disorder of copper metabolism with clinical manifestations of the liver and CNS damage. Ceruloplasmin is multifunctional protein with polyphenoloxidase and ferroxidase activity. It plays important role in metabolism of iron and has also antioxidative properties.

The aim of our study was to evaluate enzyme activities of ceruloplasmin in relation with levels of apoceruloplasmin in patients with WD and to find out if in these patients are changing enzyme properties of ceruloplasmin.

Methods: Examined group included 24 patients with Wilson’s disease and 20 healthy individuals. Enzyme activity was determined as polyphenoloxidase and ferroxidase. The amount of apoceruloplasmin was determined immunochemically.

Results: Ferroxidase and polyphenoloxidase activity of ceruloplasmin was in serum of patients with WD significantly decreased. Equally significantly was decreased also the level of apoceruloplasmin. Specific activity of polyphenoloxidase and ferroxidase there was no difference between patients with WD and healthy controls. The comparison of the relation of enzyme activity of ceruloplasmin and level of apoceruloplasmin indicated high significant correlation (corr. coeff. = 0.96, resp. 0.94).

Discussion/Conclusion: Equal specific activity of polyphenoloxidase and ferroxidase in patients with WD and in healthy controls, and also correlation between the level of apoceruloplasmin and enzyme activity of ceruloplasmin indicate the fact though synthesis of ceruloplasmin is significantly decreased but synthetised molecule of ceruloplasmin is functionally full valuable with do not changed properties in comparison with healthy controls.
Rifaximin treatment in hepatic encephalopathy – A single centre experience

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Introduction: The efficacy of rifaximin (1.1 g/day), a minimally absorbed antibiotic, for maintaining remission from hepatic encephalopathy and reducing the risk of hospitalisation involving hepatic encephalopathy has been established. (1) In an attempt to reduce hospital admissions & length of stay (LOS), our unit has been using rifaximin in patients in whom hepatic encephalopathy has been refractory to conservative measures.

Methods: A list of patients to whom rifaximin was prescribed from October 2007 to August 2010 was generated. Data was collected on:
- Patient demographics
- Date of starting rifaximin
- Dose of rifaximin
- The number of admissions for hepatic encephalopathy and LOS during the 12 months preceding rifaximin use and 6 and 12 months after starting.

Results: An analysis was carried out of 16 patients (13 male, 3 female). The mean age when starting rifaximin was 59.1.
5 of the patients were CTP B and 11 were CTP C at the time of starting rifaximin.
4 patients were post TIPSS. The mean final dose of rifaximin was 1.14 grams/day in divided doses.
12 out of 16 patients had been on rifaximin for at least 6 months.

<table>
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<tr>
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<th>Pre rifaximin (n = 12)</th>
<th>6 months post rifaximin (n = 6)</th>
<th>12 months post rifaximin (n = 4)</th>
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<tr>
<td>Number of admissions</td>
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<tr>
<td>Admissions per patient</td>
<td>2.33</td>
<td>0.5</td>
<td>1.25</td>
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<tr>
<td>Mean LOS per admission</td>
<td>14.6</td>
<td>10.6</td>
<td>12.4</td>
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<tr>
<td>Hospital days (per person per month)</td>
<td>2.83</td>
<td>1.78</td>
<td>1.29</td>
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</table>

After starting rifaximin, 3 died on the same admission and 3 within 6 months of starting. There were no reported cases of Clostridium difficile in any of the patients.

Discussion/Conclusion: Despite the small numbers of patients that were included in the final analysis, our study has shown that the use of rifaximin during a six or twelve month period reduces the number of hospital admissions per patient and the total LOS for each admission.
Reference:

The NPCL1 inhibitor ezetimibe improves metabolic disease via decreased LXR activity

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Introduction: Dyslipidemic patients with diabetes mellitus, including metabolic syndrome, are at increased risk of coronary heart disease. It has been reported that ezetimibe, a cholesterol absorption inhibitor, improves dyslipidemia, steatosis and insulin resistance. However, the underlying mechanism is not fully understood. Here we explored the effects of ezetimibe on lipid and glucose homeostasis.

Methods: KK-Å mice were fed a high-fat diet with or without ezetimibe for 14 weeks. Primary cultured hepatocytes obtained from SD rats were treated with oleate and liver X receptor (LXR) agonist.

Results: Ezetimibe improved dyslipidemia, steatosis and insulin resistance in high fat-fed KK-Å mice. Ezetimibe also decreased hepatic oxysterol content and suppressed LXR activity to decrease lipogenic gene expressions, especially in stearoyl-CoA desaturase-1 (SCD1), leading to a remarkable reduction of hepatic oleate content. Simultaneously, hepatic β-oxidation, NADPH oxidase and cytochrome P450 2E1 (CYP2E1) activity were reduced, and thus reactive oxygen species (ROS) and inflammatory cytokines were also diminished. Consistent with these changes, ezetimibe diminished c-Jun N-terminal kinase (JNK) phosphorylation and improved insulin signaling in liver. In rat primary cultured hepatocytes treated with oleate or LXR agonist, lipid storage was increased and insulin signaling was impaired.

