Highlights from Hepatology 2015: From Chronic Hepatitis to Hepatocellular Carcinoma

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HIGHLIGHTS FROM HEPATOLOGY 2015:
FROM CHRONIC HEPATITIS TO
HEPATOCELLULAR CARCINOMA

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Session I

Viral hepatitis I
History and global burden of viral hepatitis

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Worldwide, hepatotropic viruses are a major cause of liver diseases that can present with a broad spectrum of clinical signs and symptoms, ranging from an asymptomatic carrier state to acute/fulminant hepatitis or chronic hepatitis with the potential to progress to liver cirrhosis and its sequelae, incl. hepatocellular carcinoma (HCC). Thus viral hepatitis can be associated with significant morbidity and mortality and represents a global health care problem.

History of viral hepatitis. In the 1940s, two distinct clinical forms of hepatitis were recognized: epidemic hepatitis, after the discovery of hepatitis A virus (HAV) in 1973 by R.H. Purcell and collaborators, designated as hepatitis A, and serum hepatitis, after the discovery of hepatitis B virus (HBV) in 1963 by B. Blumberg and in 1968 by A.M. Prince, designated as hepatitis B. With the specific serological identification of HAV and HBV infection the cause of the Non-A, Non-B posttransfusion hepatitis (NANB-PTH) remained an enigma until the hepatitis C virus (HCV) was discovered in 1989 by M. Houghton and collaborators, followed by the rapid development of HCV-specific serological and molecular diagnostic assay systems, incl. HCV genotyping. In 1955 an enterically transmitted acute viral hepatitis was identified during an outbreak in New Delhi, later termed hepatitis E virus (HEV) infection. And in 1977 M. Rizzetto and collaborators discovered a novel defective virus that only occurs in association with hepatitis B, designated as hepatitis delta virus (HDV).

Global burden of viral hepatitis. Based on the specific and sensitive detection of hepatitis A-E infection the epidemiology and global burden of these infections could be studied.

HAV infection occurs worldwide and shows a distinct geographic distribution with the highest prevalence in sub-Sahara-Africa, India, Pakistan and Afghanistan and a very low incidence in Western Europe, Scandinavia, North America and Australia. Through the vaccination of individuals at risk, the incidence of hepatitis A has decreased significantly.

HBV infection is a serious global public health problem with 250–350 million people chronically infected. It accounts for 500,000–1.2 million deaths per year and is the 10th leading cause of death worldwide. The prevalence of HBV infection varies markedly in different geographic and in different population subgroups. Highly endemic areas are sub-Saharan Africa and Asia. Universal vaccination was shown to be cost-saving in countries with high and intermediate endemicity.

HCV infection is endemic worldwide with 130–170 million infected people and also shows a geographic variability. The highest prevalence rates are found in Africa and Asia. Currently, the data are inadequate to describe the true disease burden. Nevertheless, it appears that HCV infection is the most common form of viral hepatitis in the European Union. Unfortunately, there is no vaccine available to date.

HDV infection is endemic in Mediterranean countries, in parts of Africa and in Middle and South America and occurs only in association with an HBV infection. The HBV vaccine therefore also protects from HDV infection. Data regarding the global burden of HDV infection are very limited.
HEV infection is most prevalent in Asia, Africa, Middle East and Central America. Its epidemiology is similar to HAV infection. HEV is more widespread in industrialized countries than was generally believed. Apart from fecally contaminated water, transmission from consumption of certain meats, by blood transfusion and solid organ transplantation has been demonstrated. A vaccine with long-term efficacy has been developed.

The coming years are expected to improve our ability to prevent and treat viral hepatitis, making the control of these global infections feasible.
Hepatitis B: From molecular virology to new antiviral therapies

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Current therapies of chronic hepatitis B remains limited to either pegylated-interferon-alpha, or one of the five approved nucleoside analogues (NAs) treatment. While viral suppression can be achieved in the majority of patients with high-barrier-to-resistance new-generation NAs, HBsAg loss is achieved in only 10% of patients with both classes of drugs after a follow-up of 5 years. Therefore, there is a renewed interest to investigate a number of steps in the HBV replication cycle and specific virus-host cell interactions as potential targets for new antivirals. These include:

1) Inhibition of HBV entry: lipopeptides mimicking pre-S1 domain compete with Dane particle for binding to sodium taurocholate co-transporting polypeptide (NTCP). Myrcludex B has entered phase II clinical trials;

2) Damage and destruction of cccDNA via cytokines (Lymphotoxinβ, IFNα, IFNγ, TNFα) or cccDNA sequence-specific nucleases: zinc-finger nucleases (ZFNs), transcription activator-like effector nuclease (TALENs) and CRISPR/cas9;

3) Functional silencing of cccDNA via modulation of host cellular epigenetic-modifying enzymes by IFNα or by inhibition of the HBV core (HBc) and X (HBx) nuclear functions;

4) siRNA approaches or anti-sense oligonucleotides targeting viral mRNAs to block viral replication and viral protein expression (to potentially restore adaptive immunity) are in pre-clinical or early clinical evaluation;

5) Targeting HBV Polymerase: reverse transcriptase inhibitors of the NA family are part of the standard of care; RNAseH inhibitors are in pre-clinical evaluation;

6) Targeting Nucleocapsid assembly and pregenomic RNA (pgRNA) packaging: Capsid assembly modulators can affect nucleocapsid assembly, pgRNA encapsidation, and the nuclear functions of HBc (cccDNA regulation and interferon stimulated gene expression). Several compounds are in phase I/II clinical evaluation;

7) Targeting HBsAg: Nucleic acid polymers inhibit HBsAg release and are in early clinical evaluation. Monoclonal antibodies to decrease circulating HBsAg load, form immune complexes and restore immune responses are under evaluation;

8) Boosting Innate immune responses: IFNα exhibit antiviral activity in infected cells but also contribute to cell-mediated immunity *in vivo*. TLR7 agonists to boost type I/III IFN and other antiviral cytokines (eg. IL6, IL12, IL18) production and NK and T cells activation, are in phase II clinical evaluation;

9) Defeating HBV-specific T-cell exhaustion: approaches to block inhibitory pathways (check point inhibitors, i.e. PD1 blockade) and immunosuppressive cytokines (IL10 and TGF beta) to achieve recovery of HBV-specific T cells and NK cells from CHB patients are in pre-clinical evaluation;

10) Engineering of redirected T cells: Transfer of HBV-specific T cell receptors or HBV-specific chimeric antigen receptors (CAR) *ex vivo* in patient’s T cells is in pre-clinical evaluation as well as re-targeting of immune effector cells towards HBV-infected cells using bispecific antibody constructs;

11) Therapeutic vaccines: specific peptides or recombinant DNA vaccines delivered by diverse approaches are currently being evaluated in Phase I/II clinical trials in association with NAs to promote CD4+ and CD8+T cell antiviral activity as well as antibody responses to reduce reduce viral load and induce long-term immunity.

All these research efforts should lead to novel treatment concepts towards a cure of chronic HBV infection.
Hepatitis C in the era of direct antiviral therapies

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Hepatitis C virus infection represents a major cause of chronic hepatitis, liver cirrhosis
and hepatocellular carcinoma worldwide. Progress in the molecular virology of
hepatitis C over the last 25 years has translated into effective and well tolerated new
treatment options. The introduction of directly acting antivirals, including protease,
NS5A and polymerase inhibitors, has revolutionized the treatment of chronic
hepatitis C. These advances will be highlighted and new challenges will be discussed.

Recommended reading

- American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases
  Society of America (IDSA). Hepatitis C guidance: AASLD-IDSA recommendations
  for testing, managing, and treating adults infected with hepatitis C virus. Hepatology.

- European Association for the Study of the Liver. EASL recommendations on
www.easl.eu).

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- Webster DP, Kleinerman P, Dusheiko GM. Hepatitis C. Lancet. 2015;385(9973):
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Session II

Viral hepatitis II
Chronic hepatitis D; at a standstill?

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Chronic hepatitis D (CHD) is a severe liver disease of world-wide distribution caused by the Hepatitis D Virus (HDV), the smallest infectious agent in human virology. It is defective, depends on the HBV for infectivity and has a circular RNA genome of about 1700 nt which codes for a single protein (the HD antigen) of 190 aminoacids.

Therapy of CHD is at a standstill. It still relies on Interferon (IFN), first introduced empirically in the 1980s; results, however, are limited. With the pegylated form of IFN now in use (PegIFN) only 25% of CHB reach a sustained viral response, i.e. have apparently cleared the HDV-RNA six months after stopping therapy. However, HDV remains infectious and ready to reactivate even at very low titers if the HBsAg persists in serum, as it does in most treated cases; therefore relapses of HDV and hepatitis D post-therapy are frequent and further diminish the rate of therapeutic responses.

The major obstacle to CHD therapy is the minimalist nature of the HDV. It does not encode for any enzymatic function but is replicated by host RNA polymerases deceived to recognize the viral RNA as it were a cellular DNA; it has no replicative machinery of its own to be targeted by antivirals. The only help required from HBV is the HBsAg coat whereby it attaches to the hepatocytes and assembles in the virion; HBV antivirals that effectively decrease HBV-DNA but leave HBsAg unaffected, are of no avail in CHD.

Two novel therapeutic strategies are under evaluation. One targets either the entry of the virion into the liver cell by blocking the attachment of the HBsAg to the Na+-taurocholate cotransporting polypeptide (NTCP), or the production of HBsAg particles to deprive the virion of its capsid. Myrcludex B, a peptidic inhibitor of HBV entry has been used with some success in vitro in and the mouse model and the nucleic acid polymer REP-2139 was recently shown to profoundly diminish serum HBsAg and HDV-RNA by blocking HBsAg entry and by inhibiting its intracellular synthesis. The second strategy targets the process of prenylation of the large-HDAg, which is critical for the interaction of this antigen with the HBsAg in order to assemble the virion. A recent proof of concept study in humans has used the prenylation inhibitor Lonafarnib, demonstrating in short-term studies a reduction of HDV-viremia by a few logs.

At the present outlook, there seems yet to be no resolutory therapeutic alternative for CHD. However, the new unconventional therapeutic strategies might act together (and with PegIFN?) to shield hepatocytes from infection and ultimately clear HDV.
Hepatitis E virus: Time to change the textbooks!

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Until recently, HEV was thought not to occur in developed countries. It is now clear that locally acquired HEV is common in many developed countries. HEV infection acquired in these areas differs from that in developing countries in a number of important aspects: it is caused by genotype 3 (and 4 in China and Japan); it mainly affects middle-aged/elderly males; it is zoonotic with a porcine primary host. Pig herds worldwide are infected with HEV genotype 3 and HEV has been found in the human food chain in a number of developed countries. However, the route of transmission is not fully understood, since most cases are not obviously associated with pigs/pig products. HEV can be transmitted by blood transfusion and surprisingly high numbers of asymptomatic blood donors are viraemic at the time of donation: Germany 1:1200, Netherlands 1: 2671, England 1:2848.

Our understanding of the clinical phenotype of HEV infection in humans has undergone a sea-change in recent years. Previously, HEV was thought to cause only acute self-limiting hepatitis. However, HEV may cause persistent disease in the immune-compromised. Patients with chronic HEV infection have no symptoms, but some develop rapidly progressive liver cirrhosis. The full clinical spectrum of HEV is still emerging. HEV has important extra-hepatic manifestations, which deserve further investigation. For example, HEV can cause a wide range of neurological illness. In particular, very recent data suggests that Guillain-Barré syndrome and neuralgic amyotrophy are associated with locally acquired HEV in approximately 5% and 10% of cases respectively.
Challenges in special populations: HIV/HCV coinfection, liver transplantation and patients with end-stage renal disease

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Until recently, the combination of peg-interferon (IFN) and ribavirin (RBV) was the main stay of treatment for all genotypes of chronic hepatitis C virus (HCV). During that treatment era, sustained virological response (SVR) rates varied significantly across patient subgroups and the concept of “special populations” emerged. Now, in the era of direct acting antivirals (DAAs), with a better security profile and higher efficacy rates, those patients with comorbidities or conditions that limited IFN-based antiviral treatment but with unmet medical needs have been considered for therapy again. With currently approved all-oral antivirals, patients coinfected with HIV and HCV have SVR rates similar to patients with HCV monoinfection. However, drug-drug interactions (DDIs) with current antiretroviral drugs are still challenging. In the setting of HCV-related liver transplant recipients (LT), in whom there is an accelerated course of the disease, previous IFN-RBV treatments were poorly tolerated and attained low SVR rates. Today, all-oral therapies have proven to be efficacious and with a good security profile in this population. Nevertheless, the extension of treatment duration or the addition of ribavirin still remain useful tools to achieve a higher chance of success. In this population as well, DDIs are an issue as some regimens require adjustments of immunosuppressive drugs and monitoring of drug levels during treatment. Finally, preliminary data show promising results in terms of efficacy and safety in patients with end-stage renal disease (ESRD). However, the need for more clinical studies in patients with ESRD remains high as these patients still have very limited options up-to-date.
Session III

Autoimmune liver disease
Pathogenesis of autoimmune and cholestatic liver diseases

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Autoimmune liver diseases span a spectrum of immune mediated hepatobiliary injuries. These processes are usually chronic in nature and often lead to the development of end-stage liver disease. Disease can be characteristically siloed into four major forms – autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and IgG4 associated cholangitis/autoimmune pancreatitis. For all of these diseases we recognise the important roles played by environmental triggers in the context of complex host genetic risk. Immune reactivity to self is then established and perpetuated with inflammatory driven liver injury alongside the consequences of resultant cholestasis where appropriate. Underlying mechanistic pathways are likely to be shared across these diseases, as is evident from the rare patients who present with cross-over features of disease. Therapy to date has not always been effective, and strategies for the future to prevent end-stage liver disease and to improve the quality of life of patients, are hoped to be based on better mechanistic disease insights.
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 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:


Overlap syndromes: Classification, diagnosis and management

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Autoimmune Hepatitis is sometimes associated with either of the two cholestatic liver diseases, primary sclerosing cholangitis (PSC) or primary biliary cholangitis / cirrhosis (PBC). Various terms and descriptions have been used for these associations, and overlap-syndromes was most often used. However, it is most likely, that the majority of these cases do not actually represent an overlap of two diseases, but usually the cholestatic liver disease (PSC or PBC) is the pathogenetically dominant, or primary, disease, and AIH is secondary, more like an aggressive or hepatitis form of these conditions. However, despite these pathogenetic considerations, most of these patients benefit from immunosuppressive therapy, and thus the AIH component of their condition is clinically dominant: AIH is the autoimmune liver disease with the gravest prognosis if untreated, and at the same time with the best prognosis if treated. Therefore, patients with AIH, irrespective of underlying, co-existent or associated PSC or PBC, should receive immunosuppressive therapy analogous to other AIH patients. Often, lower doses of immunosuppressants are sufficient to show a good response of the hepatitis component in these cases.
Novel aspects in the management of cholestatic liver diseases

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Ursodeoxycholic acid (UDCA) is the current backbone of the treatment of chronic cholestasis. Its use is universal in primary biliary cirrhosis (PBC) and depends on local policy in primary sclerosing cholangitis. Nevertheless, not all patients respond to UDCA and there is a clear need for second-line therapy. Major insight has been gained into bile acid (BA) physiology during the last decade including the role of BA as metabolic modulators and the gut-liver axis. As a consequence, alongside drugs targeting immune response or fibrotic processes, a number of novel anti-cholestatic agents have undergone pre-clinical and clinical evaluation and have shown promising results although none has been approved yet.

Novel therapeutic approaches aimed at decreasing hepatic BA load (or ensuring liver protection against overload) include agonists of nuclear receptors: farnesoid X receptor (FXR), retinoid X receptor (RXR), pregnane X receptor (PXR), glucocorticoid receptor (GR), peroxisome proliferator-activated receptor α (PPARα) and vitamin D receptor (VDR) that are transcriptional modifiers of bile formation and, regarding BA membrane receptors, agonists of TGR5 that is expressed in various tissues and inhibitors of the ileal apical sodium bile acid transporter (ASBT). Derivatives of the FXR-induced fibroblast growth factor 19 (FGF19) from the ileum that suppresses hepatic BA synthesis are also under development as is norUDCA, a 23-C homologue of UDCA with specific physicochemical and therapeutic properties (results of a large phase II trial expected by the end of 2015). In addition, a number of these agents have also anti-inflammatory and anti-fibrotic effects.

The most advanced clinical evaluation (PBC patients) relates to agonists for PPARα, FXR and GR/PXR in combination with UDCA, namely fibrates, obeticholic acid (OCA) and budesonide respectively, even though most of the data are issued from uncontrolled and/or short term studies. Numerous open studies have found that fibrates added to UDCA have clear favourable effects (biochemical normalization or marked improvement together with decrease of pruritus). OCA has been shown to induce a significant decrease in alkaline phosphatase (and IgM) but pruritus is a common side effect, limiting treatment at doses higher than 10 mg/day. In non-cirrhotic PBC, budesonide (6–9 mg/day) combined with UDCA was more effective (biochemistries and histology) than UDCA alone in two randomized trials but this was not observed in another study including late stage PBC patients who also developed serious side effects. Results of the large ongoing phase III studies are eagerly awaited.

Lastly, novel potential targets for treating pruritus have been also identified since lysophosphatidic acid (LPA), a potent activator of itch neurons, and autotaxin (ATX), the enzyme which forms LPA, are likely to be key elements of the pruritogenic signalling cascade (ATX inhibitors and LPA receptor antagonists).

Promising times for patients with cholestatic diseases seem likely in the near future!
Session IV

Alcoholic and metabolic liver disease
Pathogenesis and management of alcoholic liver disease

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Alcoholic liver disease (ALD) is the leading cause of liver-related morbidity and mortality worldwide and is a major cause of death among adults with prolonged alcohol abuse. Despite its burden, the incidence, natural history and modifying factors of ALD remain largely unknown. ALD encompasses a range of disorders including simple steatosis, alcoholic steatohepatitis (ASH), fibrosis, cirrhosis and hepatocellular carcinoma (HCC). In addition, patients with advanced ALD (in most cases cirrhosis) and active drinking can develop an episode of acute-on-chronic liver failure named “alcoholic hepatitis” (AH). In most alcoholic patients with this clinical syndrome, the histological analysis shows the presence of ASH and advanced fibrosis. In its severe forms, AH carries a poor prognosis and current therapies are not fully effective. The pathogenesis of ALD is incompletely understood. Most studies have been performed in animal models that do not reproduce the histological findings of patients with severe ALD. Recent translational studies in human samples have revealed several key molecular drivers and potential targets for therapy. These targets include: (1) CXC chemokines, (2) IL-22/STAT3, (3) TNF receptor superfamily, (4) osteopontin, (5) gut microbiota and LPS, (6) endocannabinoids, and (7) inflammasomes. Moreover, recent evidence indicate that severe AH is characterized by incomplete liver regeneration, systemic inflammatory response and immune paralysis, leading to liver failure, sepsis and multiorgan dysfunction.

The most effective therapy for all patients with ALD, regardless of the disease stage, is prolonged abstinence from alcohol. Improved clinical outcomes are observed with abstinence across the spectrum of ALD, from the early to most severe cases. Therefore, prolonged alcohol abstinence is the first and most important clinical endpoint for patients with ALD. The pharmacological management of patients with ALD has evolved little in the last decades and lacks targeted therapies. The absence of developments on ALD contrasts with the spectacular advances in the management of viral hepatitis B and C, which can be treated successfully using highly active oral therapies. This fact is mainly related to the difficulties of conducting clinical trials in patients with an active alcohol addiction, the lack of interest in this field from drug companies and the drawbacks of current experimental models of ALD. Moreover, public funding for research into alcohol-related disorders has been scarce, especially in the field of hepatology. Thus, there is an urgent need to devote more clinical and research attention to ALD in order to provide novel diagnostic and therapeutic tools for these patients.
NASH: From pathogenesis to novel therapies

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Non-alcoholic fatty liver disease is defined by an accumulation of liver fat exceeding 5% of its weight in the absence of significant alcoholic intake. In 5–20% there is a progression from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) [1]. Until now it is not well understood why only some patients develop non-alcoholic steatohepatitis and currently no drugs are licensed for this indication. The pathogenesis of NAFLD is commonly explained by a “two hit” hypothesis. The first hit leading to steatosis is favored by insulin resistance, obesity, hyperlipidemia while the second hit leads to an inflammation in the fatty liver resulting in steatohepatitis.

Several studies point out, that bile acid receptor FXR-mediated signals (such as the enterohepatic hormone Fibroblast Growth Factor (FGF) 15/19), are involved in the regulation of triglyceride and glucose metabolism, next to their well characterized functions in cholesterol homeostasis, fat absorption and control of their own synthesis [2, 3]. Interestingly, insulin-resistant NAFLD patients are also affected by an altered hepatic response to FGF19 despite a normal post-prandial rise of its plasma levels [4]. In line with a potential active role of FGF19 in obese patients, a recent mechanistic study in mice provided evidence for a substantial contribution of FXR-mediated signaling to the beneficial effects arising from sleeve gastrectomy [5]. The exact mechanistic contribution of FGF19 to the pathophysiology of NAFLD, T2DM and MetS as well as the impact of bariatric surgery on FGF19 will require further investigation. Of note, recent clinical trials have revealed a beneficial impact of the FXR agonist Obeticholic Acid (OCA) on body weight, insulin sensitivity and liver histology in patients with NASH [6, 7]. Since OCA administration was associated with a dose-dependent increase in serum FGF19, this indicates a potential usefulness of pharmacological FXR activation to correct FGF19 levels in patients [7].

Serum 25-OH Vitamin D3 (VD3) levels negatively correlate with BMI, insulin resistance and NAFLD [8]. The causal relation between VD3 status and NAFLD as well as the potential underlying mechanisms are, however, not fully understood. Reduced VD3 levels can be found in NAFLD patients with a close association to the histological severity of hepatic steatosis, necroinflammation and fibrosis [9]. Recent data from our laboratory in HFSD mice with histologically defined NASH and fibrosis indicate that high dietary VD3 supplementation has a beneficial effect on the liver phenotype in terms of reduction of NAS and improved pro-fibrogenic gene expression. Whether therapeutic application can be beneficial in human NASH patients with VD3 deficiency is currently investigated in a randomized placebo-controlled clinical trial (SASL34).

Different T cell populations such as T regulatory (Tregs), Th1 and Th17 cells play a central role in the immunopathogenesis of fatty liver disease [10]. The inflammatory process underlying NASH is characterized by elevated expression of pro-inflammatory cytokines such as TNFα, IL-1β and IL-6. Current data suggest that Th17 cells play an important role in the inflammatory processes characterizing NASH. A recent study showed hepatic Th17 cell infiltration in NASH patients [11] and
IL17A-/- mice are resistant to the development of steatohepatitis [12]. Studies using multicolor FACS analysis in peripheral blood and liver tissue indicate that NAFL patients show a “prehepatitic” immune cell profile similar to NASH. Progression from NAFL to NASH is marked by an increased frequency of IL-17+ cells among intrahepatic CD4+ T cells and a higher Th17/rTreg ratio in peripheral blood. These findings suggest that immune cell interventions could be an attractive target for future therapeutic strategies.

Proinflammatory cytokines such as IL-1 have been shown to play a crucial role in NASH. The transformation of steatosis to steatohepatitis and liver fibrosis is markedly reduced in mice deficient in either IL-1α or IL-1β [13]. Treatment of mice with the IL-1 receptor antagonist (IL-1Ra) improves hepatic steatosis significantly [14]. Recent data from our laboratory indicate that IL-1 also plays a crucial role during the early phase of hepatic lipid accumulation. Using a novel vaccination approach we show that even at early time points of NAFLD without signs of steatohepatitis hepatic lipid accumulation is mediated by IL-1. Based on these findings, anti-cytokine interventions have started in human metabolic disease. Anakinra, a recombinant version of IL-1Ra shows promising metabolic effects with improved hyperglycemia and beta-cell secretory function in a double-blind placebo controlled randomized trial in 70 T2DM patients [15]. However, such studies are still in their preliminary stages for metabolic organ damage such as NASH.

Further potential novel therapeutic targets in NASH include incretins (GLP-1), PPARα/δ agonists, chemokine inhibitors and caspase inhibitors which are currently in clinical development [16].

References:


Hereditary hemochromatosis: Pathogenesis, diagnosis and treatment

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With a prevalence of 1:1000, hemochromatosis can be considered a common cause of chonic liver disease and the introduction of HFE genotyping allows for decisive and non-invasive diagnostic testing. However, molecular and clinical genetic studies have led to the identification of genes other than HFE in patients with inherited diseases associated with increased hepatic iron storage that can cause hemochromatosis, which adds complexity to a diagnostic approach to patients with suspected hemochromatosis. Despite major advances in genetics, hepatic iron quantification by non-invasive methods therefore remains key to the diagnosis of hemochromatosis.

Despite its association with homozygosity for the C282Y polymorphism in the HFE gene in > 80% of patients, hemochromatosis is a complex genetic disease with strong environmental disease modifiers. As testing for mutations in non-HFE hemochromatosis genes TFR2, HJV, HAMP and SLC40A1 is complex, costly and time-consuming, demonstration of hepatic iron overload by liver biopsy or MRI is therefore required before such comprehensive genetic testing is carried out.

An additional limitation of HFE genotyping for the diagnostic assessment of hepatic iron overload is its incomplete penetrance. When individuals homozygous for C282Y without iron overload are assessed and counseled incomplete disease penetrance must be considered. However, in clinical practice HFE genotyping is carried out in patients with suspected iron overload or during family screening. Recommendations based on the findings from large-scale population-based studies are therefore of limited value in this scenario and the contribution of ‘minor’ HFE to liver disease progression should be considered.

The pathogenesis of chronic liver diseases in hemochromatosis is mainly attributed to the redox potential of tissue iron and only more recent studies have focused on toxic properties of circulating iron. Considering the fact that an increased saturation of transferrin with iron in plasma is the hallmark of all hemochromatosis forms, allows for a more refined view on the pathogenesis of hemochromatosis. Recent studies have shown an increased concentration of redox-active iron in plasma in patients with increased transferrin saturation. This finding supports the hypothesis that circulating iron is the key to understand the pathogenesis of iron induced tissue damage and suggests that tissue iron is the ‘smoking gun’ of iron-induced tissue damage.

Taken together, caring for patients with suspected or established hemochromatosis still remains a challenge, where a more refined understanding of the changes in genetics, biochemistry and cell biology can aid better diagnosis and treatment of affected individuals.
Session V

Liver cirrhosis and its complications
Development and reversion of cirrhosis

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The term “cirrhosis” identifies an advanced phase of chronic liver diseases (CLD) that per se is neither morphologically or clinically an end stage, particularly with the prospective of novel treatments able to stabilise or even reduce tissue fibrosis. Regardless, patients with cirrhosis are classified along with the appearance of clinical manifestations typical of decompensated cirrhosis with little or no ability to predict these often life threatening events (so called ‘expectant’ algorithm). In addition, it is increasingly clear that different CLD are characterised by different predominant profibrogenic mechanisms and, while cirrhosis is the common result of progressive fibrogenesis, there are distinct patterns of fibrosis development in different and even within the same CLD. These aetiology-related patterns are linked to the relative prevalence of different pro-fibrogenic mechanisms, such as the activation of a chronic wound healing reaction, oxidative stress and derangement of the epithelial-stromal equilibrium around bile ducts. The knowledge of these aspects of the pathophysiology of CLD leads to the awareness that a correct interpretation of the development of cirrhosis should take into consideration the correlation between time of progression of liver disease, the aetiological agents, the dynamics of the necro-inflammatory infiltrate, the distribution of fibrosis and the onset and progression of portal hypertension (PH), depending on the aetiological agent.

Considering the immediate prospective of treating efficiently a very large number of cirrhotic patients with the new IFN-free regimens, there is a concrete possibility that a significant number of patients with compensated advanced chronic liver disease due to HCV will achieve sustained viral response (SVR) and possibly regression of liver tissue fibrosis. However, the available data obtained over the past decade in cirrhotic patients who had achieved SVR, indicate that in patients with clinically significant and severe PH, HCV clearance does not induce a significant reduction of PH and that cirrhosis, once advanced may progress to decompensation even in absence on HCV replication. In biological terms, this can be explained by the relative autonomy acquired by the fibrogenic process beyond a certain level of development over decades characterised by chronic fibro-inflammation and neo-angiogenesis. In particular, it is conceivable that, at this stage of the disease, two major determinants may condition further clinical progression independently of the reduction of hepatocellular necrosis and inflammation induced by SVR. The first is represented by the remarkable hyperplasia of different types of activated fibrogenic myofibroblasts which is associated by a strong activation of anti-apoptotic pathways in these cells. The second is due to the extensive changes in hepatic angioarchitecture consequent to neoangiogenesis and to the contraction of scar tissue leading to elevated tissue tension which are only minimally affected by the reduction of necro-inflammation following SVR.
Current management of the complications of cirrhosis and portal hypertension: Variceal hemorrhage, ascites, and spontaneous bacterial peritonitis

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Cirrhosis is not a single entity but represents a disease progression across different **prognostic stages**, with the compensated and decompensated stages being the most important.

Variceal hemorrhage and ascites are complications of cirrhosis that denote the presence of a decompensated stage of cirrhosis. Spontaneous bacterial peritonitis (SBP) is a common bacterial infection unique to patients with cirrhosis that can precipitate the development of recurrent variceal hemorrhage and hepatorenal syndrome, complications that denote the presence of a “further decompensated” stage of cirrhosis that can be associated with multi-organ failure (that is, the so-called acute-on-chronic liver failure).

Main current issues in the management of variceal hemorrhage include identification of different prognostic stages with different pathophysiological mechanisms/targets that allow for individualized patient care. Furthermore, it is now recognized that management of variceal hemorrhage cannot be performed in an isolated manner and that the presence of other complications of cirrhosis (ascites, encephalopathy) should be taken into account both in the management and in the design of future clinical trials.

Because management of ascites per se has not resulted in significant changes in mortality, main management issues consist in preventing further decompensating events by preventing factors that will lead to worsening vasodilatation and hemodynamic status (infections, vasodilators), preventing volume depletion (overdiuresis, GI hemorrhage) and preventing structural kidney injury (nephrotoxins).

Prophylaxis of bacterial infections such as SBP currently consists of the administration of antibiotics. This is however a double-edged sword. On one hand by preventing infections, there is evidence that recurrent variceal hemorrhage and hepatorenal syndrome can also be prevented. However, response to recommended empirical antibiotics in patients with suspected infection such as SBP, is currently significantly lower than in the past because of an increase in infections secondary to multi-drug resistant (MDR) organisms. One of the main predictors of the development of MDR organisms is the use of prophylactic antibiotics and unnecessary and prolonged use of antibiotics in hospital settings. Therefore, appropriate antibiotics should be used in patients with a high suspicion of infection and antibiotic prophylaxis should be restricted to patients with the highest risk of infection.
Liver cirrhosis and kidney

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In patients with cirrhosis portal hypertension and splanchnic vasodilatation cause a shift of blood volume away from the central circulation. This reduction of centrally effective blood volume induces a stimulation of counterregulatory mechanisms such as activation of renin-aldosterone and of the sympathetic nervous system. This usually results in renal sodium retention and possibly a reduction of renal perfusion and functional renal failure.

Acute kidney injury (AKI) in cirrhosis is mainly due to prerenal factors such as intravascular volume depletion often triggered by hemorrhage, diuretic treatment or systemic inflammation. Less common causes are acute tubular necrosis, e.g. drug induced, glomerular or interstitial diseases. Chronic kidney disease (CKD) may be due to nephropathy or glomerulonephritis.

The diagnosis of renal failure in cirrhosis is mainly based on changes in serum creatinine concentrations. Hepatorenal syndrome type 1 and 2 are the most pronounced forms of renal failure in cirrhosis. More recently subtle changes of kidney function, such as an increase of serum creatinine of more than 0.3 mg/dl or by more than 50% are considered as AKI also in patients with cirrhosis. Novel markers of renal injury are being investigated for their prognostic value in cirrhosis such as Cystatin C or NGAL.

Hepatorenal syndrome type 1 may be treated effectively by a combination of vasopressors such as terlipressin and albumin administration. Possibly albumin administration may improve renal function also in less severe cases. Reduction of portal hypertension by transjugular intrahepatic portosystemic shunt (TIPS) is an effective means for the treatment of massive ascites and can improve renal function in cirrhosis.

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Session VI

From basic science to the clinic
Microbiota and liver disease

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Excessive alcohol consumption and overweight are the main causes of chronic liver disease in Western countries. Despite these major public health concerns, the factors that link alcohol consumption, overweight and the onset and progression of liver injury are poorly understood. Thus, among subjects with heavy alcohol drinking or overweight, only 10 to 35% will develop inflammation (hepatitis) and 8 to 20% will evolve to cirrhosis. These data show that other factors than the only amount of alcohol intake or the importance of overweight are involved in the occurrence of liver damage.

The human gastro-intestinal tract hosts a complex and diverse microbial community (10^{14} bacterial cells, more than 1000 different bacterial species), called the intestinal microbiota (IM). The genetic coding capabilities far exceed those of the human genome. Thus, the IM is considered a full organ with many metabolic, immunological and endocrine roles that affect human health. Activation of the innate immune system by lipopolysaccharide (LPS) of the digestive system has emerged as a key factor in triggering alcoholic hepatitis (AH). An increased gut permeability and associated endotoxemia has been observed in humans and animals following alcohol consumption. Impairment of the intestinal barrier by ethanol involves the IM. This increase in permeability increases the translocation of bacterial toxins (LPS particular), which may in turn alter the intestinal barrier, leading to a vicious circle.

We have shown that, in alcoholic patients, a specific dysbiosis was associated with severe AH. By transferring the human IM in germ-free mice, we showed that this dysbiosis was not a mere consequence of AH but drives the susceptibility to liver injury. Metabolomic studies suggested that changes in the enterohepatic circulation of biliary acids due to dysbiosis participate in the onset of liver damages.

We also studied the involvement of IM in the heterogeneity of ALD in mice. We have shown that the presence of liver damage was associated with decreased population of Bacteroidetes. In addition, inhibition of Bacteroidotes decrease by prebiotics of fecal transfer experiments could prevent ALD. By similar methods, we have also the importance of MI in NASH.

In parallel, other teams have demonstrated that cirrhosis was associated with a specific dysbiosis and modifications of biliary acid metabolism. Moreover, indirect evidences of the involvement of IM in hepatocellular carcinoma has been shown in animal models.

Careful attention should be given about the studies involving IM to distinguish correlations to a causal relationship between liver and IM. The IM is easily modifiable by using pre-, pro- or antibiotics or by fecal transplant. These various findings open new possibilities for manipulating the IM of patients with liver diseases.
Genetics in liver diseases

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In the past two decades we have witnessed huge advances in our understanding of liver disease and physiology. Genetic advances have played no small part in that. Initial studies in the 1970s and 1980s identified the strong major histocompatibility complex associations in autoimmune liver diseases. During the 1990s, developments in genomic technologies drove the identification of genes responsible for Mendelian liver diseases. Over the last decade, genome-wide association studies have allowed for the dissection of the genetic susceptibility to complex liver disorders, in which also environmental co-factors play important roles. Findings have allowed the identification and elaboration of pathophysiological processes, have indicated the need for recategorization of liver diseases and have already pointed to new disease treatments. In the immediate future genetics will allow further stratification of liver diseases and contribute to personalized medicine. Challenges exist with regard to clinical implementation of rapidly developing technologies and interpretation of the wealth of accumulating genetic data. The historical perspectives of genetics in liver diseases illustrates the opportunities for future research and clinical care of our patients.

Reference:

Immune responses in viral hepatitis

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Approx. 500 million people world-wide are chronically infected with the hepatitis B virus (HBV) or hepatitis C virus (HCV) and are thus at a high risk of progressive liver disease, leading to liver fibrosis, cirrhosis, and ultimately hepatocellular cancer (HCC). Innate as well as adaptive virus-specific immune responses play a major role in the course of infection, leading to viral clearance in the large majority (> 95%) of adult individuals infected with HBV, but only in a minority (approx. 30%) of those infected with HCV. Adaptive immunity includes virus-specific CD4+ and CD8+ lymphocytes as well as neutralizing antibodies. Several mechanisms contribute to the failure of the immune response in those patients who progress to chronic infection. Next to viral evasion from innate immunity, these mechanisms include viral mutations leading to escape from neutralizing antibodies and CD8+ T cells as well as exhaustion and dysfunction of virus-specific T cells. Interestingly, viral escape has been recognized as a main mechanism of HCV persistence, however, its impact in HBV infection is still under debate. T cell exhaustion and dysfunction include the reduced capacity to proliferate, produce antiviral cytokines, and kill infected hepatocytes. It is associated to the expression of inhibitory receptors and may be due to high antigen loads and additional local factors such as the tolerogenic liver environment and arginine depletion in the inflamed microenvironment. Specific host factors, such as expression of the HLA class I type B27, are associated with viral clearance and may guide the way for the development of successful vaccination and/or immunomodulation strategies. Indeed, a better understanding of the factors that contribute to the success or failure of virus-specific immunity may help to develop new therapeutic options for HBV eradication in patients with chronic HBV infection (therapeutic vaccination and/or immunomodulation) as well as a prophylactic vaccine against HCV infection.
Liver fibrosis: From pathogenesis to novel therapies

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Perpetuating liver damage that does not subside leads to scarring of the liver, termed fibrosis. This process is mainly driven by chronic inflammation in the liver. Macrophages are a critical component in injured liver promoting inflammation, fibrosis, and angiogenesis. Recent clinical studies comprising patients successfully treated for viral hepatitis showed that liver fibrogenesis may be reverted even at later stages including bridging fibrosis and cirrhosis. Intensive research in recent years has identified a multitude of potential novel targets in liver disease, and a considerable number of innovative compounds have now entered clinical trials. The outstanding epidemiological relevance of non-alcoholic steatohepatitis (NASH) and NASH-associated cirrhosis entails that many of the clinical trials involving antifibrotic drugs in liver disease are conducted in this patient cohort. In general, fibrosis regression follows four major mechanistic principles: termination of chronic damage, shifting the cellular bias from inflammation to resolution, deactivation of myofibroblasts and direct matrix degradation. Obeying these principles, several promising approaches are currently evaluated. For instance, inflammatory macrophages are targeted via inhibition of chemokine CCL2, its receptor CCR2 or galectin-3, or counteracted by the transfer of restorative macrophages. Antibodies directed against matrix-stabilizing lysyl oxidase-like-2 (LOXL2) may facilitate matrix degradation. The ongoing trials will reveal which of the many potential targets prove clinical efficacy bearing in mind that fibrosis reversibility is less likely achieved in humans than in animal models.
Acute liver failure

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**Background**: Acute liver failure (ALF) is characterized by a sudden loss of hepatic function due to hepatocyte cell death and dysfunction in previously healthy individuals. The clinical presentation of ALF is associated with coagulopathy (INR ≥ 1.5) and hepatic encephalopathy, although the latter may be less pronounced. Without appropriate and timely intensive care or liver transplantation, ALF will result in multi-organ failure and death. Various causes may induce ALF, with acetaminophen intoxication and acute hepatitis B infection as most common causes in industrialized countries. While conventional terminology discerns acute, acute-on-chronic, and acute-on cirrhosis liver failure, some chronic liver diseases [i.e. autoimmune hepatitis (AIH), Wilson’s disease] can remain undiagnosed until an initial presentation as ALF.

**Key messages**: Upon definite diagnosis of ALF the underlying cause must be identified, since etiology affects prognosis and clinical management. Individual prognosis should be evaluated with one of various available scoring systems. Most widely used are the model-for-end-stage-liver disease, the King’s College Criteria and the Clichy criteria. Other markers, i.e. cell death markers, lactate, or thyroid status, may improve diagnostic accuracy of classic scores, though routine use of these is not yet established. Etiology-specific treatment under intensive care should be performed, if possible (acetaminophen and amanita intoxication, acute viral hepatitis and AIH). Liver transplantation is the only curative option for other causes, unknown reasons of ALF, or when etiology-specific therapy fails. In ambiguous cases, i.e. suspected drug induced ALF or AIH, co-infection with hepatitis E virus should be tested, as this might be more common than currently supposed.

**Conclusions**: Despite major improvements in clinical management of ALF patients, a significant proportion of ALF cases remains without clear identification of the underlying cause or unrecognized multiple causes. In depth analyzes of ambiguous ALF cases is warranted to further improve clinical management.
Session VII

Liver cancer: molecular pathogenesis and treatment
HCC: Molecular pathogenesis and novel drivers

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Hepatocellular carcinoma (HCC) is one of the leading causes of death by cancer worldwide. It is mainly developed on cirrhosis due to chronic hepatitis B and C, metabolic and alcoholic liver diseases in western countries. In contrast, hepatocellular adenomas are rare benign liver tumors frequently developed in women after oral contraception. Recent advances in molecular classification and dissection of genetic and epigenetic drivers have increased our knowledge of the molecular diversity of benign and malignant liver tumors. Using genomic approaches, we identified several new oncogenes and tumor suppressor genes and we described a molecular classification of hepatocellular adenomas that is used in clinical routine. Recently, using sequencing, we identified TERT promoter mutations activating telomerase as the most important mechanism of malignant transformation of both adenoma in carcinoma and of cirrhotic nodules in carcinoma. We also found new etiological factors predisposing to liver tumor development and new drug targets.
Role of immunity in pathogenesis and treatment of HCC

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Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, with a continuously high mortality. Thus, the development of new therapeutic strategies is crucial to decrease recurrence rates and to improve the overall survival rates of HCC patients. The rationale for immunotherapy is based on the findings of several studies showing specific CD8(+) T-cell responses against various tumor-associated antigens (TAAs) in HCC patients and a clinical benefit of T-cell infiltration in the tumor tissue. In addition, different vaccination strategies have led to induction of TAA-specific immunity and at least some tumor control. The factors responsible for the failure of TAA-specific immune responses to fully control tumor growth and immune evasion are not completely understood. Most likely, several different mechanisms contribute to the failure of the TAA-specific immune responses, e.g. the expression of inhibitory receptors such as PD-1 and CTLA-4 on TAA-specific T cells, the action of suppressive cell populations such as regulatory T cells or myeloid derived suppressor cells or the tolerogenic liver microenvironment. The aim of immune-based therapies is to overcome these mechanisms of T-cell failure and to induce or boost TAA-specific CD8(+) and CD4(+) T-cell responses. Several preclinical and clinical studies of immune-based therapeutic approaches show encouraging results. For example, recent data indicate that immune checkpoint inhibitors may show at least partial response also in HCC. It can be expected that a better understanding of the mechanisms responsible for TAA specific failure and its restoration will lead to the development of novel immune based treatment approaches that are currently being evaluated in preclinical and in early clinical settings. Indeed, immune checkpoint blockade along with adoptive immune cell therapy and vaccine approaches are currently being tested either alone or in combination with other treatments. Here, we provide an overview for the rationale of immunotherapy in HCC, summarise ongoing studies and provide a perspective for immune based approaches in patients with HCC.
Management of liver cancer

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Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide. HCC represents more than 90% of primary liver cancers. There is a growing incidence of HCC worldwide. In the Western world, HCC arises in a cirrhotic background in up to 90% of cases, and cirrhosis itself is a progressive disease that affects patient survival. Thus, outcome in patients with HCC and the chances for antitumoral treatment and its results are dependent not only on tumor associated factors but also on liver function.