Discussion/Conclusion: In morbid obese subjects, Ezetimibe reduces LXR activity by reduction of hepatic oxysterol content followed by reduction of SCD1 to lower hepatic oleate content, so that improves steatosis. Furthermore, reduced hepatic oleate content decreases ROS production, then improves insulin resistance. These results provide insight into pathogenesis and strategies for treatment of the metabolic syndrome.
Relationship between immunoglobulins superfamily parameters and histologic changes in chronic viral liver diseases

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The aim of study is to assess the relationship between intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) serum levels and histological changes in chronic viral hepatitis (CVH) and liver cirrhosis (LC).

Material and methods: 41 patients with CVH and 9 patients with viral LC were examined. The control group included 16 healthy volunteers. Blood concentration of ICAM-1 and VCAM-1 were carried out by means of ELISA. Statistical analysis was used to fit the nonparametric statistics.

Results: ICAM-1 and VCAM-1 levels were higher in moderate and severe histological activity than in minimal hepatic morphologic changes. Parameters of ICAM-1 ≥ 462 ng/ml and VCAM-1 ≥ 1900 ng/ml were associated with increased risk of histological activity index (HAI) > 8 in chronic viral liver diseases. Sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and accuracy (Ac) of ICAM-1 ≥ 462 ng/ml and VCAM-1 ≥ 1900 ng/ml for detection of HAI > 8 were 74.2, 68.4, 79.3, 61.9, 72.0 and 87.1, 52.6, 75.0, 71.4, 74.0 accordingly.

Levels of ICAM-1 and VCAM-1 increased with intensifying of hepatic fibrotic changes. Patients with ICAM-1 ≥ 626.0 ng/ml and VCAM-1 ≥ 3980 ng/ml characterized by higher risk of severe fibrosis/cirrhosis. Se, Sp, PPV, NPV and Ac of ICAM-1 ≥ 626 ng/ml and VCAM-1 ≥ 3980 ng/ml for detection of severe fibrosis/cirrhosis were 61.1, 75.0, 57.9, 77.4, 70.0 and 83.3, 81.3, 71.4, 89.7, 82.0 accordingly.

Conclusion: The levels of adhesion molecules correlate with histological changes. ICAM-1 and VCAM-1 are markers of inflammation and tissue remodeling in chronic viral liver diseases.
Gallstones associated with nonalcoholic steatohepatosis

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Introduction: To evaluate the prevalence of NASH and the metabolic syndrome in patients with symptomatic gallstones undergoing laparoscopic or open cholecystectomy.

Methods: It is performed a study of 95 patients. The simultaneous liver biopsies were performed during cholecystectomy between 2006 and 2007. There were no postoperative complications. Patients with significant alcohol intake, hepatitis B or C (virus-positive), autoimmune diseases, and Wilson's disease were excluded. It is compared the demographics, liver function tests, lipid profile, and ultrasound findings of patients with and without NASH.

Results: A total of 95 patients completed the study. The mean age was 52.15 years, 29 patients were male and 66 female. Fifty-two patients (55%) had biopsies compatible with NASH.

Discussion/Conclusion: Fifty-five percent of patients with gallbladder Stones have associated NASH. Awareness of this association may result in an earlier diagnosis. The high prevalence of NASH in patients with Gallbladder stone may justify routine liver biopsy during cholecystectomy to establish the diagnosis, stage, and possible direct therapy.
The alcoholic liver lesion estimated by duplex-Doppler sonography

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Introduction: The progress of alcoholic liver disease (ALD) is usually latent, often non-typical. Many factors, such as drugs, nutritional habits, genetic condition, other diseases may modify the clinical picture. There are three basic steps of liver damage caused by alcohol: steatosis, steatohepatitis and cirrhosis. First two stages sometimes may be reversible, so the early diagnosis of the liver damage is important from therapeutic and prognostic point of view.

Patients and methods: We have examined 25 alcohol abuse patients with liver damage (hepatomegaly, pathological laboratory tests) the following sonographic B-mode liver parameters: gallbladder and liver size, liver shape, liver margins, parenchymal echo texture and portal vein confluence diameter were evaluated. Next we examined vessel Doppler flow in portal vein, superior mesenteric vein, hepatic veins, hepatic artery. Examinations were performed before and 60–90 min after meal consumption (about 600 kcal). Diseases (HBV and HCV infection) which may influence liver and bile duct picture were excluded during clinical observation. Control group consisted of 40 healthy volunteers.

Results: Alcoholic patients had numerous sonographic symptoms important for grading liver pathology and prognosis: visceral vessels abnormality (pathological portal/arterial flow distribution, portal vein dilatation, flat hepatic veins flow), liver lesion signs (from increased parenchymal echogenicity to irregular liver texture, hepatomegaly and/or liver deformation), ascites, bile ducts pathology, others.