Assessment of tumor extension is critical for defining staging and treatment strategy and needs to be complemented by an assessment of liver function. The current EASL–EORTC GP guidelines endorse the Barcelona-Clínic Liver Cancer (BCLC) classification. It includes prognostic variables related to tumor status, liver function and health performance status along with treatment-dependent variables.

Early HCC (BCLC stage A) is defined in patients presenting single tumors > 2 cm or 3 nodules < 3 cm of diameter, ECOG-0 and Child–Pugh class A or B. Median survival of patients with early HCC reaches 50–70% at 5 years after resection, liver transplantation or local ablation in selected candidates.

Intermediate HCC (BCLC stage B): Untreated patients at an intermediate stage – BCLC B class (multinodular asymptomatic tumors without an invasive pattern) present a median survival of 16 months or 49% at 2 year. Chemoembolization extends the survival of these patients to a median of up to 19–20 months.

Advanced HCC (BCLC stage C): Patients with cancer related-symptoms (symptomatic tumors, ECOG 1–2), macrovascular invasion (either segmental or portal invasion) or extrahepatic spread (lymph node involvement or metastases) bear a dismal prognosis, with expected median survival times of 6 months, or 25% at 1 year. This outcome varies according to the liver functional status and other variables. The only available systemic treatment option to date is the TK inhibitor Sorafenib which improves overall survival in the Western population by about 3 months.

Reference:

From emerging phase I to failing phase III trials

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Hepatocellular carcinoma (HCC) is a major health problem. Mortality owing to liver cancer has increased in the past 20 years, with recent studies reporting an incidence of 780,000 cases/year. Most patients with HCC are still diagnosed at intermediate or advanced disease stages, where curative approaches are often not feasible. Among the treatment options available, the molecular targeted agent sorafenib is able to significantly increase overall survival in these patients. Afterwards, up to 7 randomized phase III clinical trials investigating other molecular therapies in the first-line and second-line settings have failed to improve survival. Potential reasons for this include lack of predictive biomarkers of response, intertumor heterogeneity and problems in trial design. The most frequent molecular alterations reported by exome sequencing in this tumors include mutations in the TERT promoter, CTNNB1, TP53 and ARID1A along with other amplifications (FGF19, VEGFA) or homozygous deletions (p16). This knowledge points toward specific drivers as candidate for druggable therapies. Thus, progressive implementation of proof-of-concept and enrichment might improve results in clinical trials testing of molecular targeted agents. In parallel, recent appealing data is emerging in phase I–II studies testing immunotherapy, such as checkpoint anti-PD1 inhibitors in HCC. Data from future phase III trials is eagerly awaited.
Assessment of tumor response in hepatocellular carcinoma

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Tumor response in oncology is usually measured according to Response Evaluation Criteria in Solid Tumors (RECIST). The RECIST guideline defines standard measurement methods for converting radiology image observations into a quantitative and statistically tractable framework for measuring the response of tumor size to therapy. The RECIST model – developed in 2000 and revised in 2009 with the publication of the version 1.1 – was designed for evaluation of cytotoxic agents. It offers a simple approach to determining anatomic size and lesion changes during treatment as an indicator of response. However, it does not address measures of antitumor activity other than tumor shrinkage. The RECIST panel acknowledged that amendments to the guideline could be needed for the evaluation of cytostatic agents as well as for the assessment of specific tumors or anatomic sites presenting unique complexities. In the setting of hepatocellular carcinoma (HCC) patients receiving liver-directed or molecular targeted therapies, statistically significant and clinically meaningful improvements in overall survival occurred in the absence of substantial tumor reduction as assessed by using standard RECIST. Given the poor correlation observed between response evaluation by conventional metrics and overall survival, a group of experts in HCC clinical trials convened by the American Association for the Study of Liver introduced the concept of viable tumor in HCC response assessment, and proposed specific amendments to standard RECIST. The resulting criteria were named modified RECIST (mRECIST) for HCC. The mRECIST criteria have been endorsed by several scientific societies and organizations and have been increasingly used in HCC research. The present article summarizes the key recommendations of mRECIST for tumor response assessment and performs a critical appraisal of the available data on the use of mRECIST in HCC clinical trials.
Molecular pathogenesis and treatment of intrahepatic cholangiocarcinoma

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Intrahepatic cholangiocarcinoma (ICC) comprises one of the most rapidly evolving cancer types. An underlying chronic inflammatory liver disease, which precedes liver cancer development for several decades and creates a pro-oncogenic microenvironment that frequently, impairs progress in therapeutic approaches. Depending on the cellular target of malignant transformation, a large spectrum of molecular and morphological patterns is observed. As such, it is crucial to advance our existing understanding of the molecular pathogenesis of ICC, particularly its genomic heterogeneity, to improve current clinical strategies and patient outcome. This has been achieved for other cancers, such as breast carcinoma, facilitated by the delineation of patient subsets and of precision therapies. In ICC, many questions persevere as to the evolutionary process and cellular origin of the initial transforming event, the context of tumor plasticity and the causative features driving the disease. Molecular profiling and cyto-/histological techniques have begun to underline persistent alterations that may trigger inherited drug resistance (a hallmark of liver, biliary tract and pancreatic tumors), metastasis and disease recurrence. However, a complex issue remains interpreting the heterogeneous pool of genome aberrations in the tumor genotype, in which a causal alteration may influence, for example, the therapeutic response. In this review, we will focus on the key molecular achievements that are currently advancing the characterization and stratification of ICC. We will discuss current clinical practice and how genomic achievements may advance diagnosis and therapy as well as ultimately improve patient outcome.

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Surgical management of hepatocellular carcinoma and cholangiocarcinoma

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Hepatocellular carcinoma

Liver resection: according to the Barcelona guidelines, should be performed for single tumours in patients without portal hypertension and with normal bilirubin. These guidelines are being challenged in tertiary care centres but careful examination of the literature reveals that generally, the traditional contraindications make sense:

Portal hypertension: the contraindication relates to the poor long-term results of liver resection in these patients. Studies challenging the 10 mmHg portal-venous gradient limit claim the low early mortality of surgery, but reproduce the same late mortality figures than in the published BCLC experience. The limit has to be interpreted as an incentive to seek for alternative (less invasive: percutaneous; or more radical: OLT) means of local control of the HCC.

Multiple tumours: the limit here is again be interpreted as an incentive to compare resection to more radical or less invasive means of local control of the HCC, as the probability of recurrence (under the form of hepatic metastases or de novo tumours) are much higher than for single tumours. Similar to portal hypertension, the literature on the results of resection for multiple tumours shows long-term recurrence and survival results equivalent to the BCLC experience. Exceptions are possible, and indeed should be pursued in specialized centres, and cases in which better local control of the disease is offered by resection do exist (e.g. peripheral lesions, large lesions).

Vascular invasion: signs a high probability of extrahepatic and intrahepatic multifocal disease in which alternatives for local control are less invasive (such as radioembolisation) or of systemic treatment (sorafenib) are more effective. However, some patients with slowly progressive disease who are diagnosed at an advanced yet resectable stage benefit from this form of local control (preserved functional reserve, good general conditions). Such patients, often selected by a referral bias in specialized surgical centres, represent the most fertile field in which exceptions to the BCLC guidelines should be explored by cohort studies for tentative prognostic factors or direct comparison to alternatives (radioembolisation).

Extrahepatic spread: there are only very anecdotal cases of successful survival after resection. They should be taken as a memento that some patients do have an exceptional clinical course and part of our craft is to recognise them and adapt our treatment accordingly.

Liver Transplantation:
The traditional Milan criteria (up to 3 nodules up to 3cm, or single tumour < 5 cm, without vascular invasion and extrahepatic spread) can be carefully expanded by including tumours of larger size (Metroticket criteria: “up to 7”, without vascular invasion, or TTV < 115 cm³ and AFP < 400 are being validated. A waiting from 3 to 6 months and response to bridging treatments are additional tools to select patients at low risk of recurrence.
Cholangiocellular carcinoma

*Intrahepatic cholangiocarcinoma* is generally treated by surgical resection, and the limits of resectability are being pushed back by the use of neoadjuvant chemotherapies such as Gemox or Folfirinox, possibly with the addition to a monoclonal antibody. In patients with cirrhosis impeding resection, the outcomes of liver transplantation are being explored: recent initial evidence suggests that recurrences are for single tumours < 2 cm.

For *perihilar cholangiocarcinoma* liver resection, a very challenging operation, has become routine in hepatobiliary units, and results have improved thanks to the diffusion of well-codified surgical techniques. Liver transplantation is carried out with competitive results in some units, but so far, the reproducibility of the results at the Mayo clinic, although confirmed in a review of the UNOS experience, has been hampered by the complexity of the original protocol and by the difficult case selection in centres with a lower patient load.

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POSTER ABSTRACTS

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Comparative study between serum and salivary cortisol levels in order to assess adrenal cortisol insufficiency in patients with liver cirrhosis

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Introduction: As a result of impairments in the synthetic function of the liver, total serum cortisol measurements are invalid in patients with liver cirrhosis. This is due to the prevalence of hypoalbuminemia and decreased levels of cortisol-binding globulins in these patients. Salivary cortisol concentrations are an accurate reflection of free cortisol levels in non-cirrhotic patients because the unbound proportion of cortisol in the blood freely diffuses into the saliva, and thus represents the amount that is transported to target tissues in the body.

The aims was to evaluate salivary cortisol, serum total cortisol, calculated free cortisol and the prevalence of cortisol insufficiency using salivary and serum assays.

Methods: Fasting serum cortisol levels were assessed at 8:00 am using the ADIVA Center auto-analyzer together with salivary cortisol levels using the Salimetrics Salivary assay kit. Pituitary hypoadrenalism was excluded in patients with total cortisol levels exceeding 4 micrograms/dl.

Calculated free cortisol was estimated directly using the Coolens formula.

Results: Salivary cortisol and calculated free cortisol were correlated with adrenal function in cirrhotic patients to a significantly greater extent than serum total cortisol. Salivary cortisol was significantly low in 60% of patients, yet not low enough to diagnose adrenal insufficiency, indicating relative adrenal insufficiency.

Discussion/Conclusion: Salivary cortisol was correlated to a significantly greater extent than calculated free cortisol and serum total cortisol, signifying that salivary cortisol is more accurate and more strongly related to the free active proportion of cortisol, thus providing a better reflection of adrenal function in patients with liver cirrhosis.

Calculated free cortisol was of limited usefulness and should be used with caution. Measuring salivary cortisol in patients with low corticosteroid-binding globulin levels or hypoalbuminemia is simple, and provides a direct reliable and practical assessment of free cortisol concentrations during critical illnesses.

Relative adrenal insufficiency in liver cirrhosis is more prevalent than previously thought as current methods of diagnosis are not reliable.
Presepsin a new diagnostic and prognostic marker in spontaneous bacterial peritonitis

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Introduction: Spontaneous bacterial peritonitis is the most frequent and life threatening bacterial infection in cirrhotic patients with ascites. Presepsin (sCD 14-ST) has been identified as new marker whose levels increase in the blood of patients with bacterial infections and sepsis.

Aim of work: To evaluate diagnostic and prognostic value of presepsin in patient with SBP.

Materials and methods: This study was conducted on 30 cirrhotic patients with ascites. 10 of them had sterile ascites (Group I) and 20 had SBP (Group II). Other bacterial infections were excluded.

Serum presepsin levels were measured in all patients (T0), then repeated in group II 10 days after start of treatment (T1). We used pathfast assay system to detect levels of presepsin. A value > 377 pg/ml was considered positive as indicated by manufacturers.

Results: Serum presepsin levels at (T0) were significantly higher in patients with SBP (mean level was 3473.0 ± 1911.6 pg/ml, median level was 4621.5 pg/ml) than in those with sterile ascites (mean level was 148.6 ± 34.9 pg/ml, median level was 145.0 pg/ml), p = 0.000.

Serum presepsin levels in (Group II) at (T1) were significantly lower than (T0) in (Group II) (mean levels were 673.4 ± 245.0, 3473 ±1911.6, median levels were 705.0, 4621.5 in T1 and T0 respectively), p = 0.000.

Mortality rate among patients with SBP (Group II) was 20% (4 cases out of 20). Serum presepsin levels were significantly higher in dead cases than in resolved cases (median level was 4631, 3915 pg/ml in dead and resolved cases respectively), p = 0.049.

Conclusion: Presepsin is a new additional diagnostic marker for early diagnosis of SBP in cirrhotic patients as it showed 100% sensitivity in detecting SBP. Also it showed significant prognostic value as its levels were significantly correlated with clinical outcome of SBP patients. Greater number of patients is necessary to confirm these data.
Endoscopic variceal ligation followed by argon plasma coagulation versus endoscopic variceal ligation alone: A randomized controlled trial

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Introduction: After the first attack of acute variceal hemorrhage patients have a very high risk of recurrent variceal bleeding and death. Rebleeding rates after endoscopic variceal ligation (EVL) are high, thus current recommendation is to combine non-selective beta-blockers (NSBB) to EVL but side effects and relative contraindications to NSBB are common and hinder treatment or require discontinuation in 15-20% of cirrhotic patients. Induction of fibrosis of distal esophageal mucosa using argon plasma coagulation (APC) may suppress capillary proliferation and invasion of perforating veins thus decreasing esophageal varices (EV) recurrence.

Methods: This study included 40 subjects with post viral liver cirrhosis and previous history of upper gastrointestinal bleeding. They were submitted for EVL and obliteration of varices. Then patients were randomly assigned to either APC (group 1) or just observation (group2).

Results: During 2 years follow up 20% of subjects in group 1 experienced EV recurrence but no one needed rebanding. In group 2, 68.4% experienced EV recurrence (p = 0.002) and 63.2% underwent rebanding (p < 0.001). (Figure) No subject in group 1 experienced rebleeding during the 2 year follow up, while 10.5% of subjects in group 2 experienced rebleeding from EV (p = 0.231). No subject in both groups showed development of gastric varices. 3 subjects in group 1 and 4 subjects in group 2 showed development of new severe portal hypertensive gastropathy (p = 0.695).

Conclusions: APC can decrease the risk of recurrence, the need for rebanding of EV and the frequency of endoscopic follow up after EVL. APC after EVL may be recommended in secondary prophylaxis against esophageal variceal bleeding especially in those who have contraindications, intolerant or incompliant to NSBB.
Figure: Kaplan-Meier analysis of patients without need for rebanding curves
Adiponectin: A differential maker between steatosis and steatohepatitis

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Non-alcoholic fatty liver disease (NAFLD) is becoming a worldwide public health problem. It represents a spectrum of diseases ranging from simple steatosis to steatohepatitis (NASH). Adipocytokines refer to adipocyte-derived biologically active molecules TNF-α, leptin and adiponectin, all of which have been implicated in the development of hepatic inflammation and fibrosis in NAFLD patients. This new hormone differs from its predecessors in important ways. Production and concentration of this hormone are decreased in obese patients, while all adipose-derived hormones are increased. It is possible that adiponectin expression is activated during adipogenesis. Adiponectin may exert a hepatic protective effect.

The aim was to evaluate the level of adiponectin as a differential marker between steatosis and steatohepatitis.

Subjects and methods: The study included 20 NAFLD patients, 20 NASH patients (confirmed by biopsy) and 20 control subjects, matched for age, sex and BMI. All subjects underwent an abdominal ultrasonography and routine biochemical evaluation: liver function ALT & AST, lipid profile (cholesterol, triglycerides, HDL-C, LDL-C), CRP and adipocytokines (TNF-α, IL-6, leptin and adiponectin).

Results:
1. Plasma adiponectin levels were significantly lower in NAFLD patients than in the control group (6.15 ± 1.39 ng/ml vs. 12.03 ± 3.46 ng/ml).
2. Adiponectin was significantly lower in NASH patients than in NAFLD patients (1.80 ± 0.96 ng/ml vs. 6.15 ± 1.39 ng/ml).
3. Leptin levels were significantly higher in NAFLD patients than in NASH patients (69.50 ± 18.70 ng/ml vs. 43.20 ± 6.93 ng/ml).
4. The adiponectin ROC curve showed an AUROC curve in the NAFLD group (0.945, p = 0.049). In the NASH group, this was 0.995, p = 0.007.
5. TNF-α and IL-6 were significantly higher in the NASH group than in the NAFLD group (79.25 ± 13.89 pg/ml vs. 41.25 ± 17.53 pg/ml) and (110.20 ± 55.34 pg/ml vs. 43.85 ± 16.13 pg/ml).
6. Plasma adiponectin levels were inversely correlated with TG (r = -0.368, p = 0.111), GOT (r = -0.037, p=0.878) and GPT (r = -0.022, p = 0.926) in the NAFLD group and positively correlated with cholesterol (r = 0.317 p = 0.174) and TG (r = 0.042 p = 0.861) in the NASH group.

Conclusion:
1. These data show that low circulating adiponectin plays a role in the pathogenesis of NAFLD, and hypoadiponectinemia was found to be a feature of NASH.
2. Adiponectin was found to be a non-invasive differential marker between NAFLD and NASH.
Serotonin: Is it a marker for the diagnosis of hepatocellular carcinoma in cirrhotic patients?

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Hepatocellular carcinoma (HCC) is the third most frequent cause of cancer mortality among men worldwide. Serotonin is biogenic amine, ligand for family of 5-HT receptors reflect the diversity of serotonergic actions. Majority of serotonin in body 90% synthesised by enterochromaffin cells of the gastrointestinal tract and exported to various sites. Serotonin regulate blood flow and vascular tone at portal and sinusoidal levels, serotonin mitogen for hepatocytes and promotes liver regeneration. 5-HT emerging as mediator of different pathological conditions (double edged sword). It contributes to liver fibrosis, mediates oxidative stress in non-alcoholic steatotic hepatitis and aggravates viral hepatitis, these conditions involved in tumorgenesis of hepatocellular carcinoma (HCC). Impaired metabolic function in liver cirrhosis and slow uptake and storage of serotonin by the platelets is sequelae of kinetic change of serotonin transport mechanisms or abnormal serotonin release from dense granules of activated platelets condition defined “platelet exhaustion”, contributes to elevated plasma serotonin which may facilitate tumor growth of primary liver hepatocellular carcinoma.

Aim: Was to determine whether serotonin is a marker for the diagnosis of hepatocellular carcinoma in cirrhotic patients.

Methods: Patients were classified into 2 groups; 45 patients with cirrhosis only and 30 patients with cirrhosis and HCC. 10 healthy subjects was taken as controls. Patients underwent; full history taking, clinical examination, abdominal ultrasonography. Laboratory methods include SGOT, SGPT, GGT, bilirubin, alkaline phosphatase, total proteins, albumin, CBC, prothrombin, INR, APRI score, Child-Pugh score, MELD score, αFP and serum serotonin.

Results: Plasma serotonin was significantly higher in patients group with cirrhosis with a median level 119.4 ng/ml than in control group showed median value of 51.5 ng/ml p < 0.001. Also a significance difference between cirrhosis & HCC group with median value 478.35 ng/ml than control group and cirrhosis group p < 0.001 was found.

Conclusion: Plasma serotonin level was significantly higher in patients with cirrhosis and HCC than in those with cirrhosis only and it was involved in tumorigenesis of hepatocellular carcinoma.
Lipocalin: A novel diagnostic marker for hepatocellular carcinoma in chronic liver disease patients in Egypt

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Hepatocellular carcinoma most prevalent life-threatening human cancers with etiological factors chronic viral hepatitis B and C infections. Tumor cell dispersion relies on the loss of homotypic cell-cell adhesion. Invasion through basement membrane and interstitial extracellular matrix another key event for metastatic progression, which requires the action of a series of proteolytic enzymes named matrix metalloproteinases, secreted by tumor cells that enhance tumor invasiveness and metastasis. TIMPs are dominant inhibitors of MMPs and able to control MMP-mediated ECM breakdown by binding active forms of MMPs. Lipocalin-2 known as neutrophil gelatinase associated lipocalin promotes matrix degradation and tumor progression.