Comments: The manifestation of the following liver lesion periods – steatosis, steatohepatitis, compensated and decompensated cirrhosis are not always easy for diagnosis even during clinical observation. Numerous data obtained from USG duplex Doppler examination, such as liver size, shape, surface, echogenicity, vessel diameter, vessel flow analysis and out-liver signs give possibility to grade liver damage. But the prognostic importance has detection of periportal fibrosis. Liver biopsy is usually essential to make final grade the severity of the alcoholic liver disease (eg fibrotic periportal transformation diagnosis).

Conclusions:
1. Numerous pathological signs observed in duplex-Doppler examination allow to grade the advancement of liver lesion in alcoholic patients independently from others diagnostic methods.
2. Results of examination by duplex-Doppler sonography of the liver may constitute important suggestions for liver biopsy decision, prognosis, and therapy in alcoholic patients.
The hepatic lesion in metabolic syndrome patients – Assessment by duplex-Doppler sonography

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Introduction: The grade the advancement of metabolic syndrome and detection of organs impairment are fundamental issues for treatment and prognosis. Some unfavorable organic alterations e.g. liver steatosis may be reversible. Both physical and laboratory tests do not answer all problems in patients suffering from metabolic syndrome with liver lesion. New interesting possibilities for non-invasive evaluation the advancement of liver damage gives duplex-Doppler sonography.

Patients and methods: We have examined 25 patients with liver damage (hepatomegaly, pathological laboratory tests) which accompanied metabolic syndrome and 35 metabolic patients without liver lesion. The following sonographic B-mode liver parameters: size, shape, liver margins, parenchymal echo texture, portal vein confluence diameter, gallbladder diameter were evaluated. Next we examined vessel Doppler flow in portal vein, superior mesenteric vein, hepatic veins and hepatic artery. Examinations were performed before and 60–90 min after the meal consumption (about 600 kcal). Diseases which may influence liver and bile duct picture were excluded during clinical observation.

Results: Numerous USG abnormalities were observed in both groups of patients. Following liver alterations were important for clinical assessment: liver enlargement and deformation, different degree of the hyperechogenic liver texture, dilatation of the portal vein, decreased portal flow, enlargement and lack of the gallbladder postprandial reaction, others.

Comments: Physical symptoms of the liver lesion in metabolic patients are vague and not characteristic: persistent fatigue, right upper quadrant discomfort or pain, hepatomegaly. Results of laboratory tests – elevated level of AST, ALT, sometimes gamma-GT, alkaline phosphatase, bilirubin have similar significance. The confrontation of sonographic and clinical symptoms may approach to diagnose consecutive stages of liver damage (steatosis, steatohepatitis, periportal fibrosis or cirrhosis) and may be helpful for determining decision about liver biopsy. Intensive hyperechogenic liver often precedes parenchymal evolution to cryptogenic liver cirrhosis.

Conclusions:
1. USG duplex-Doppler abnormal symptoms not always were confirmed by laboratory tests in metabolic patients.
2. Abnormal laboratory hepatic tests were met in metabolic patients with normal sonographic picture.
3. USG duplex-Doppler examination seems to be independent factor for clinical value of the liver condition.
Early on-treatment response as a predictor of sustained virological response in genotype 4 HCV naive Egyptian patients treated with peginterferon plus ribavirin

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⁵Universal Supervisor of Kafr El Sheikh Liver and Cardiac Center, Kafr EL Sheikh, Egypt
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Introduction: The effect of peginterferon and ribavirin treatment on chronic hepatitis C virus (HCV) infection has been established in several controlled clinical studies. However, predictors of treatment success in routine clinical practice remain to be established.

Aim of the work: To estimate the importance of rapid virological response (RVR), seronegative for hepatitis C virus (HCV) RNA at 4 weeks and other host and viral factors in naïve Egyptian patients treated with 48 weeks of pegylated interferon and ribavirin.

Methods: A total of 129 naïve patients with chronic hepatitis C genotype 4 were randomly assigned to 48 weeks of either peginterferon-alpha-2a (180 μg/week) or peginterferon-alpha-2b (1.5 μg/kg/week) plus oral ribavirin (10.6 mg/kg/day) with a 24-week follow-up. The primary endpoint was sustained virological response (SVR), seronegative for HCV RNA at 24-week follow-up. RVR, baseline HCV-RNA and pretreatment fibrosis stage were evaluated as predictors of SVR in an ‘on-treatment’ analysis.

Results: Overall, SVR was achieved by 85 patients (70.2%), while 26 patients relapsed (21.5%). RVR occurred in 95 patients where 77 of them achieved SVR (81%) and 14 of them relapsed (14.7%). Also patients with pretreatment low fibrosis stage achieved SVR by 75.4%, 70.8% and 25% and relapsed by 18.5%, 18.8% and 62.5% for F1, F2 and F3 (according to Metavir score) respectively.

Discussion/Conclusion: RVR is a strong predictor of SVR. However, it is independent of patients’ pretreatment status, including age, weight, gender and grade of hepatocytes inflammation. Low pretreatment fibrosis stage is a good predictor of SVR.
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