**Aim:** Evaluate importance of lipocalin for diagnosis HCC in Egyptian chronic liver disease patients.

**Subjects and methods:** 50 patients and 25 controls. (G-1) 25 hepatitis C, (G-2) 25 HCC on top of hepatitis C. The following done: schistosoma antibodies, ASAM, LKM-1, ANA AKA and CBC. Hepatitis B surface antigen, hepatitis C antibodies AFP, cupper and zinc, matrix metalloprotnase-9, TIMP-1 and neutrophil gelatinase-associated lipocalin.

**Results:** Median value of MMP-9 level in G-1 (206 µg/l) significantly higher than G-2 (100 µg/l) and G-3 (49 µg/l) \( p < 0.001 \). TIMP-9 median value G-1 (48 µg/l) significantly lower than G-2 (54 µg/l) and G-3 (113 µg/l) \( p < 0.001 \). Lipocalin-2 median levels significantly higher in G-1 (389 ng/ml) than G-2 (166 ng/ml) versus G-3 (60 ng/ml) \( p < 0.001 \). Lipocalin-2 associated with increasing lobular inflammation, ballooning and fibrosis with MMP-9 has an important role in pathogenesis of liver cirrhosis and HCC.

**Conclusion:** Elucidated predictive value for MMPs, TIMPs, for progression metastasis of hepatocellular carcinoma. Liver cell impairment alter metabolism of trace metals as zinc and copper, with possible relationship of these changes to pathogenesis of chronic liver disease. Lipocalin-2 can be used as future diagnostic marker with better sensitivity and specificity than MMP-9 for the progression of hepatocellular carcinoma.

**Key words:** Lipocalin-2, MMP-9, TIMP-1, Cu, Zn, HCC
Vitamin D inhibits development of liver fibrosis in animal model but cannot ameliorate established cirrhosis

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²Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel
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⁵Faculty of Medicine, Hebrew University, Jerusalem, Israel

Background and aims: 1,25(OH)₂D₃, the active form of vitamin D has anti-proliferative and anti-fibrotic effect on hepatic stellate cells. Our aim was to investigate the potential of 1,25(OH)₂D₃ to inhibit the development of liver fibrosis and to ameliorate established fibrosis in vivo.

Methods: The anti-fibrotic effect of 1,25(OH)₂D₃ was investigated in thioacetamide (TAA) model (as a preventive treatment and as a remedial treatment) and in a bile duct ligation model. In the preventive model, rats received simultaneously intra-peritoneum injection of TAA and/or 1,25(OH)₂D₃, for 10 weeks. In the remedial model, rats were treated with TAA for 10 weeks and then received 1,25(OH)₂D₃ or saline for eight weeks. Fibrotic score was determined by Masson staining. Collagen I, α-smooth muscle actin (αSMA), tissue inhibitor of metalloproteinase (TIMP1), platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β) expression were measured by western blot analysis and real-time PCR. Hypercalemia was detected by chemistry measurements.

Results: Preventive treatment of 1,25(OH)₂D₃ significantly suppressed liver fibrosis both macroscopically and microscopically and significantly lowered the fibrotic score of TAA+1,25(OH)₂D₃ group compared to the TAA group. 1,25(OH)₂D₃ significantly inhibited expression of PDGF and TGF-β by ~50% and suppressed the expression of collagen Iα1, TIMP1 and αSMA by ~3-, 2-, 3-fold, respectively. In contrast, 1,25(OH)₂D₃ was inefficient to ameliorate established liver fibrosis. Furthermore, administration of 1,25(OH)₂D₃ to BDL rats, led to high mortality rate probably caused by hypercalemia.

Discussion/Conclusion: 1,25(OH)₂D₃ may be considered as a potential preventive treatment in an in-vivo model but failed to ameliorate established cirrhosis.
Comparison of performance of transient elastography with liver biopsy in patients with primary biliary cirrhosis: Case series

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Introduction: Transient elastography is a novel non-invasive method recently used to determine the fibrosis grade in patients with chronic hepatitis B and C. Its use in non-viral chronic liver diseases like primary biliary cirrhosis and autoimmune hepatitis has not been clearly defined yet. In this case series we tried to show the correlation of transient elastography (FibroScan) with liver biopsy in patients with primary biliary cirrhosis.

Methods: 10 patients with primary biliary cirrhosis who had liver biopsies taken previously were evaluated with transient elastography.

Results: Female/male ratio was 8/2. Mean age of the patients was 53.1 ± 8.1 years. Patients' demographic data and laboratory results are shown in Table 1. In all but one patient numbered as 1 liver biopsy and transient elastography showed good correlation.

Discussion/Conclusion: Liver biopsy is not a requisite for diagnosis of primary biliary cirrhosis but determination of the fibrosis level may provide valuable information about the patient’s prognosis and may aid in treatment decisions. Being non-invasive and practical tool transient elastography can be useful in evaluation of grade of liver fibrosis in patients with primary biliary cirrhosis.

Table 1: Demographic data and laboratory results of patients with primary biliary cirrhosis.

<table>
<thead>
<tr>
<th>No</th>
<th>Initials</th>
<th>Gender</th>
<th>Age</th>
<th>AST U/l</th>
<th>ALT U/l</th>
<th>ALP U/l</th>
<th>GGT U/l</th>
<th>T.bil/D.bil mg/dl</th>
<th>Alb g/dl</th>
<th>AMA</th>
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<th>inr</th>
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<td>695</td>
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<td>59</td>
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<td>265</td>
<td>0.9/0.6</td>
<td>4</td>
<td>+</td>
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<td>F</td>
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<td>1.6/1.2</td>
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<td>M</td>
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<td>1.3/0.9</td>
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<td>0.6/0.2</td>
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</table>

Discussion/Conclusion: Liver biopsy is not a requisite for diagnosis of primary biliary cirrhosis, but determination of the fibrosis level may provide valuable information about the patient’s prognosis and may aid in treatment decisions. Being a non-invasive and practical tool, transient elastography can be useful in evaluation of grade of liver fibrosis in patients with primary biliary cirrhosis.
Analysis of CD4+ T-cell response to a novel alpha-fetoprotein derived epitope in hepatocellular carcinoma patients

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Introduction: Alpha-fetoprotein (AFP) is a tumour associated antigen in hepatocellular carcinoma (HCC) and is a target for the development of a cancer vaccine. Four immunodominant AFP-derived HLA-A*0201-restricted peptides have been identified and the administration of these peptides with an adjuvant has stimulated AFP-specific cytotoxic T lymphocyte (CTL) responses in HCC patients. However, no AFP-derived CD4 T-cell epitope has been reported and the status of AFP-specific CD4+ T-cell responses in HCC patients is not fully understood.

Methods: We analyzed the ability of CD4+ T cells to recognize an HLA-DR-restricted AFP-derived epitope in 41 HCC patients and 24 non-HCC control patients using intracellular cytokine assays for IFN-gamma.

Results: We identified an AFP derived CD4+ T-cell epitope that is recognized by circulating lymphocytes from HCC patients in association with HLA-DR. The absence of detectable responses in healthy donors and patients with chronic liver disease suggested that AFP-specific CD4+ T-cells in the responder patients had been previously expanded in vivo in response to the tumour. The anti-AFP CD4+ T-cell response was only detected in HCC patients with normal or mildly elevated serum AFP levels who were in the early stage of disease.

Discussion/Conclusion: We reported a dominant role of 364-373 region of AFP antigen in the induction of specific CD4+ T-cell responses in HCC patients. The identified epitope was presented to specific CD4+ T cells by HLA-DR molecules. Identification of a larger number of AFP-derived CD4+ T-cell epitopes and analysis of the CD4+ T-cell response to these epitopes in cirrhotic patients and HCC patients may cast a light on the role of the AFP-specific CD4+ T-cell response in disease progression and may be used as a prognostic/diagnostic marker and may contribute significantly to the development of AFP-based vaccines to HCC.
Managing spontaneous bacterial peritonitis in liver cirrhosis: A local general hospital experience

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Introduction: Spontaneous bacterial peritonitis (SBP) carries high mortality. Our aim was to identify the factors that affect the mortality due to SBP in our local hospital.

Methods: A retrospective study of all cases of SBP admitted to our local district hospital over 7 year period. We excluded cases with malignant ascites, secondary peritonitis, and no clear diagnosis of SBP. Results were analysed statistically using SPSS software.

Results: Twenty-one cases with SBP were identified. The median age was 47 years for survivors and 68 years for non-survivors. Seven cases (33%) were Child-Pugh grade B and 14 (67%) were Child Pugh grade C. The median MELD score was 40. Eight cases (38%) presented with painless ascites and only 2 (10%) had abdominal pain. Seven cases (33%) only had fever and raised White cell count in blood. Eleven cases (52%) had raised neutrophils count > 250/mm³ in the ascetic fluid and ascetic fluid culture was positive in 16 (76%) cases.

The in-patient mortality rate was 57%. The age was significantly higher (p < 0.05) in the non-survivor group. Creatinine level > 100 mmol/l at time of presentation with SBP and developing hepatorenal syndrome were associated with high mortality rate (p < 0.05). There was no statistical difference between the two groups with regards to sex, having albumin infusion, timing of antibiotics treatment, timing of ascetic tapping and whether SBP was hospital acquired or not.

Discussion/Conclusion: The mortality rate in our hospital was (57%). In our study, the median MELD score was > 40. Developing hepatorenal syndrome and high creatinine at SBP presentation were the main mortality predictor with mortality of 90%.
The prevalence of hepatitis B seromarkers and hepatitis C antibodies in blood donors in Basra, Iraq

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³Director of the Department of Public Health, Basra, Iraq

Introduction: Transfusion caused hepatitis remains a major problem in Iraq. Therefore, testing for hepatitis B surface antigen (HBsAg), antibodies to hepatitis B core antigen (anti-HBc), and antibodies to hepatitis C antigen (anti-HCV) is very important to prevent transfusion caused hepatitis. The objective of this study was to establish presence of hepatitis B and C virus seromarkers among blood donors as a foundation for safe blood transfusion in Iraq.

Methods: A retrospective cohort study was conducted in the blood transfusion unit in Basra, Iraq from 1st of January to 31 of December in 2013. All blood donors during the study period were included in the study. Blood samples were collected and were tested for HBsAg, anti-HBc, anti-HCV using the standard laboratory techniques.

Results: A total of 69,915 blood donors were enrolled for the study. The prevalence of HBsAg and anti-HBc were very low at 0.22% (150 donors) and 2.29% (1600 donors) respectively. There was no significant difference between males than females (p = 0.28). The prevalence of anti-HCV was 0.12%. A total of 1475 (2.11%) donors had anti-HBc antibodies as the only serological evidence of hepatitis B virus infection.

Discussion/Conclusion: The prevalence of Hepatitis B and C among blood donors is very low in Basra. Around 2% of blood donors had anti-HBc as the only serological evidence of HBV infection. Inclusion of anti-HBc in routine screening of blood donors in Iraq should be encouraged. This is the first large population study of its kind in Basra, Iraq.
Serum chitotriosidase levels in malignant diseases of liver: Is it a new tumor marker?

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Aim: In our previous study (J Cancer Treat Res. 2014;2[1]:5–8), we found that serum chitotriosidase levels were significantly higher in HCV related liver diseases especially in patients with hepatocellular carcinoma (HCC). Based on these results, we aimed to study serum chitotriosidase levels in malignant liver diseases.

Material and method: A total of 149 patients were included in this study. Of those, 62 patients had HCC (clinically, radiologically and histopathologically confirmed), 50 patients had liver metastasis due to primary malignancies (clinically, radiologically and histopathologically confirmed) and 37 patients were in control group (C group). Serum samples of the patients were collected at the time of diagnosis and stored at -80 degrees centigrade. Serum samples were tested using a commercial ELISA kit (CircuLex Human Chitotriosidase). Age, gender, etiology of cirrhosis (HBV, HCV, other), Child-Pugh scores, MELD scores, prothrombin times, platelet counts, levels of AFP, ALT, AST, ALP, GGT, number of tumors and portal vein thrombosis of the patients with HCC were recorded. The association between these variables and serum chitotriosidase levels were investigated in this study. Cut-off points were determined using ROC analysis.

Results: Age and gender ratio of the patients were similar between three groups. Serum chitotriosidase levels of the patients in C group were lower compared with other groups (metastasis group and HCC group) and this difference was found statistically significant (p < 0.000353). Mean serum chitotriosidase levels were 214,380 ng/ml (13,00–827,82 ng/ml) in C group, 439,575 ng/ml (13,86–4186,40 ng/ml) in metastasis group and 428,735 ng/ml (13,18–4005,87 ng/ml) in HCC group. Metastasis group and C group were compared with ROC analysis and cut-off point was determined as 311.8 ng/ml (p = 0.0001, 95% CI, sensitivity 72%, specificity 75.68%). HCC group and C group were compared with ROC analysis and cut-off point was determined as 240.93 ng/ml (p < 0.0001, 95% CI, sensitivity 74.19%, specificity 67.57%). (95% CI: PPD 74.19%, NPD 67.57%). In HCC group, there was no significant association between serum chitotriosidase levels and tumor diameter, number of tumors, portal vein thrombosis, AFP, Child-Pugh score, MELD score, etiology of cirrhosis.

In conclusion: Serum chitotriosidase can be a tumor marker to distinguish malignant liver diseases from benign liver diseases. It can be used as a screening test in HCC like AFP.

Key words: hepatocellular carcinoma, chitotriosidase
An analysis of HBV and HCV infections in patients undergoing hemodialysis in a community hospital in Lahore, Pakistan

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Lahore General Hospital, Lahore, Pakistan

Introduction: HBV and HCV infections are prevalent in the community and expected to be common in chronic hemodialysis patients. The prevalence of chronic hepatitis ranges from 5% to 17% and correlates with the length of dialysis. This real world audit aimed to find the prevalence of HBV and HCV infections in chronic hemodialysis patients and the correlation with the duration of dialysis.

Material and methods: A retrospective, cross-sectional study of 171 registered patients from 2009–2014 was carried out at a single community hospital in Lahore. Data on biological information, duration of dialysis, cause of ESRD, comorbidity conditions, and vaccination status for HBV were collected. Viral serology was checked using rapid ICTs.

Results: 103 (60.23%) males and 68 (39.77%) females with a mean age of 43.82 (SD 14.44) presented with hypertension (58.5%) and DM (33.2%) as the common causes of CKD. Polycystic kidney disease, as well as drug-induced and postpartum hemorrhage, was much less frequent in the cohort. 25% of patients had IHD as a major comorbidity. Only 54 (31.57%) were vaccinated for HBV. 118 patients (69%) were found to have HBV and HCV infections, of which 94 (54.97%) tested positive for HCV and 19 (11.11%) for HBV, while 5 (0.029%) suffered from both. Out of 94 HCV-positive patients, 25 were vaccinated for HBV. 59 (34.5%), 55 (33.5%), 20 (11.7%), 14 (8.2%), 20 (11.7%) and 3 (1.8%) patients were found to be in the 6th month, 1st year, 2nd year, 3rd year, 4th year and 5th year of dialysis respectively, and the frequency of HCV infection was 23 (38.98%), 27 (49.09%), 12 (60%), 14 (100%), 17 (85%) and 1 (33.33%), respectively.

Conclusion: Blood borne infections like HBV & HCV are common in chronic hemodialysis patients in resource-poor countries with a low HBV vaccination rate. Furthermore, seroprevalence for HCV increases sharply with the duration of dialysis, indicating cross-infection in dialysis units.
36 months follow-up to evaluate survival patterns in patients with hepatocellular carcinoma since the initial diagnosis

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Lahore General Hospital, Lahore, Pakistan

Introduction: Evaluate the survival pattern in patients with HCC after 36 months follow-up.

Material and methods: A prospective cross-sectional ongoing study conducted in 140 patients of HCC presenting at GI departments of Lahore General Hospital and Sheikh Zayed Hospital, Lahore from January–April 2012 and followed for 36 months to check survival, outcome of an intervention, and event leading to death.

Results: In this cohort, median age at the time of diagnosis of HCC was 57 years (range: 30–60) with sex ratio of 71:29. At 36 months follow up, 3 patients (2.14%) are alive, and 137 patients (97.8%) died. Etiological cause of CLD and HCC has been 94 (67%), 20 (14%) and 17 (12%) for HCV, HBV and coinfection respectively. 9 (6.4%) patients had negative viral serology. Amongst the patients suffering from HCV-related HCC, at 36 months follow up 2 (2.12%) are alive and 92 (97.8%) have died and the terminal event was UGIB in 35 (37.23%), Ascites in 19 (20.12%), LGIB in 12 (12.76%) and PSE in 28 (29.78%) patients. HBV-related HCC patients were 20 (14%), 01 (5%) is alive and 19 (95%) died. In this cohort of patients, an UGIB in 7 (35%), Ascites in 5 (25%), LGIB in 2 (10%) and PSE in 5 (25%) patients was the terminal event. At diagnosis, 107 (76.5%) patients received a specific therapy, and 33 (23.5%) did not. Amongst the treated, 57 (53%) underwent surgical resection and none are alive at 36 months of follow up, 38 patients (35.5%) received oral sorafenib and none are alive, TACE has been done in 7 (6.5%) and none are alive, RFA was done in 2 (1.8%) and 1 is alive, liver transplant in 3 patients (2.8%), two are alive and stable at 36 months follow-up.

Conclusion: HCC is a sinister diagnosis with grave prognosis.
Hepatitis C virus infection in Bulgarian dialysis unit

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Introduction: Despite the reduction of hepatitis C prevalence after recognition of the virus and testing of blood products, hemodialysis patients still comprise a high risk group. Hepatitis C virus (HCV) infection in hemodialysis patients runs a “silent” clinical course and laboratory tests are essential for diagnosis. The objective of this study, the first of its kind in our country, was to assess more precisely the prevalence of HCV infection among dialysis patients using a combination of HCV antibody testing and HCV RNA detection.

Methods: In this both cross-sectional and longitudinal study we investigated the patients undergoing chronic hemodialysis at the dialysis unit of University Hospital, Plovdiv, Bulgaria, between July 2013 and November 2014. On enrollment of the patients HCV RNA and anti-HCV were detected by reverse transcription-polymerase chain reaction (PCR) and forth generation ELISA, respectively. The patients with negative HCV results were tested again at least twice, at an interval of ≥ 6 months (up to 12 months). HCV RNA was tested in plasma and peripheral blood mononuclear cells (PBMCs) using commercial real-time PCR assays.

Results: Ten out of 68 patients (prevalence 14.7%) were with viremia – HCV RNA(+)/anti-HCV(-), including one patient with acute infection. Another four (5.9%) were anti-HCV(+), but HCV RNA(-), probably as a result of self-limited cleared infection. If these patients were screened only for anti-HCV, which is the common practice in Bulgaria, they would have been erroneously diagnosed as infected and HCV prevalence would have been incorrectly higher -20.6%. The dialysis vintage significantly correlated with HCV infection (p = 0.02; OR = 1.01, 95% CI). Blood transfusions were not a risk factor for HCV infection, probably because of the small number of cases.

No occult HCV infection was detected (HCV RNA[-] in PBMCs) in 38 patients tested.

Discussion/Conclusion: The findings of our study confirm the results of previous works that the combination of serological and molecular methods allows for a more accurate estimation of prevalence of HCV infection. Further longitudinal studies including a larger number of patients are required to determine whether this approach could be applied to the entire Bulgarian dialysis population.
Biologic abnormality in B-cell lymphoma associate with hepatitis C virus infection

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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 hematological parameters.

Results: The frequency of HCV virus infection was detected in 13.56% of B NLH 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 myeloma and 3 (8.57%) acute lymphoblastic leukemia. The age of patients with HCV infection and B NLH was between 18 and 84 years, with an average of 55 years, which is not significantly different from the general B NLH group. Sex distribution favors females 62.85% and 54.28% of patients was from urban areas. (51.42%) presented at least 1 extrahepatic laboratory abnormality, including mixed cryoglobulinemia (38.8%), anemia (33.3%), thrombocytopenia (27.6%), thyroid autoimmunity (16.6%), dermatological disorders (5.5%) and type 2 diabetes (5.5%). 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 NLH 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-cell 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 (2.85%) 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 favors females 62.85% and 54.28% of patients was from urban areas. 56.66% of these patients have extranodal lesions, compared with 18.83% 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.
Lactulose alone versus lactulose and L-ornithine-L-aspartate for the prophylaxis of overt hepatic encephalopathy in acute variceal hemorrhage: A prospective case-control study

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Introduction: Acute variceal hemorrhage (AVH) is known to precipitate the development of overt hepatic encephalopathy (OHE). Although lactulose and L-ornithine-L-aspartate (LOLA) are therapeutic agents used for the treatment of hepatic encephalopathy, there is little data about the role of lactulose and LOLA for the prevention of OHE after AVH. Our aim was to determine the efficacy of lactulose and LOLA versus lactulose alone for the prevention of OHE after AVH.

Methods: In this prospective case-control study we enrolled 104 cirrhotic patients with AVH. Subjects were divided into two equal groups (n = 52) with similar age, gender, liver disease and variceal bleed characteristics. Group 1 (Gp-1) received lactulose alone and Group 2 (Gp-2) lactulose and LOLA. All patients received standard AVH treatment according to Baveno 5 guidelines. The primary end-point was the development of OHE in the first 120 hours after study enrollment.

Results: A total of 23 patients (22.1%) developed OHE: 16 patients (30.7%) in Gp-1 and 6 patients (11.5%) in Gp-2 (p = 0.03). The median time period until development of OHE was 53 hours and the median grade of OHE was 2 (ranging from 1 to 4). Higher baseline model for end stage liver disease score (19.3 ± 4.4 vs. 14.8 ± 4.7; p = 0.03), Child-Pugh score (10.3 ± 1.6 vs. 9.3 ± 1.8; p = 0.05), serum creatinine (1.8 ± 1.7 vs. 1.2 ± 1.4; p = 0.04), total bilirubin (2.7 ± 1.5 vs. 1.5 ± 1.9 mg/dl; p = 0.01) and venous ammonia level (110.3 ± 20.7 vs. 92.7 ± 18.3 umol/l; p = 0.008) were observed in patients who developed OHE as compared to patients who did not develop OHE. 15 patients (14.4%) died: 9 patients in Gp-1 (17.3%) and 6 patients (11.5%) in Gp-2.

Discussion/Conclusion: Lactulose and LOLA is superior to lactulose alone for the prevention of OHE in cirrhotic patients with AVH.
Mother-to-child transmission of HBV and HCV in Mongolia

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Introduction: Chronic viral hepatitis infection is endemic in Mongolia. It is widely accepted that vertical source is one of the main routes of transmission. However, currently there are no systemic intervention is given to prevent vertical transmission, except HBV vaccination, in our country.

Aim of study: To study mother-to-child transmission rate of HBV and HCV in Mongolia.

Methods: This study included 55 subjects, who were born to hepatitis B surface antigen (HBsAg) positive mothers, 42 subjects born to anti-HCV positive mothers, 1 subjects born to HBsAg and anti-HCV positive, 2 subjects born to HBsAg and a-HDV. All children and mothers were tested once for the presence of HBsAg and anti-HCV within 2-24 months of delivery.

Results: Six (10.9%) infants who were born from mothers with HBV infection were tested positive for HBsAg, 7 infants (19.9%) who were born from mothers with HCV infection were tested positive for anti-HCV. But 4 children were older than 12 months and one of them tested positive for anti-HCV.

Conclusion: This study results indicate that the vertical transmission rate of HBV is relatively high in Mongolia. Therefore, it recommends the need of combination strategy of both passive and active immunoprophylaxis. Further follow-up is needed to determine the vertical transmission rate of HCV infection. It is planned that the subjects who were anti-HCV positive will be tested in every 6 months for 2 years.
Risk factors for development of spontaneous bacterial peritonitis and subsequent mortality in cirrhotic patients with ascites

Gastroenterology Department, Charles Nicolle Hospital, Tunis, Tunisia

Introduction: Patients with ascites are at risk for developing spontaneous bacterial peritonitis (SBP) a severe complication associated with high mortality. We aimed to identify risk factors for SBP development and mortality.

Methods: 255 patients with cirrhosis and ascites undergoing paracentesis at our hospital were included in this retrospective cohort study. Demographic, clinical, and laboratory parameters were recorded at first paracentesis and during follow-up. Multivariate logistic regression analysis was used to identify independent predictors of SBP development and mortality.

Results: Child Pugh stage C (p = 0.001), thrombopenia (p = 0.01), and serum sodium (p = 0.03) emerged as independent risk factors for SBP development. SBP-naive patients undergoing paracentesis and presenting with thrombopenia ≤ 110 Giga/l or hyponatremia < 125 mmol/l were at highest risk for developing SBP. Increases in CRP levels indicated SBP development. MELD score (p = 0.001) were identified as independent risk factors for 30-day mortality after SBP diagnosis. In particular, SBP patients with MELD ≥ 20 and development hepatic encephalopathy showed highest mortality.

Discussion/Conclusion: Low serum sodium levels, high MELD, and thrombopenia indicate a significant risk for SBP development. SBP-related mortality is highest in patients with MELD ≥ 22. Identification of these parameters would be interesting to optimize stratification for primary prophylaxis and therapeutic strategies to improve survival.
Usefulness of C-reactive protein for evaluating clinical outcomes in cirrhotic patients with infection

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Introduction: The purpose of this study was to evaluate the value of initial C-reactive protein (CRP) as a predictor of clinical outcome and to investigate whether follow-up CRP measurement is useful for the prediction of the clinical outcome of infections in patients with liver cirrhosis, whose CRP production in response to infection may be attenuated.

Methods: A retrospective, observational study including 85 liver cirrhosis patients with infection was conducted to assess the usefulness of serial CRP measurements in predicting clinical outcome in liver cirrhosis patients.

Results: The overall 30-day mortality rate of the study population was 22.3% (19/85). In the multivariate analysis, advanced age (≥ 65 years), healthcare-associated or nosocomial infections, model for end-stage liver disease (MELD) score of ≥ 22 were significant factors associated with mortality (all p < 0.05). No association between initial CRP level and mortality was found. A decrease in CRP level was associated with 30-day survival, whereas persistently elevated or increasing CRP levels were associated with further deterioration and a poor prognosis.

Discussion/Conclusion: Variation of CRP level seems to be a true prognostic marker in cirrhotic patients. It allows identifying cirrhotic patients with poor short-term prognosis.
Portal vein thrombosis – Marker of severity in chronic liver diseases

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Imagistic finding of portal vein thrombosis, symptomatic or not, requires proper diagnosis management, regarding various ethiopatogenic implications and the possibility of being a severe disease manifestation, such as hepatocellular carcinoma.

**Aim:** The assessment of portal vein thrombosis diagnosis, in the evolution of chronic liver disease, with gravity significance in tumor etiology.

**Patients and methods:** The study was conducted on a group of 10 patients, diagnosed by ultrasound investigation with portal vein thrombosis. They were investigated in order to identify etiopathogenic causes leading to thrombosis. Abdominal ultrasound, contrast substance ultrasound, computer-tomography, MRI, endoscopy, tumor markers, explorations for liver viruses and standard tests were performed.

**Results:** In 7 of the 10 cases, portal vein thrombosis was associated with hepatocellular carcinoma, these patients having highly elevated L1-fetoprotein level. Contrast substance ultrasound, besides visualization of thrombus that captured contrast substance in the arterial phase and showed “wash-out” in the later phase, suggesting malignant thrombosis, revealed perfusion disturbances, as diffuse hypocaptant areas in the affected segments. 6 patients described a chronic form of viral hepatitis: type C-4 patients or B-2 patients. Although the decreased portal flow speed due to fibrosis and liver regeneration processes may predispose to thrombosis (often without significant symptoms), the hypocoagulability in liver diseases caused by liver failure, does not involve a thrombotic risk. Imagistic findings of portal system thrombosis and its clinical consequences require proper research for a liver carcinoma development. Non-tumor portal thrombosis is rare; in evolution, recanalisation and cavernomatous transformation occurred.

**Conclusions:**
1. Assessment of portal vein thrombosis in the evolution of chronic liver disease requires multiple explorations in order to establish certain etiopathology.
2. Portal vein thrombosis represents an imagistic marker of severity, being often associated with hepatic carcinoma.
3. In the presence of portal thrombosis, after differential diagnosis, the therapy management is difficult, tumor-type thrombosis requiring cytostatics.
The estimation of electrical cerebral activity in patients with hepatic cirrhosis

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Cerebral activity electrical recording in patients with hepatic cirrhosis is important for precocious assessment and monitoring of hepatic encephalopathy modifications.

Aim: Presenting the modifications of cerebral activity, by two methods: electroencephalography-EEG and visual evoked potentials-VEP, induced by hepatic insufficiency and portal hypertension in patients with hepatic cirrhosis.

Patients and methods: The study was conducted on 140 patients with hepatic cirrhosis, in equal ratio, compensated and decompensated cirrhosis and a control group of 100 healths, aged 54 ± 10. In all patients, EEG and VEP were recorded.

Results: Electroencephalography and visual evoked potentials permit the appreciation of neuroelectrophysiological status of cirrhotic patients and their modified aspect may have significance. They measure the degree of initially perturbations and association with clinical manifestations of encephalopathy in evolution. Modified aspects of EEG were recorded in 46% of patients with cirrhosis and described: a decreased percent of normal alpha rhythm (< 50%), with diminished amplitude (< 40 µV), without modulation, in 1/4 of patients; a hypo volted or plate electrical activity (< 15 µV) in 1/3 of patients; the appearance of slow waves (δ and θ) in high percentage (55–30%) with small amplitude, in 1/4 of patients; the presence of triphasic waves, in 1 patient, with severe encephalopathy and marked increase of ammonia (> 400%). The aspects of VEP modifications parameters were: elongation of latency and duration, diminution of amplitudes, abruptness and surfaces and the increase of the differences in cerebral answer between eyes by one and other visual excitation, being observed in 53% of cirrhotic patients, almost in first stages of disease.

Conclusions:
1. Electrical cerebral activity shows an important decrease in 1/2 of patients with hepatic cirrhosis.
2. EEG and VEP are necessary in cerebral investigation at cirrhotic patients, recording objective modifications.
3. The perturbations in bioelectrical cerebral activity are caused both by hepatic insufficiency and portal hypertension.
Rising to the challenge of increasing hospital admissions for liver disease

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¹Joint First Author

Introduction: Liver disease is the 5th commonest cause of death in the UK; there has been an 88% increase in age-standardised mortality from 1993–2010. Alcohol misuse is estimated to cost the NHS £3.5 billion per annum. Newham University Hospital (NUH) is a district general hospital serving a socially deprived, ethnically diverse population of 296,000 with a mortality rate due to liver disease in those under 75 of 20.6 per 100,000.

Methods: Admissions data was collected retrospectively from 1st January 2012 to 31st December 2014. Patients were identified from admission lists with clinical details confirmed from electronic patient records and clinical notes.

Results: 315 admissions were identified (144 males, 68 females); the mean age was 53 years (range 21–93). The patient demographic was representative of the local population. 82% of patients were managed by a hepatologist. Median LoS was 6 days (range < 1–66). 44 patients had > 1 admission with 50% requiring ≥ 2 admissions; 22 readmissions were due to alcohol.

Figure 1

Aetiology of liver disease

- Alcoholic liver disease: 51%
- Viral hepatitis: 22%
- NASH: 5%
- Acute hepatitis: 1%
- Drug induced: 4%
- Autoimmune: 1%
- HCC: 1%
- Other: 14%
- Metastatic cancer: 1%
115 patients had cirrhosis with 30.4% newly diagnosed at presentation. 15 patients required a total of 43 admissions to ICU; alcohol was implicated in 74.4% of these admissions. 23 patients were referred to a tertiary liver unit. There were 21 deaths (9.9%), 66% were secondary to alcoholic liver disease. 19% of patients did not attend outpatient follow up.

**Discussion/Conclusion:** Our results demonstrate the increasing burden of alcohol related liver disease; with multiple admissions to hospital, ICU and poor engagement with follow up. Our data supports recommendations that patients should be managed by a hepatologist and our mortality data is lower than the national average. Evidence suggests that outcomes could be improved through care bundles\(^{iii}\) and new models of ambulatory care are required.


\(^{iii}\)http://fingertips.phe.org.uk/search/liver%20disease#gid/1/pat/6/ati/101/page/0/par/E12000007/are/E09000025
Prevalence of acute hepatitis D in Mongolia

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Introduction: Mongolia has the highest prevalence of hepatitis D virus (HDV), leading to high morbidity and mortality from liver diseases and hepatocellular carcinoma. In a recent study, it was estimated that anti-HDV prevalence is 67.5% among HBsAg positive population. Therefore, we have conducted a retrospective analysis in order to determine prevalence of acute HDV incidences in Mongolia.

Methods: A retrospective study was carried out to review records for all acute HBV cases admitted between 2010–2014 at the National Center for Communicable Disease of Mongolia. All data were analyzed using MS Excel and SPSS17 programs.

Results: A total of 2562 patients were admitted to the National Center for Communicable Disease of Mongolia due to acute hepatitis B over the last 5 years (Table 1).

<table>
<thead>
<tr>
<th>Year</th>
<th>Total acute HBV incidences</th>
<th>Total acute HDV incidences</th>
<th>Acute HDV distribution by age group Anti-HDV, n/</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0–9</td>
</tr>
<tr>
<td>2010</td>
<td>479</td>
<td>122</td>
<td>1/0.8</td>
</tr>
<tr>
<td>2011</td>
<td>421</td>
<td>155</td>
<td>3/1.9</td>
</tr>
<tr>
<td>2012</td>
<td>340</td>
<td>142</td>
<td>5/3.5</td>
</tr>
<tr>
<td>2013</td>
<td>319</td>
<td>174</td>
<td>6/3.4</td>
</tr>
<tr>
<td>2014</td>
<td>284</td>
<td>126</td>
<td>6/4.8</td>
</tr>
<tr>
<td>Total</td>
<td>2562</td>
<td>719</td>
<td>21/2.9</td>
</tr>
</tbody>
</table>

As shown in Table 1, prevalence of acute hepatitis D was 28% (719) of all HBsAg positive patients. Predominantly male (67%) and majority were 20–29 years old (67.6%). No apparent risk factors of HDV transmission were identified for 94.9% of patients.

Conclusion: Prevalence of acute HDV infection among the Mongolian population is high, especially those 20–29 years old population. It clearly demonstrates that more work needs to be done to prevent new HBV/HDV infections.
An assessment of prior hepatitis A virus exposure in HBsAg-positive individuals

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²Bozyaka Training and Research Hospital, Infectious Disease, İzmir, Turkey

Objective: This study aims to evaluate whether individuals found to be positive for HBsAg has been investigated for prior hepatitis A virus (HAV) exposure.

Materials and methods: This is a cross-sectional and descriptive study. The study included inactive carrier individuals who were being followed up by İzmir Bozyaka Training and Research Hospital and Manisa State Hospital Viral Hepatitis Polyclinic and had HBsAg positivity for more than 6 months and patients with chronic hepatitis B virus (HBV) infection who were receiving treatment. Individuals selected by random sampling were assessed to determine whether they had been studied for prior HAV exposure and whether they had been vaccinated. The data were taken from medical records of the patients.

Results: A total of 1211 patients were evaluated, of whom 679 (56%) had HAV investigation results in their files, and 532 (44%) have had undergone no investigations for HAV. When the results of a total of 679 individuals whose investigations had been performed were evaluated, 634 (97%) were positive for HAV IgG and 45 (3%) were negative. Distribution of seronegative individuals not immune for hepatitis A infection by age is provided in Table 1. When the data are evaluated, it is of note that 44% of the individuals with chronic HBV infection had not been investigated to find out whether there had been HAV exposure. When the distribution of seronegative individuals by age is examined, seronegativity was observed to be higher especially in younger ages. As the age increased, so did the ratios of HAV exposure and immunity. On the other hand, 6% of the individuals in the 31–40 years ago group were seronegative for HAV, although the number was small.

Table 1: Age distribution of HAV IgG positivity in HBsAg-positive individuals

<table>
<thead>
<tr>
<th>Age groups</th>
<th>HAV IgG positive individuals</th>
<th>HAV IgG negative individuals</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>17–20</td>
<td>7 (54%)</td>
<td>6 (46%)</td>
<td>13</td>
</tr>
<tr>
<td>21–30</td>
<td>116 (83%)</td>
<td>23 (17%)</td>
<td>139</td>
</tr>
<tr>
<td>31–40</td>
<td>236 (94%)</td>
<td>15 (6%)</td>
<td>251</td>
</tr>
<tr>
<td>41–50</td>
<td>144 (100%)</td>
<td>0</td>
<td>144</td>
</tr>
<tr>
<td>51+</td>
<td>131 (99%)</td>
<td>1 (1%)</td>
<td>14</td>
</tr>
<tr>
<td>TOTAL</td>
<td>634 (93%)</td>
<td>45 (7%)</td>
<td>679</td>
</tr>
</tbody>
</table>
Discussion and conclusion: Our study determined that investigations to find out prior HAV exposure were neglected in almost half of the patients with chronic HBV infection. Because serious complications can develop and may even result in mortality due to fulminant course in the presence of infection with another viral hepatitis factor in patients with chronic hepatic disease, it is very important that patients with chronic viral hepatitis be assessed accordingly. Considering that acute HAV infection has a severer and fulminant course as the individual ages and that this risk is particularly higher in patients with chronic hepatitis, it should be borne in mind that this should not be overlooked. Therefore, investigation of chronic HBV patients for prior exposure to HAV and vaccination of seronegative individuals should not be neglected.
Family member’s HBV exposure in individuals with chronic HBV infection

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Objective: The major routes of transmission of hepatitis B virus (HBV) infection is from maternal transmission, sexual intercourse and horizontal transmission in cases in disrupted skin-mucosal integrity. These ways of transmission indicate that it is necessary to investigate HBV in the close family members of individuals with chronic HBV infection. This study aims to evaluate presence of HBV infections in family members of a group of individuals with chronic HBV.

Material and method: A face-to-face questionnaire was performed with patients with chronic HBV who were being followed up by the Infectious Disease and Clinical Microbiology Clinic, Viral Hepatitis and Gastroenterology Polyclinics of İzmir Bozyaka Training and Research Hospital and Manisa State Hospital, and presence of any other HBsAg-positive individuals and their degree of relation (mother, father, sibling, child, spouse and other relatives) were questioned.

Results: A total 300 patients, aged 17–78 years, 150 females and 150 males, participated in the study. With the questionnaire, 179 (60%) reported that at least one family member was HBsAg-positive, while others reported that no family member were HBsAg-positive or that they did not know. The distribution of family members reported by these 179 patients to be HBsAg-positive is provided in Table 1.

Table 1: Distribution of chronic HBV individuals’ other family members known to be HBsAg-positive

<table>
<thead>
<tr>
<th>HBSAG-POSITIVE INDIVIDUAL’S DEGREE OF RELATION n:179</th>
<th>NUMBER</th>
<th>PERCENTAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>THOSE WITH HBSAG-POSITIVE MOTHER</td>
<td>24</td>
<td>13%</td>
</tr>
<tr>
<td>THOSE WITH HBSAG-POSITIVE FATHER</td>
<td>6</td>
<td>3%</td>
</tr>
<tr>
<td>THOSE WITH AT LEAST ONE OR MORE HBSAG-POSITIVE SIBLINGS</td>
<td>67</td>
<td>37%</td>
</tr>
<tr>
<td>THOSE WITH HBSAG-POSITIVE MOTHER AND SIBLING(S)</td>
<td>39</td>
<td>22%</td>
</tr>
<tr>
<td>THOSE WITH AT LEAST ONE OR MORE HBSAG-POSITIVE CHILDREN</td>
<td>22</td>
<td>12%</td>
</tr>
<tr>
<td>THOSE WITH HBSAG-POSITIVE SPOUSE</td>
<td>15</td>
<td>8%</td>
</tr>
<tr>
<td>THOSE WITH ANOTHER HBSAG-POSITIVE RELATIVE</td>
<td>6</td>
<td>3%</td>
</tr>
</tbody>
</table>
Considering the importance of HBV transmission during pregnancy and delivery, the total number of individuals whose mothers, siblings or both were HBsAg-positive was 130 (73%), which suggest that HBV transmission is mainly vertical in our country.

**Discussion and conclusion:** It is well known that HBV infection is mostly asymptomatic and that the diagnosis of infected individuals is delayed because it often goes unnoticed. Given the routes of HBV transmission, there is a clear need to investigate mother and siblings of an individual who is found out to be HBsAg-positive. Although transmission from father or spouse, i.e. horizontal transmission, has a relatively lower ratio compared to the ratios in mother and siblings, investigating them for HBV and vaccinating as necessary must not be neglected. This is supported by the data from our study.
Transarterial chemoembolization in hepatocellular carcinoma – A single center experience from Romania

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Introduction: Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver. According to Barcelona Clinic Liver Cancer staging system, transarterial chemoembolization (TACE) is considered a recommended option for intermediate HCC.

The aim was to evaluate the various factors affecting the outcome of TACE and to study the efficacy of TACE.

Methods: One hundred and two patients with HCC treated with chemoembolization in our department between 2012 and 2014 were studied retrospectively. Baseline laboratory and imaging characteristics were obtained. Univariate and multivariate Cox's regression survival analysis was performed.

Results: All patients (M = 74, F = 28) with an average age of 62 years (± 8.4) that were included had cirrhosis (HCV-related in 55.9%). Median AFP value was 21ng/ml. Mean MELD score at TACE was 9.7 ± 1.7. Partial non-malignant portal vein thrombosis was present in 8 patients (8.2%). Sixty-one patients (62%) had one HCC nodule and 6 patients had a multicentric tumor. Mean diameter of the biggest nodule was 40.9 ± 18.6 mm; 66.7% of patients had HCC within Milan criteria. In 81 patients a classic lipiodol TACE was performed, while 18.8% of patients had a drug eluting microsphere procedure. 35 patients had complete tumor response after one procedure. Liver transplantation was performed in 15 patients. Overall patient survival was 95.7% at 1 year and 77.7% at 5 years. Independent negative factors affecting survival were: high AFP value (p = 0.002), a higher MELD score at first TACE (p = 0.01), HCC outside Milan criteria (p = 0.02) and lack of complete response after one session of TACE (p = 0.04).

Conclusion: Chemoembolization was shown to be a safe and effective therapy in patients with HCC with Child A and early Child B stages. Negative prognostic factors in patients with HCC that undergo TACE as therapy were: high baseline alpha-fetoprotein levels, higher MELD scores, nodules outside Milan criteria and partial response with need of other TACE session.

Key words: hepatocellular carcinoma, chemoembolization, survival outcome
Primary biliary cirrhosis and quality of life – Results from a UK patient survey

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Introduction: Primary biliary cirrhosis is a chronic autoimmune disorder characterised by cholestasis, inflammation and liver fibrosis and, if left untreated, can progress to cirrhosis. Independent of biochemical abnormalities and histopathological changes, many patients are symptomatic at the time of diagnosis or develop symptoms over their disease course. Treatment of the underlying disease with ursodeoxycholic acid has been shown to improve transplant free survival but has little effect on symptomatology.

Methods: A survey of patients in the UK was carried out between February and November 2014. As part of the survey, patients were asked to describe their initial and current symptom profile and rate their quality of life.

Results: 477 patients responded. The average age was 51 (range 26–72) and 82.9% of respondents reported being on treatment in the form of ursodeoxycholic acid. Average duration of diagnosis was 6.9 years.

At diagnosis, the most commonly reported symptoms at diagnosis were joint aches and pains (24%), fatigue (23%) and itch (20%). When asked about symptomatic improvement, 47% reported no symptomatic improvement, 24% reported improvement in itch but only 10% reported improvement in fatigue.

Patients reported that PBC affected their ability to care for their family (40%) and their relationship with their partners (53%). 72% reported that it had affected their work life, with over half having given up work entirely as a result.

Fatigue had the greatest reported affect on quality of life with 69% rating it as the most important factor.

Discussion/Conclusion: The majority of patients with PBC are affected by one or more symptoms with a resultant negative impact their quality of life. Of particular note is the impact of fatigue on quality of life and this remains an area of PBC where few advances have been made in developing pharmacological therapies.
How does primary biliary cirrhosis present? – Results from a UK patient survey

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Introduction: Primary biliary cirrhosis (PBC) is a chronic disorder characterised by cholestasis, inflammation and liver fibrosis. If left untreated it can progress to cirrhosis. In a patient with suspected PBC, confirmation of the diagnosis is straightforward and is based on the presence of two of the following three features: 1) cholestatic liver function tests; 2) positive antimitochondrial antibody (AMA); 3) characteristic features on biopsy. One of the main barriers to diagnosis is the non-specific presentation.

Methods: A survey of patients in the UK was carried out between February and November 2014. Patients were asked to recall the first symptom that caused them to see their doctor and the date of onset. They were also asked how many visits they had with their doctor before a diagnosis of PBC was made.

Results: 477 responses were received. 10% were asymptomatic with a diagnosis being made following a routine blood test. Of those who had symptoms, the most common were joint aches and pains (24%), fatigue (23%) and itch (20%). Other less common symptoms included indigestion (10%), dry eyes/mouth (6%) and abdominal pain (4%). Patients reported a mean of 3.45 visits (range 1–40) over a mean duration of 28.5 months (0–252 months).

Discussion/Conclusion: The majority of patients in this survey presented, not with a sign or symptom of established liver disease (where AMA testing is routinely used) but with non-specific symptoms that have a wide differential diagnosis. Increasing awareness of this rare but important condition and its broad symptomatology is required especially amongst primary care doctors. Whilst PBC is rare, once considered, it can be diagnosed or excluded non-invasively and with a high degree of accuracy, and patients can be started on treatments that can improve quality of life and transplant free survival.
The diagnostic value of a globulin/platelet model for evaluating liver fibrosis in chronic hepatitis B patients

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Backgrounds: Liver biopsy, which is considered the best method for evaluating hepatic fibrosis, has important adverse events, such as pain, intraperitoneal bleeding and death. Therefore, non-invasive tests have been developed to determine the degree of hepatic fibrosis in patients with CHB without performing liver biopsy.

Aim: To verify the usefulness of a new fibrosis index the globulin/platelet [GP] model in patients with CHB and to compare it with other non-invasive tests for predicting significant fibrosis. This study was the second to evaluate the GP model in HBV patients.

Methods: We retrospectively investigated 217 patients with CHB who performed liver biopsy from 2013 to 2014. The GP model, APGA, FIB4, fibrosis index (FI), cirrhosis discriminate score (CDS) and Fibro-quotient (Fibro Q) were calculated, and the diagnostic accuracies of all of the fibrosis indices were compared between the F0–2 (no-mild fibrosis) and F3–6 (significant fibrosis) groups.

Results: All of the non-invasive markers were significantly correlated with the stage of liver fibrosis (p < 0.001). To predict significant fibrosis (F ≥ 3), the AUC (95% CI) was found to be greatest for APGA (0.83 [0.74–0.86]), followed by FIB-4 (0.75 [0.69–0.80]), the GP model (0.74 [0.68–0.79]), FI (0.72 [0.6–0.78]), CDS (0.71 [0.64–0.76]) and Fibro Q (0.69 [0.61–0.75]). The AUROC of APGA was significantly different than that of the other non-invasive fibrosis markers (p < 0.05).

Conclusions: The GP model had moderate diagnostic utility for the prediction of significant fibrosis in patients with CHB, and the diagnostic accuracy of GP model was equal to that of other non-invasive markers, except for APGA index.
The lessons of the outbreak (that occurred in BAZ county in Hungary) caused by hepatitis “A” virus, in connection with a case, which ended fatally (case report)

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Introduction: The transmission of the infections caused by hepatitis “A” virus is facilitated by the long incubation period, the high amount of asymptomatic cases and the resistance of the virus against environmental effects.

After the epidemic of 2004, a new outbreak surfaced again in 2014. The number of hepatitis cases is known to be much higher this time. In 2013, 62 patients diagnosed with hepatitis “A” were treated in the Department of Infectology (Semmelweis University Hospital). By contrast, in 2014 we hospitalized 525 patients and provided ambulatory care for another 680 people. There were a few cases where in spite of the decreasing transaminase levels, the serum bilirubin level was protractedly high.

We enrolled the 64-year-old patient with the suspicion of hepatitis infection. His past medical history included hypertonia and rheumatoid arthritis, which was treated with methotrexate. We stopped the methotrexate immediately. His hepatitis infection, which showed high elevations of serum transaminases levels was serologically confirmed to be caused by hepatitis “A” virus. Because of his rapidly deteriorating jaundice, we started parenteral fluid replacement and ursodeoxycholic acid treatment. In order to avoid hepatic encephalopathy, we continued his therapy with a laxative, rifaximine and Aminosteril-N-Hepa infusion. For the purpose of decreasing the extremely high serum bilirubin levels, with the permission of the Aferezis Society, plasmapheresis and haemodialysis were performed several times. These treatments were only temporarily decreasing the levels of serum bilirubin. After the procedures, bilirubin levels started to increase again.

Methods: Case report based on the data collected in our department.

Results: The autoimmune disease of the patient and the therefore applied immunosuppressive therapy, along with the serious, viral hepatitis, all contributed to the patient’s fatal liver failure.

Discussion/Conclusion: The question arises whether liver transplantation would have resulted in recovery, but for this we have to take into consideration the length of preparation.
Transient elastography in monitoring chronic hepatitis B (CHB) patients during antiviral therapy

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Introduction: Fibroscan® is widely used to assess hepatic fibrosis in chronic liver diseases. Recent studies demonstrated its usefulness for monitoring response to therapy and regression of liver fibrosis in CHB. Aim of this study was to evaluate changes in liver stiffness (LS) and fibrosis tests in patients treated with nucleos(t)ide analogues for CHB.

Methods: Our study retrospectively evaluated consecutive CHB patients who underwent nucleos(t)ide analogues therapy from January 2011 to June 2015 with at least 2 elastographic examinations by Fibroscan®. Inclusion criteria: Chronic hepatitis/cirrhosis due to HBV demonstrated histologically or by elastography. We analyzed sex, age, BMI, histology according to Ishak, LS, portal vein diameter, spleen size, ultrasound steatosis score according to Hamaguchi (0–6), biochemical parameters, APRI, quantitative HBsAg and HBV DNA. The LS was measured every 12 months through Fibroscan® (Echosens, Paris, France), by two experienced operators, as previously described. Data are expressed as mean ± SD. Pearson correlation coefficient is used to analyze the correlation between the values of liver stiffness and other variables. The differences between means were analyzed using parametric tests.

Results: Forty-two patients were enrolled in the study. Mean age was 52.7 ± 13.4 years. 29% of enrolled patients had F4 fibrosis. 26 patients were treated with Entecavir and 16 with Tenofovir. At baseline LS was 11.1 ± 7.5 KPa while it was 7.9 ± 4.8, 6.6 ± 3.3, 6.3 ± 2.4 at 1, 2, 3 years of follow-up, respectively. The degree of LS regression was 29%, 16%, 4% after 1, 2, 3 years of therapy. After 1-year therapy an improvement of ALT levels and APRI score has been observed (53.6 ± 75.8 vs. 29.5 ± 20.6; p < 0.05; 0.87 ± 0.87 vs. 0.45 ± 0.31; p < 0.05).

Conclusion: Long-term antiviral therapy for CHB with analogues resulted in fibrosis regression as revealed by LS just after one year treatment. These data correlates with reduction in APRI test and ALT levels.
Transjugular intrahepatic portosystemic shunt insertion is safe and effective in district general hospital setting

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Introduction: Transjugular intrahepatic portosystemic shunt (TIPS) insertion is a recognised rescue treatment for uncontrollable bleeding due to portal hypertension and is also used for refractory ascites. TIPS is usually performed by interventional radiology (IR) and normally in a 'teaching' hospital setting. Reported mortality rates are 27–50%.

At our institution, a large DGH with 2 hepatologists, a 24-hour IR-led TIPS service has been established since 2007. The aim of this study was to assess technical success, complications and mortality associated with TIPS.

Methods: Using a prospective TIPS database, we conducted analysis of patients who had undergone a TIPS procedure between 2007 and 2014. Data collected included demographics, indication, success rate, short and long term complications and mortality. A total of 32 patients were identified and case notes were available for 25.

Results: Of the 25 patients identified, 18 (72%) were male. The mean age was 48.4 (25–73). Child's score was A in 5 (20%), B in 11 (44%) and C in 9 (36%). Six patients (24%) had a MELD < 12, 11 (44%) 12–18 and 8 (32%) > 18. The commonest underlying aetiology was alcohol in 12 (48%), alcohol and HCV in 6 (24%) and NASH in 3 (12%). The commonest indication was uncontrolled bleeding in 15 (60%), refractory ascites in 4 (16%) and gastric varices in 3 (12%). Six (24%) had undergone an OGD once before TIPS, 9 (36%) had 2 OGDs and 4 (16%) had three.

Technical success was achieved in 23 (92%). Two patients underwent further TIPS refashioning. There was one TIPS thrombosis soon after insertion. Of 21 patients receiving TIPS for bleeding, 18 (86%) required no further endoscopies. Three patient rebled (14%) requiring more endoscopy. There were no significant procedure-related complications. Severe refractory hepatic encephalopathy occurred in only 1 patient (5%).

The 30-day mortality was 28% (7 patients) and 1-year mortality was 44% (11). Most deaths occurred in patients with Child's C disease (4 patients at 30-days and 7 at 1-year) with no 30-day mortality in Child's A. Three patients aged over 65 underwent TIPS, 2 died within 30 days (Child's B) and 1 within 1 year (Child's A). All patients who died had a MELD score > 15. Most common cause for death was either rebleeding or multiorgan failure.

Discussion/Conclusion: TIPS can be safely and effectively performed in a DGH setting with success, complication and mortality rates comparable to larger 'teaching' centres. As with other studies, severity of liver disease and age are important predictors of mortality.
Acute on chronic liver failure in a tertiar center in North-Eastern Romania

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Introduction: Acute on chronic liver failure (ACLF) that can occur in a patient with cirrhosis is beginning to be a recognized entity that, although reversible, is accompanied by a high mortality. It appears secondary to an acute damage of liver function caused by precipitating factors such as infection, hemorrhage that can lead to multiple organ dysfunction. The study aims to analyze the etiological, clinical, biological data and precipitating factors that may cause ACLF.

Methods: We performed a retrospective study that analyze the cirrhotic patients hospitalized in the Institute of Gastroenterology and Hepatology Iasi between 1 January 2014–31 December 2014. We have noted: the historical data of the disease, etiology, a complete biological tests, the presence of ascites, jaundice, presence of infections, alcohol consumption. Patients were divided into two groups: a group without ACLF criteria and another group with the criteria for diagnosis of ACLF.

Results: There were analyzed 1837 patients with cirrhosis. In 871 of them etiology was alcoholic, and 965 patients had viral etiology (372 – viral hepatitis B, 593 – viral hepatitis C). Criteria for acute liver failure were found in 422 patients (23%). Patients with acute liver failure were younger ($p < 0.05$), with alcoholic etiology of liver cirrhosis ($p < 0.05$). Precipitating factors significantly associated with the ACLF were bacterial infections (15% vs. 33.1%, $p < 0.001$) and recent use of alcohol (14% vs. 35.5%, $p < 0.001$). The number of leukocytes, serum potassium level, serum creatinine and CRP were significantly higher in the patients with ACLF.

Discussion/Conclusion: ACLF is a common entity in cirrhotic patients, especially younger patients with alcoholic etiology. Infections and recent alcohol consumption are the most important precipitating factors. Inflammation, electrolyte disturbance and impaired kidney function are significantly associated with the ACLF.
Effectiveness and safety of orally administered slymarin (milk thistle) for pegylated interferon unresponsive chronic delta hepatitis patients

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Aim: Slymarin is a natural extract from milk thistle (Silybum marianum), a natural herb which contains flavonoids. Slymarin has also antiinflammatory properties and lipid peroxidation effects on human hepatocytes. It has been also used for treatment of acute alpha-amanitin poisoning and chronic hepatitis C infection. Chronic Hepatitis D virus (HDV) infection is a serious health problem leading to fibrosis and hepatocellular carcinoma. Patients with chronic HDV infection can be treated with pegylated-interferon therapy with a lower treatment success. The majority of patients with chronic HDV are unable or unwilling to use interferon (IFN)-based treatment due to liver cirrhosis. Our objective was to establish the long term clinical outcomes with Slymarin for interferon experienced chronic HDV patients.

Methods: We studied ten patients from one center with interferon experienced chronic HDV of which 8 had cirrhosis and 2 had chronic hepatitis who received HDV treatment with slymarin 600 mg/day after a median period of 12 months. Information collected included demographic, clinical, virologic and outcomes data. MELD and Child-Pugh scores were also obtained. Friedman test was used to evaluate the laboratory parameters during the study period.

Results: 10 chronic HDV patients (median age 54 years, 6 female, all of them previous null responders to peg-interferon) with mildly decompensated cirrhosis (CP 7 [range 6–11], MELD 11 [range 6–20]) were followed for 12 months from start of slymarin 600 mg/day. There were no decompensation both of MELD and CP scores among patients at the end of therapy. In addition, no patients stopped slymarin treatment early due to side effects. At the end of treatment, there was no significant change on prothrombin time (p = 0.949) AST (p = 0.662) and AFP (p = 0.983) levels and platelets counts (p = 0.988) compared to pre-treatment period (all p > 0.005). Finally, HDV-RNA suppression were seen in all patients at the end of treatment (p = 0.009).

Conclusions: In the light of the presented data, slymarin seems to be effective in the treatment of chronic HDV infection. Further research is needed for validation. The study is ongoing with collection of data on sustained viral response.
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Epidemiology of the hepatitis B and hepatitis C in patients with hydatid cyst and the impact of albendazole therapy on liver tests in hepatitis B antigen-positive subjects

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Background and aims: Asia and many parts of Middle East are the major endemic areas for HCV infection. HCV causes chronic infection in more than 80% of cases. Other hand chronic hepatitis B infection are also prevalent in Middle East. The tapeworm-related liver diseases has been rapid over the past decades. In patients with hydatid cyst (HC), concomitant hepatitis B and C infections may cause severe drug induced liver disease (DILI) during long-term albendazole theraphy. Presently there are no definitive guidelines for the management of HC in patients with hepatitis B infection. We therefore assessed the prevalence both of HBV and HCV infections in liver HC. We also examined the rate of DILI during albendazole therapy, particularly in subjects with hepatitis B.

Methods: 211 treatment naive patients (124 female; mean age 36.2 ± 19.4 years), who presented to the gastroenterology clinic of university hospital between May 2010 and June 2015 and diagnosed with active echinococcal liver disease, were included in the study. Patients with coexistent liver disease were excluded. All patients received weight-based (15 mg/kg/day) albendazole. Liver transaminases and cholestatic enzymes were observed during anti-helminthic treatment. DILI was defined as 3-fold increase of transaminases and two fold increase of cholestatic enzymes during therapy. Control group was selected among 1062 (405 male, 657 female) patients who admitted to Gastroenterology clinic of Yuzuncuyıl University Faculty of Medicine for another reasons. Presence of HBV and HCV infections was assessed by the routine ELISA method. Positive results for HBs antigen (HBs Ag) and anti-HCV antibody were accepted as positive. All data was recorded on SPSS.

Results: In HC group, 23 patients (11%) had HBs Ag seropositivity. 3 (1.42%) patients tested positive for anti-HCV antibody. There was no patient tested positive for HIV. In control group, the mean age was 46.1 ± 17.9 years in males and was 42.5 ± 17 years in females. 3 men and 6 women had anti-HCV antibody. Total Anti-HCV seropositivity was 0.8%. Other hand, the prevalence of HBV infection (HBs antigen seropositivity) was 5.7% (61 individuals; 31 female). There was statistically significant difference between groups in terms of HBs Ag seropositivity (11% vs. 5.7%; p < 0.005). In addition, the rate of DILI was higher in patients with HBs Ag than those without HBs Ag (17.3% vs. 2.1%; p < 0.001).
Discussion: The higher rate of hepatitis B infection among patients with HC disease may have been due to poverty and lack of health infrastructure in the rural areas of Turkey. While there may be a number of possible explanations for the higher rate of HBs Ag seropositivity in patients with HC, these data highlight urgent need for prevention and treatment for hepatitis B infection in this unique patient group. These findings also suggest that hepatitis B screening could be an important, economically feasible public health strategy for preventing DILI in patients with HC disease. Given the observed HBV infection prevalence, hepatitis B screening may reveal substantial numbers of cases with previously unknown HBV infection.
Expression of epithelial cell adhesion molecule and alpha-fetoprotein in hepatitis C virus-related hepatocellular carcinoma: Relation to tumor vascularization

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Introduction: Cancer stem cells (CSCs) play an important role in tumorigenicity and may be involved in tumor vascularization by forming non-endothelial vascular channels described as vasculogenic mimicry (VM). Therefore, the aim of the present work was to study the expression of epithelial cell adhesion molecule (EpCAM), a marker for CSCs and alpha fetoprotein (AFP) in hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC) in relation to tumor vascularization.

Methods: Twenty-five HCV-related cirrhotic patients with HCC who underwent surgical resection were enrolled in the study. Tumor stage was classified according to the Barcelona Clinic Liver Cancer (BCLC) staging and the Cancer of the Liver Italian Program (CLIP). Histological tumor grading was performed according to Edmondson and Steiner's criteria. Immunohistochemical analysis was done for HCCs and adjacent non-neoplastic liver tissues using anti-human antibodies against EpCAM, AFP, hepatocyte for identification of VM and CD105 and CD34 to quantify microvessel density (MVD).

Results: Positive cytoplasmic immunostaining for EpCAM was demonstrated in 44.0% patients with HCV-related HCC while EpCAM expression in the adjacent non-neoplastic liver tissues was observed mainly in proliferating bile ductules in the portal tracts. The CD105-MVD and CD34-MVD in HCC tissues were significantly higher than those in the adjacent non-neoplastic liver tissues (p < 0.001). Vasculogenic mimicry was identified in 60.0% of HCC samples but in none of the adjacent non-neoplastic liver tissues. The cells lining the VM channels showed also positive immunostaining with EpCAM. Compared with EpCAM− HCC patients, EpCAM+ HCC patients showed significantly higher HCC size (p = 0.006), CLIP stage (p = 0.004) and histological grade (p = 0.001), AFP expression (p = 0.024) and VM formation (p = 0.006).

Discussion/Conclusion: EpCAM positivity may identify a subpopulation of HCCs originated from CSCs with aggressive biological behavior and may be involved in tumor vascularization through VM formation.
Correlation of transient elastography with APRI, FORNS and FIB4 in patients with chronic liver diseases of different etiology

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Introduction: Fibroscan® is widely used as a non-invasive tool to assess hepatic fibrosis in chronic liver diseases (CLD) of different etiology. The aim of this study is to compare the diagnostic accuracy of Fibroscan® with the most popular and accurate Liver Fibrosis Tests (FT).

Methods: We prospectively enrolled 472 consecutive patients that underwent transient elastography by Fibroscan® in our Unit from April 2014 to April 2015. The variables analyzed were: AST, ALT, GGT, PLT, sex, age, cholesterol, APRI, FORNS, FIB4, NAFLD fibrosis score, liver stiffness (LS), diagnosis. The LS was measured through Fibroscan® (Echosens, Paris, France) by two experienced operators as previously described. Data are expressed as mean ± SD. Pearson correlation coefficient is used to analyze the correlation between the values of liver stiffness and other variables. The differences between groups will be analyzed using one-way ANOVA, Mann-Whitney or Kruskal-Wallis test when appropriate.

Results: 472 patients were enrolled in the study. Mean age was 55.5 ± 14.2 years. Diagnosis was CHC in 190, CHB in 106, NAFLD in 95, non-viral cirrhosis in 28, autoimmune liver diseases (AILD) in 26, genetic hemochromatosis in 10, other in 17. In CHC LS significantly correlated with APRI, FORNS and FIB4 (r = 0.64, 0.51, 0.65; p < 0.001), while in CHB LS did not significantly correlate with FT. In AILD, LS significantly correlated only with FORNSs and FIB4 (r = 0.77, 0.63; p < 0.005). In hemochromatosis LS correlated only with APRI (r = 0.83; p < 0.005). Nor in NAFLD, neither in cirrhosis, any correlation has been observed.

Conclusion: Our data confirm the strong correlation between LS and FT values in CHC, but not in CHB, NAFLD and cirrhosis. Interestingly, our study demonstrated a correlation between LS and FT in AILD and hemochromatosis.
L-ornithine-L-aspartate improves health-related quality of life in cirrhotic patients with hepatic encephalopathy

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¹Institute of Gastroenterology and Hepatology, “Spiridon Hospital” Iasi, Romania
²University of Medicine and Pharmacy “Gr. T. Popa”, Iasi, Romania

Introduction: Hepatic encephalopathy (HE) is a serious complication of cirrhosis. Clinical trials have consistently shown that L-ornithine-L-aspartate significantly improves HE symptoms. Health-related quality of life (HR-QOL) is impaired in HE patients and represents an important outcome measure for therapeutic intervention.

Aim: To assess the impact of L-ornithine-L-aspartate on HRQoL in patients with HE.

Methods: This was an prospective observational study that included 75 cirrhotic patients with HE. Patients were administered three sachets daily of L-ornithine-L-aspartate 6 g dissolved in water taken during or after meals. L-ornithine-L-aspartate was administered over a period of 8 weeks. QoL was assessed by the SF-32 (Short Form-32), one of the most widely used generic instrument for measuring physical and mental health.

Results: Treatment with L-ornithine-L-aspartate for 8 weeks markedly improved all HR-QoL domains, in particular fatigue (67.5% improvement), resulting in a mean ± SD SF-32 sum score improvement from 3.53 ± 1.03 at baseline to 5.04 ± 0.93 at the end of treatment. Symptom severity also improved, with particular benefits seen in fatigue, sleep quality and concentration deficits.

Discussion/Conclusion: Treatment of HE with oral L-ornithine-L-aspartate in cirrhotic patients markedly improved HR-QOL and was well tolerated by 97.8% of patients.
Comparative assessment of the safety and the tolerability of the usual therapies in treatment of autoimmune hepatitis

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Introduction: The aim of this retrospective study was the assessment of the safety and of the tolerability of the budesonide-azathioprine combined therapy in comparation with prednisone-azathioprine combined therapy or prednisone monotherapy in patients with autoimmune hepatitis (AIH).

Methods: We studied 52 patients with AIH (pretreatment aggregate score > 15 in all cases). This comparative study was performed on three groups: the A group composed of 25 patients who received a combined therapy with prednisone (40 mg/day and tapered to 10 mg/day) and azathioprine (1–2 mg/kg/day), the B group with 17 cases treated with Budenofalk® (3 x 3 mg/day) in association with azathioprine (1–2 mg/kg/day) and the C group with 10 patients treated with prednisone monotherapy (60 mg/day and tapered to 20 mg/day). After the normalization of the liver enzymes level, the dose of budesonide was reduced at 6 mg/day. The tolerability of therapies, the incidences and severity of adverse events was monitored for a 12 months period.

Results: At 6 months, complete biochemical remission occurred in 9 cases (36%) of the A group, in 11 cases (64.7%) in B group and in 5 cases (50.0%) in C group. In the A group the side effects were: mild anemia (4 cases), osteoporosis (5 cases), severe leukopenia (2 cases), steroid diabetes (2 cases) and Cushing’s syndrome (3 cases). Multiple side effects were observed in 6 patients (24%). Comparative, the rate of side effects in B group was significantly reduced (27.77%) and 15 patients (83.3%) did not develop steroid-specific side effects. The rate of side effects in prednisone monotherapy was 40.0%. After 6 months, disappearance of clinical symptoms, normal liver biochemistry and histological remission was observed in 21 cases: 7 patients in the A group, 10 cases in B group and 4 cases in the C group. The incidences of the side-effects which appeared in a period between 6 and 12 months were significantly reduced in the B group: only one case with leukopenia due to azathioprine maintenance therapy and one case with thrombocytopenia. In the A group have appeared most side-effects: osteoporosis (2 cases), gastrointestinal bleeding (3 cases), diabetes (one case) and thrombocytopenia (one case). For whole 12 months period, the rate of the discontinuation of the therapy was: 36.0% in group A, 17.6% in B group and 30.0% in the C group.

Discussion/Conclusion: The combined therapy with budesonide and azathioprine assure a high efficacy in patients with AIH and determined low rate of steroid specific side effects. In association with azathioprine, budesonide is more tolerable than prednisone.
The risk of quick development of hepatocellular carcinoma in alcoholic patients with hepatitis C virus infection

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Introduction: The aim of this retrospective 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: the A group consist of 37 heavy alcohol drinkers (intake-over 80 g ethanol/day for more than 10 years) and B group composed of 51 non-alcoholic patients. We monitored and evaluated the clinical manifestations, 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 the A group was 116.25 g/day. In B group, all patients was 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 the A group (89.19%), comparative with B group (68.62%). At 24 and 36 months, the steatosis grade was significantly higher in the 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 the A group and 15.68% in B group. HCC was developed in 9 cases (10.22%): 6 cases in A group and 3 in B group.

Discussion/Conclusion: Association of the HCV infection with alcohol abuse was correlated with high steatosis grade and severe fibrosis. The risk of shortly development of HCC was higher in patients with chronic alcohol consumption and long history of C virus infection.
IL-17 association with CD8+(Tc), CD4+(Th) and CD56+ cells and with liver APCs

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Introduction: IL-17-producing T helper cells (Th-17 cells) (CD4+ IL-17+) have potent pro-inflammatory properties in hepatocellular carcinoma (HCC). However, > 80% of IL-17-producing CD8+ T cells (CD8+ IL17+), Tc17 were found to prevail in the border in HCC. Antigen-presenting cells (APCs) are critical for initiating and maintaining tumor-specific T cell responses and macrophages (Mψ) markedly outnumber other APCs.

The aim of our study was to determine immune cells number in HCC and to comment their cooperation the tumor microenvironment.

Methods: We investigated immunohistochemically HCC (n = 16) and liver hemangioma (n = 4) with IL-17, CD4, CD8, CD68, HLA-DR Ag, FoxP3, CD56 and CD57 antibodies.

Results: IL-17+, CD68+, HLA-DR+, CD8+ and CD4+ cells are significantly higher in number in tumor stroma and border of HCC patients as compared to hemangiomas. IL-17+, CD8+, CD4+, CD56+/CD57+, CD68+ and HLA-DR+ cells prevailed in tumor border than in tumor stroma. On opposite, FoxP3 cells in HCC were less in tumor border as compared to stroma. CD8+ T cells are statistically significantly higher in tumor border and stroma as compared to IL-17+ cells (p < 0.001; p = 0.026, respectively).

Therefore, peritumoral tissue of HCC contained a marked percentage of IL-17-producing Tc17 cells and Th17 cells could be found in the same location.

IL-17-producing cells were statistically significantly higher in number in tumor border and stroma as compared to CD56+ NK/NKT cells (p = 0.023; p = 0.02 respectively). That means that inmate immune response is reduced and the suppressive immune response prevailed in HCC tissue.

Concerning APCs CD68+ Mψ and HLA-DR+ cells were almost similar in number in HCC border and stroma. Therefore tumor associated Mψ showed signs of activation.

In conclusion we may state that IL-17-producing T cells infiltrated HCC tissue and that they might be Th-17 and Tc17 type. It could be supposed that the main APCs (CD68+cells) in the tumor milieu modulate the tolerogenic and immunosuppressive immune response.
MLKL-dependent programmed necrosis in autoimmune hepatitis

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Introduction: Chronic hepatocellular death typically induces compensatory tissue injury responses that finally culminate in severe liver fibrosis, a major cause of morbidity. Although cell death is of fundamental importance to the pathogenesis of many hepatic diseases, precise knowledge about the underlying mechanisms of cell death regulation are still incomplete. MLKL has been identified as a key mediator and potential biomarker of regulated necrosis.

Methods: In vivo mice experiments, human liver tissue analysis.

Results: In order to identify a potential contribution of regulated necrosis to hepatic injury, we initially determined the expression levels of MLKL in cohorts of diverse liver diseases of viral, toxic, or autoimmune origin. Notably, we observed high expression levels of hepatic MLKL in autoimmune hepatitis (AIH) patients, but not in samples of other liver diseases. Interestingly, similar to biopsies from AIH patients, the expression of hepatic MLKL was significantly increased both in mRNA and protein level during ConA induced liver injury, an experimental model of autoimmune hepatitis (AIH). Interestingly, MLKL-deficient mice were almost completely protected from ConA-induced liver injury as demonstrated by low AST and ALT plasma levels as compared to control animals. Correlating necrotic area as demonstrated by H&E staining and measured by TUNEL staining was around 1% in MLKL deficient mice compared to 30% in B6/J mice.

Discussion/Conclusion: The etiology of AIH remains elusive, and there are no reliable biomarkers, which makes it difficult to diagnose. Other diseases that resemble AIH have to be excluded before making a save diagnosis. Here, we identified MLKL as a central mediator of necrotic hepatocellular cell death in a murine model of AIH. We anticipate our finding to be a starting point for the identification of novel biomarkers specific for AIH and the development of novel therapeutic options for liver disorders caused by regulated necrosis.
The precipitating factors of acute-on-chronic liver failure in hospitalized cirrhotic patients: A single center, retrospective study in Belarus

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Introduction: Patients with cirrhosis may develop acute decompensation of cirrhosis as failure of one or more organs so-called acute-on-chronic liver failure (ACLF) syndrome which is usually associated with a precipitating event. Recognition of precipitating event may allow preventing occurrence of multiorgan failure. Aim of the present study was to assess the most common precipitating factors of ACLF in hospitalized patients.

Methods: Consecutive 151 cirrhotic patients who admitted to the Department of Gastroenterology between 2009 and 2011 were analyzed retrospectively. CLIF-C score was calculated for each patient according to the criteria from EASL-CLIF Consortium.

Results: Of the 151 patients 44 were fulfilling to diagnostic criteria for ACLF (29.1%; 95% CI: 22.0–37.1). Median age was 55 (IQR 43–61) years; male 57%. The underlying cause of cirrhosis was alcohol (61%). Among the patients with ACLF the in-hospital mortality rate was 16% and was higher compared to patients without ACLF (p = 0.001). The most common of the organs failure were liver 70.5% (95% CI: 57.0–83.9) and kidney 27.3% (95% CI: 14.1–40.5). Stratification according to the CLIF-C was following: ACLF grade 1 – 68.2% patients, ACLF grade 2 – 15.9% and ACLF grade 3 – 15.9%. The occurrence of ACLF was associated with the upper gastrointestinal bleeding OR = 4.1 (95% CI: 1.5–11.2; p = 0.01). Bacterial infections was not associated with ACLF OR = 2.0 (95% CI: 1.0–4.1; p = 0.05). The white blood cell count was significantly higher in patients with ACLF 12.0 (8.4–19.2) vs. 7.1 (IQR 5.1–9.8), respectively (p = 0.001).

Discussion/Conclusion: In our study the most common precipitating event for ACLF was upper gastrointestinal bleeding. Bacterial infections were not significantly associated with ACLF, but the white blood cell count was significantly higher in patients with ACLF.
Etiology of culture-positive bacterial infections in hospitalized cirrhotic patients

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Introduction: Traditionally, treatment third-generation cephalosporins for the majority of infections in cirrhotic patients due to their efficacy against the main etiologic agents are recommended. In all culture-positive patients antibiotic coverage should be narrowed. We aimed to determine of etiologic agents and antibiotic resistance in hospitalized cirrhotic patients’ group.

Methods: This was a prospective study of 151 patients with cirrhosis in Department of Gastroenterology (between 2009 and 2011). Cirrhosis was clinically and/or histologically confirmed. The types of infections were defined according to the standard criteria.

Results: Out of the 151 patients, 67 patients (44.4%; 95% CI: 36.3–52.7%) had various infections, from which urinary tract infections (UTI), pneumonia and spontaneous bacterial peritonitis (SBP) were the most frequent. Characteristics of the patients with infections were: median age was 52 (IQR 41–59) years; male 39%. Mostly alcohol induced cirrhosis (55%). The culture-positive samples were found in 33 cases from 27 patients. Gram-positive cocci (73%) were the most common causative bacteria in nosocomial infections such as bacteremia/sepsis and SBP. UTI were caused by Enterobacteriaceae’s family (75%) mainly. Among of uropathogens 56% were resistant to third-generation cephalosporins, which are most used in our unit. Multi-resistant etiologic agents of UTI were the following: E. coli, P. agglomerans, Acinobacter spp. The rate of multi-resistant bacteria was 18.5% (95% CI: 6.3–38.9). At the same time among bacteria which caused UTI were susceptible to quinolones 93%.

Discussion/Conclusion: The rate of third-generation cephalosporins-resistance gram-negative bacteria is high among cirrhotic patients with UTI in our unit. Gram-positive cocci were responsible for 73% of severe nosocomial culture-positive infections. The current management of infections in cirrhotic patients’ group should be correct according to the results of microbiological monitoring in local unit.
Spleen stiffness – Predictor factor of clinical decompensation in hepatic cirrhosis

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Introduction: Recently, baseline spleen stiffness measurement (SSM) and MELD score have been proved to be predictors of clinical decompensation (CD) in patients with HCV related cirrhosis. We present here our real life experience using SSM and modified SSM (mSSM) as long-term predictors of CD in cirrhotic patients.

Methods: Fifty-two consecutive compensated cirrhotic patients were enrolled. All patients underwent at inclusion LSM, SSM, abdominal ultrasound and liver function tests. CD was defined as the occurrence of one of the following: variceal bleeding, development of ascites, hepatic encephalopathy, jaundice (total bilirubin > 3 mg/dl), infection, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatocellular carcinoma, death or liver transplantation. Multivariate logistic regression was used to identify independent predictors of CD, based on which a decompensation prediction score (DPS) was computed and further analyzed.

Results: During the median follow-up period of 13 months (range 1–28), 23 (44%) patients became decompensated: ascites 7 patients, infection/SBP 6 patients, variceal bleeding 4 patients, HE and HCC 3 patients. Three (5.6%) patients died and 14 (26.4%) had more than one episode of CD. Bilirubin, Albumin, portal vein and spleen diameter and mSSM were associated with CD, but only mSSM (OR = 1.085 [95% CI: 1.02–1.15]; p = 0.01), Albumin (OR = 0.17 [95% CI: 0.03–0.76]; p = 0.02) and Bilirubin (OR = 1.64 [95% CI: 0.99–2.71]; p = 0.05) were found to be independent predictors.

Discussion/Conclusion: In this heterogeneous population of cirrhotics mSSM was found an independent predictor of CD. Data support the conclusion that SSM may have an even more important clinical relevance, besides its previously demonstrated roles: non-invasive prediction of large esophageal varices and clinically significant portal hypertension.
Hepatitis C virus-related cryoglobulinemic vasculitis: Russian single-center experience

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Introduction: Hepatitis C virus (HCV)-induced mixed cryoglobulinemia (MC) vasculitis is autoimmune disorder with significant morbidity and mortality. The best treatment for this disorder is still a matter of debate.

Aims: To analyze the prevalence, clinical presentation, outcomes of HCV-MC vasculitis and efficacy of the therapeutic approach.

Methods: 1352 patients with chronic hepatitis C were analyzed in 1995–2013. Prospective study included 72 patients (m/f – 23/49, age – 49.4 ± 10.3) with HCV-MC vasculitis. The Birmingham vasculitis activity score (BVAS) was utilized before treatment and during follow-up (3.5 ± 4.1 years). The response to antiviral treatment (IFN-α or PEGIFN-α and ribavirin at least 6 months) was analyzed 6 months after completion of therapy in 25 cases, the response to conventional immunosuppressive drug (CID) or rituximab (RTX) – in 31 and 15 cases respectively.

Results: We have found MC and MC-vasculitis in 453 (33.5%) and 72 (5.3%) of 1352 patients respectively. Among 72 patients with MC-vasculitis 24 (33,4%) had liver cirrhosis, 47 (65.3%) – genotype 1 HCV and other – genotype 2 or 3. BVAS before treatment was 11.9 ± 7.2 (ranges from 2 to 36). 22 (30.6%) patients had BVAS ≥ 15. 7 (9.7%) patients had B-cell non-Hodgkin lymphomas.

We established the superiority of RTX over CID in patients with MC vasculitis: complete clinical response 73.4% vs. 12.9% (p = 0.001). After antiviral treatment, complete clinical and immunological responses were achieved in 68.0% and 32.0% respectively, and associated with sustained viral response (48.0%). Most these patients showed a persistent recovery. Frequency of relapse after antiviral therapy was significantly lower than after CID or RTX treatment (21.4% vs. 73.9%; p = 0.005) and duration of remission was longer (30.6 ± 22.7 vs. 8.7 ± 9.0 months; p = 0.005).

16 patients had dead mainly of infection (37.5%), cardiovascular complications of vasculitis and renal failure (37.5%) and end-stage liver disease (25%). Age > 55 years (HR = 4.49), liver cirrhosis (HR = 3.64), renal insufficiency (HR = 4.66) and use of CID (HR = 3.91) significantly associated with a poor prognosis. Only antiviral treatment (HR = 0.01) was associated with good prognosis.

Conclusion: 5% of patients with HCV-infection have MC-vasculitis. MC-vasculitis can determine a poor long-term outcome. All patients with HCV-induced MC-vasculitis irrespective of the stage of the liver fibrosis should be offered the best available antiviral treatment. The interferon-free options are highly welcome. RTX is a very good option for severe MC-vasculitis.
Current situation of antiviral therapy in patients with chronic hepatitis B in Mongolia

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Background: It is estimated that about 240 million people are suffering from chronic hepatitis B infection worldwide. A recent population based study reported that 10.6% of 20 years and older Mongolians are HBsAg-positive. In addition, 67.5% of HBsAg-positive subjects tested positive for anti-HDV. Although, there are effective antiviral treatments available for chronic hepatitis B patients, the coverage of antiviral treatment is not ideal. The coverage is mainly hindered by lack of health professionals training, drug costs, long-term treatment and monitoring. The aim of study to evaluate current care level for chronic hepatitis B infection in tertiary care hospital in Mongolia.

Methods: A retrospective study was carried out to review records of all chronic hepatitis B patients who had HBV-DNA viral load testing between 2014–2015 at the UB Songdo hospital in Mongolia. All data were analyzed MS Excel and SPSS17 programs.

Results: A total of 372 patients were included, male 199 (53.5%), age range 10–75 years (41.36 ± 11.5). There were 294 (79%) patients had chronic hepatitis B infection, 19 (5.1%) were coinfected with chronic hepatitis B and D, 53 (14.3%) had cirrhosis caused by HBV, and 6 (1.6%) had hepatocellular carcinoma. All patients were tested for HBV-DNA viral load, ALT level, for some patients HBeAg and anti-HDV status were determined (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>HbeAg</th>
<th>Anti-HDV</th>
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<tbody>
<tr>
<td>Positive</td>
<td>9 (2.42% of total patients)</td>
<td>37 (9.94% of total patients)</td>
</tr>
<tr>
<td>Negative</td>
<td>56 (15.05% of total patients)</td>
<td>10 (2.69% of total patients)</td>
</tr>
<tr>
<td>Total</td>
<td>65 (17.47% of total patients)</td>
<td>47 (12.63% of total patients)</td>
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<table>
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<tr>
<th>ALT level</th>
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<th>2000–20,000 IU/ml</th>
<th>&gt; 20,000 IU/ml</th>
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<td>19</td>
<td>110</td>
<td>16</td>
<td>19</td>
<td>164</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
<td>238</td>
<td>42</td>
<td>31</td>
<td>372</td>
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</tbody>
</table>

With existing test results if use current treatment standard 88 (23.7%) patients would have required antiviral treatment. However, only 28 (7.5%) patients had antiviral treatment (3 (0.8%) had tenofovir, 4 (1.07%) had Peg-IFN, 20 (5.38%) had entecavir, and 1 (0.27%) patient was treated with lamivudine).

Conclusion: This results show that current clinical care level for HBV patients are not adequate. Essential diagnostic tests such as HBeAg and anti-HDV were not offered for all HBsAg-positive patients. Furthermore, only fraction of patients were offered treatment.
Immunomodulating effect of UDCA in patients with autoimmune hepatitis type 1

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Introduction: Ursodeoxycholic acid (UDCA) has been reported to be a safe and effective therapy for patients with cholestatic liver diseases, suggesting that UDCA has immunomodulating effects. Autoimmune hepatitis (AIH) is chronic liver disease which is characterized by immunological abnormalities and continuing hepatocellular inflammation which can progress to cirrhosis.

Methods: Eleven patients (9 female, 2 male) with AIH type 1 were treated with 15 mg/kg/day of UDCA in the period of 2 to 12 years. Based on the criteria of the AASLD, ten patients were diagnosed as definite and one as probable type 1 AIH. Liver function tests were performed every 8 weeks, before and during UDCA therapy and the serum levels of anti-nuclear antibodies (ANA), smooth muscle antibodies (SMA), immunoglobulin G and gamma globulin were determined every 6 months. Liver biopsy was performed every 2 years of the treatment.

Results: The levels of serum aspartate aminotransferase and alanine aminotransferase significantly decreased after 6 months of treatment in 10/11 patients. After 1 years of treatment, the levels of serum immunoglobulin G and gamma globulin significantly decreased (p < 0.05) and ANA titres (6/11 patients) were reduced. SMA (4/11 patients) and ANA (3/11) became negative. The beneficial effect of UDCA on the liver histology was assessed in 8 out of 11 patients. One patient underwent liver transplantation because of stage of the disease (after 12 years of the therapy).

Discussion/Conclusion: Our results suggest that UDCA therapy improves biochemical and immunological variables in patients with AIH type 1 and can be useful therapeutic agent for autoimmune-associated chronic diseases.
Non-invasive estimation of disease activity and liver fibrosis in non-alcoholic fatty liver disease using anthropometric biochemical characteristics, and \textsuperscript{13}C-methionine breath test

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Introduction: Non-alcoholic fatty liver disease (NAFLD), which occurs in patients with no or low daily alcohol consumption ($\leq 30$ g/day for men, $< 20$ g/day for women), encompasses simple steatosis (fatty liver), non-alcoholic steatohepatitis (NASH; characterized by steatosis and necroinflammatory activity commonly associated with varying fibrosis stages), and NAFLD-associated cirrhosis. NAFLD is currently the most common liver disease worldwide with a prevalence of 20–30% in Europe and in the Middle East, and 10–35% in the United States. The purpose of this study was to investigate the non-invasive estimation of disease activity and liver fibrosis in patients with non-alcoholic fatty liver disease (NAFLD) using anthropometric, biochemical characteristics and the \textsuperscript{13}C-methionine breath test (MeBT).

Methods: A total of 164 patients with histologically proven NAFLD and 56 healthy controls were included in the study. Anthropometric, biochemical analysis and the MeBT were performed on all patients and controls.

Results: Body mass index, waist circumference, waist-hip ratio, transaminases, lipids, gamma glutamyl transpeptidase (GGT), glucose, insulin, and insulin resistance were significantly higher in the patients with NAFLD than in the controls. GGT and the MeBT were independent predictors of non-alcoholic steatohepatitis (NASH). Fibrosis was correlated with GGT, bilirubin, cholesterol, insulin, and the MeBT, but the test was the only independent predictor of significant fibrosis. Patients with simple steatosis had similar MeBT values as controls. The MeBT values were significantly lower in NASH and NASH-cirrhosis patients ($p < 0.001$) compared to the values in patients with simple steatosis and the controls. Patients with advanced fibrosis (F2–3) had significantly lower MeBT values than patients with mild fibrosis (F0–1; $p < 0.001$). The area under the receiving operator characteristic curve for NASH and advanced fibrosis was estimated to be 0.95 in the total cohort.

Discussion/Conclusion: This study indicates that anthropometric and biochemical parameters are insufficient for estimating the presence of NASH or the fibrosis stage. However, the MeBT is a suitable non-invasive method for accurately predicting which subjects suffer from simple steatosis, NASH, or NASH-cirrhosis.
Blood levels of immunoglobulins superfamily molecules in dynamics of treatment of non-alcoholic steatohepatitis

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By present time the schemes of therapy of non-alcoholic steatohepatitis are not developed and far from desirable efficiency. There are no data on dynamics of parameters of immunoglobulins superfamily during treatment of non-alcoholic steatohepatitis that would give us the chance to predict occurrence and stability of disease remission.

The aim of study is to assess the influence of treatment of non-alcoholic steatohepatitis on plasma levels of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), platelet-endothelial cell adhesion molecule-1 (PECAM-1).

**Methods:** 42 patients with non-alcoholic steatohepatitis were examined. The patients were divided into three groups: 17 patients received endothelioprotector with antiTNFα activity pentoxyphylline (group I), 10 patients were treated by insulin sensitizer metformin (group II), in 15 patients treatment included only modification of diet and physical activity (group III). The control group included 60 healthy volunteers. Blood concentration of ICAM-1, VCAM-1, PECAM-1 were carried out by means of ELISA. Statistically significant values were considered for p < 0.05.

**Results:** Plasma levels of all adhesion molecules were increased in non-alcoholic steatohepatitis. In group I blood levels of ICAM-1 and VCAM-1 decreased and plasma concentration of PECAM-1 normalized during 3 month of treatment. In group II parameters of PECAM-1 and VCAM-1 decreased and plasma concentration of ICAM-1 normalized during 3 month of treatment. In group III reduction of plasma levels of all molecules of immunoglobulins superfamily was observed, however their values were more than in control group.

**Conclusion:** In patients with non-alcoholic steatohepatitis positive changes of adhesion molecules in blood are observed in dynamics of three months of therapy which are more expressed in cases of use of endothelioprotector or insulin sensitizer treatment.
Non-invasive biomarkers of liver fibrosis in primary biliary cirrhosis overlap syndrome: A retrospective study in Albania

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Introduction: Autoimmune hepatitis (AIH) is an uncommon disease in Albania. Information on non-invasive predictors of primary biliary cirrhosis (PBC) overlap syndrome in Albanian patients with AIH is scarce. Our aim was to evaluate the immunological features and non-invasive biomarkers of AIH-PBC overlap syndrome in Albanian patients.

Methods: 96 consecutive patients (69% in Tirana, Albania) were included in the study from 2005 until 2013. The Model for End-Stage Liver Disease (MELD) was used to assess patients with AIH or PBC overlap syndrome at the University Hospital Center Mother Teresa by means of non-invasive biomarkers of fibrosis: AST to platelet ratio index (APRI), platelet count to spleen diameter (PC/SD), AST to ALT ratio (AST/ALT), the age-spleen-platelet ratio index (ASPRI), and fibrosis-4 score based on age, ALT, AST and platelet count (FIB-4).

Results: Of the 96 patients, 16 (16.7%) were diagnosed with AIH-PBC overlap syndrome. The mean age of patients with overlap PBC was 54; the range was 28–74 years old and all tested positive for antimitochondrial antibodies. The mean values of non-invasive biomarkers and immunological features of all patients can be found in the table below. At the time of diagnosis, the mean MELD score was significantly higher among overlap PBC patients than pure AIH patients (16.5, range: 7.0–34.0 vs. 14.0, range: 6.0–22.0; p < 0.05). The liver biochemical profiles did not differ significantly between the two groups. Other AI diseases were observed in 31.2% of patients with overlap PBC versus 27.5% of the remaining AIH patients.
Table: Differences in immunological and non-invasive biomarkers between patients with AIH and patients with overlap PBC

<table>
<thead>
<tr>
<th>Features</th>
<th>Pure AIH (80 patients)</th>
<th>Overlap PBC (16 patients)</th>
<th>P value&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive for antinuclear antibodies; n (%)</td>
<td>48 (60%)</td>
<td>6 (37.5%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Positive for smooth muscle antibodies; n (%)</td>
<td>53 (66.3%)</td>
<td>13 (81.3%)</td>
<td>0.09</td>
</tr>
<tr>
<td>APRI&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2.0 (1.0–26.0)</td>
<td>1.0 (1.0–29.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>PL/SD&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1074.0 (125.0–3758.0)</td>
<td>1269.0 (167.0–4330.0)</td>
<td>0.45</td>
</tr>
<tr>
<td>AST/ALT&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1.18 (0.28–3.62)</td>
<td>1.0 (0.25–3.0)</td>
<td>0.31</td>
</tr>
<tr>
<td>ASPRI&lt;sup&gt;2&lt;/sup&gt;</td>
<td>12.0 (5.0–80.0)</td>
<td>10.0 (2.0–64.0)</td>
<td>0.99</td>
</tr>
<tr>
<td>FIB-4&lt;sup&gt;2&lt;/sup&gt;</td>
<td>3.0 (0.57–33.15)</td>
<td>4.29 (0.47–26.24)</td>
<td><strong>0.04</strong></td>
</tr>
</tbody>
</table>

<sup>1</sup>Unpaired test/Fisher’s exact test; p < 0.05 was considered significant.
<sup>2</sup>Median values are shown with ranges in parentheses.

Conclusions: Overlap PBC is frequently observed in patients with AIH. Our findings show that MELD and FIB-4 may become first-line tools for predicting overlap PBC among AIH patients. Further prospective studies are required to monitor patients’ outcome.
Serum sterol levels indicate distorted cholesterol homeostasis in cirrhotic patients with primary biliary cirrhosis

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Introduction: In humans new cholesterol derives from de novo synthesis and intestinal absorption. Serum cholesterol precursor (e.g., lathosterol, desmosterol) and plant sterol levels (e.g., sitosterol, campesterol) represent valid surrogate marker for cholesterol biosynthesis and intestinal absorption, respectively. Since chronic liver diseases modulate cholesterol homeostasis, we systematically investigated sterol serum levels in patients with primary biliary cirrhosis (PBC) with and without liver cirrhosis.

Methods: Overall, we recruited 111 non-transplanted PBC patients (age 22–83 years, 101 females). In this cohort, a total of 30 individuals presented with liver cirrhosis at diagnosis. Serum concentrations of plant sterols, cholesterol and its precursors were measured by gas chromatography/mass spectrometry (GC/MS). Individuals with results suggesting familial hypercholesterolemia or phytosterolemia were excluded. Serum sterols were compared between cirrhotic and non-cirrhotic patients using non-parametric tests.

Results: PBC patients with liver cirrhosis demonstrated significantly higher serum sitosterol and campesterol concentrations than non-cirrhotic individuals (p = 0.0002 and p = 0.007, respectively). Serum levels of lathosterol and desmosterol were lower in these patients (p = 0.0001 and p = 0.01, respectively), who also displayed a trend to lower serum cholesterol (p = 0.06). In cirrhotic patients we identified increased sitosterol:cholesterol and campesterol:cholesterol but decreased lathosterol:cholesterol ratios (all p < 0.0001). Overall, the ratios of phytosterols to cholesterol precursors were significantly (all p > 0.0001) increased in patients with liver cirrhosis as compared to non-cirrhotic patients.

Discussion/Conclusion: PBC patients with liver cirrhosis are characterized by decreased cholesterol synthesis and increased sterol absorption as compared to non-cirrhotic individuals. The determination of serum sterols may improve the clinical assessment and stratification of patients with PBC.
Identification of PXR haploinsufficiency by next generation sequencing in a patient with anabolic steroid-induced cholestasis

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Introduction: Use of anabolic steroids (AAS) is increasing among amateur athletes. Many AAS users report side effects, including severe cholestasis in selected cases. The lack of genome-wide association study signals for drug-induced liver injury (DILI) beside the known major histocompatibility complex risk alleles supports the concept that strong genetic determinants of DILI may be largely drug-specific and reflect rare genetic variations.

Methods: A 32-year-old Caucasian male with no significant medical history was admitted to our department with acute AAS-induced cholestasis. He had taken AAS for two months. Acute jaundice and pruritus developed two weeks after termination of AAS. Laboratory tests revealed increased serum bilirubin level but normal alkaline phosphatase and aminotransferase activities. Viral and non-viral liver diseases were excluded. Liver biopsy showed blunt cholestasis. To investigate the genetic predisposition for this severe cholestatic phenotype, we performed targeted next generation sequencing (NGS: Illumina MiSeq) covering all coding sequences of selected genes (ABCB4, ABCB11, ATP8B1, ABCC2, ABCG5/8, CIRH1A, CLDN1, JAG1, NOTCH2, NR1H4, NR1H2, VIPAR, VPS33B, UGT1A) involved in hepatobiliary transport.

Results: The genotyping revealed the presence of a heterozygous 2 base pair deletion in exon 1 of the pregnane X receptor (PXR: nuclear receptor NR1II2). The mutation results in a frameshift (c.43_44del: p.R15fs), which causes complete loss of functional protein and thereby haploinsufficiency of PXR. Under therapy with prednisone, rifampin and ursodeoxycholic acid as well as albumin dialysis, pruritus and jaundice normalized, and the patient was discharged without any signs of persistent liver disease.

Discussion/Conclusion: To our knowledge this is the first case report of a patient with inherited PXR insufficiency who developed acute AAS-induced cholestasis. Our results pinpoint the genetic predisposition to develop cholestasis after use of AAS, and further NGS-based studies are encouraged to determine the full spectrum of private mutations in nuclear receptor genes that increase the risk of drug-induced cholestasis.
Reduction of caloric intake overrides the prosteatotic effects of the PNPLA3 p.I148M variant in patients with fatty liver: Ultrasound-based prospective study

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Introduction: The PNPLA3 (adiponutrin) polymorphism p.I148M represents the common genetic risk factor for non-alcoholic fatty liver disease (NAFLD) (Krawczyk, Portincasa, Lammert. Semin Liver Dis. 2013). High-caloric diet, in turn, represents the major modifiable (i.e. non-genetic) trigger of hepatic steatosis. In the current study we assess the effects of caloric restriction on liver phenotypes in patients with NAFLD in relation to PNPLA3 genotypes.

Methods: We genotyped the PNPLA3 variant in 143 Caucasian individuals with NAFLD (55 females, age 18–74 years, BMI 22.5–48.1 kg/m²) and 180 controls (85 females, age 33–66 years, BMI 17.6–46.3 kg/m²). Liver steatosis was assessed using the ultrasound-based Hamaguchi score. A 4-month dietetic intervention, consisting of restriction of daily caloric intake without changes in physical activity, was performed.

Results: The PNPLA3 variant increased the risk of NAFLD (OR = 2.35, 95% CI: 1.08–5.12, p = 0.033). Overall, 93 NAFLD patients completed the dietetic intervention, which led to a significant decreases of hepatic steatosis (p < 0.0001), serum ALT activities (p < 0.0001), BMI, hip and waist circumferences as well as waist-hip ratio (p < 0.0001). Hepatic steatosis, metabolic and anthropometric traits significantly (p < 0.05) improved in carriers of PNPLA3 mutations. The degree of improvement of phenotypic traits, apart from the waist-hip ratio (p = 0.02), was not affected by the presence of the PNPLA3 risk allele.

Discussion/Conclusion: We replicate the association between the PNPLA3 polymorphism and NAFLD in individuals from Central Europe. A caloric restriction, even without changes in physical activity, rapidly improves hepatic steatosis, with the presence of the PNPLA3 risk allele not impairing the response to the dietetic intervention in patients with NAFLD.
The soluble form of cluster differentiation 14 and the lipopolysaccharide binding protein plasma level in liver cirrhosis

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Objective: To examine changes of the soluble form of cluster differentiation 14 (sCD14) and the lipopolysaccharide binding protein (LPB) in the blood plasma of patients with liver cirrhosis (LC).

Methods: sCD14 and LPB were studied in 120 patients with LC (66 men and 54 women aged from 30 to 60 years). The control group (CG) – 25 healthy donors. The level of sCD14 and LPB were determined by ELISA using the test – systems of “Hycult Biotech” (Netherlands).

Results: sCD14 and LPB concentrations in LC were significantly higher than in CG (mean 5.4 ± 0.2 mcg/l vs. 2.7 ± 0.3 mcg/l; \( \chi^2 = 16.8; p = 0.002 \) and mean 43.0 ± 1.4 mcg/l vs. 13.5 ± 0.9 mcg/l; \( p = 0.001 \)). sCD14 and LPB values were correlated in LC (\( r = 0.63; p = 0.001 \)). sCD14 and LPB concentrations associated with the activity of inflammation and severity of LC class on the Child-Pugh. Mean values for sCD14 and LPB in LC class “A” (55.8% patients) were 4.8 ± 0.2 mcg/l and 37.9 ± 2.1 mcg/l; class “B” (24.2%) – 5.3 ± 0.3 mcg/l and 43.8 ± 2.5 mcg/l; class “C” (20%) – 5.8 ± 0.3 mcg/l and 48.9 ± 2.3 mcg/l. Reliability of distinctions was noted between classes “A” and “C” (\( p = 0.042 \) and \( p = 0.048 \)). Growth of the concentration of sCD14 and LPB was observed in a high portal hypertension and gastroesophageal varices of high gradation.

Conclusion: An average concentration increase of markers of the innate immune system – sCD14 and LPB was shown in patients with LC. The growth of sCD14 and LPB showed the appearance small bowel bacterial overgrowth syndrome, bacterial translocation, systemic endotoxemia and anti-endotoxin immunity stimulation in LC. sCD14 and LPB growth was associated with the activity of the pathological process in the liver, the severity of clinical manifestations of LC and hepatocellular insufficiency.
Study on knowledge awareness of viral hepatitis among Mongolian population

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**Introduction:** Worldwide, 1 out of 3 people affected by hepatitis B virus infection, approximately 150 million people living with chronic hepatitis C infection and each year more than 1 million people dying of viral hepatitis and its complications. In Mongolia, it is estimated that around 400 thousand people living with chronic viral hepatitis. However, most of the affected people are not aware of their infection status and most of the people are not educated about liver diseases. Therefore, in this study we evaluated the current understanding about transmission and prevention of hepatitis B and C virus within the general population and the main source they are getting the information.

**Methods:** Overall 1383 people participated in this study. All participants are inhabitants of 14\textsuperscript{th} khoroo’s family health center, Khan-Uul district, Ulaanbaatar. Subjects answered detailed questionnaire based survey. All analysis was done using MS Excel and SPSS v17.

**Results:** Among the population knowledge about B and C virus transmission identified the following questions. The majority of participants (63\%) identified used syringes and needles are not safe. Similarly, 61\% of participants agreed that sharing razor blades, toothbrush and other personal hygiene tools with infected person carries a risk of infection transmission. In addition, sexual transmission was identified as a risk in 35\% of the participants. Also, there were some subjects (9\%) believe that shaking hands with infected person put them in risk for infection. Overall, 43.8\% of all participants answered they do not know enough about viral hepatitis transmission pathways. The majority 61\% of all participants answered that hepatitis B and C lead to liver cancer. Despite the understanding of its seriousness only 56\% knew HBV can be prevented by vaccines and 46\% think that there is a vaccination against HCV. Results of these survey also indicate that TV programme (41\%) and internet based (24\%) information could reach these participants better.

**Conclusion:** This study results indicate that despite the high burden of viral hepatitis and liver cancer, the awareness of viral hepatitis is not adequate. Awareness campaign may be carried out using TV and internet based information distribution.
The role of non-alcoholic steatohepatitis in potentiating risk of drug-induced liver injury in patients with acute leukemia

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Polychemotherapy (PCT) in patients with leukemia acute (LA) is fraught with a high risk of liver injury, which is associated with the direct and indirect hepatotoxic effect of cytotoxic drugs on hepatocytes. Liver injury can be a limiting factor of the PCT, in accordance with the doses and administration regimens of cytotoxic drugs under the protocols, thereby reducing the percentage of clinical remission achievement. From this point of view, deserves particular attention the risk assessment of hepatotoxic reactions development.

The aim – to determine the frequency and nature of drug-induced liver injury in patients with LA in the dynamics of chemotherapy, depending on the presence of concomitant non-alcoholic steatohepatitis (NASH).

Materials and methods: The study involved 74 patients with newly diagnosed LA 18 (24.3%) – acute lymphoblastic leukemia (ALL), 56 (75.7%) – acute myeloid leukemia (AML), age 17–69 years, including man – 39 (52.7%), women – 35 (47.3%), according to ECOG I–II. NASH was diagnosed in 18 (24.3%) patients. We determined the activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltranspeptidase (GGT), alkaline phosphatase (AP), with their assessment according to CTCAE before treatment and after the first course of remission induction under the protocols of ALL and AML treatment.

Depending on the presence of NASH patients were divided into 2 groups: I group (n = 56) – LA without NASH; II group (n = 18) – LA with NASH.

Results: Before chemotherapy in patients of group I the functional liver condition parameters did not differ from normal: ALT 28.07 ± 6.34 U/l, AST 23.94 ± 5.79 U/l, AP 136.24 ± 24.56 U/l, GGT 39.08 ± 6.91 U/l. In patients of group II ALT activity was 59.9 ± 6.6 U/l, AST 32.94 ± 7.24 U/l, ALP 184.61 ± 30.09 U/l, GGT 69.07 ± 8.71 U/l. On the 28th day from the beginning of PCT in the group I the studied parameters increased up to 2 upper limits of normal (ULN) in 16 (28.6%) patients, grade I on CTCAE, ALT activity was 38.11 ± 16.14 U/l, AST 29.08 ± 13.06 U/l, ALP 198.19 ± 44.08 U/l, GGT 46.18 ± 15.01 U/l.

In patients with AL and concomitant NASH (group II) the studied parameters increased up to 2 ULN grade I on CTCAE – in 11 (61%) patients, from 2 to 5 ULN grade II on CTCAE – in 7 (39%) patients. The ALT activity in patients of group II was 68.04 ± 18.01 U/l, AST 46.03 ± 19.07 U/l, ALP 284.61 ± 41.01 U/l, GGT 109.2 ± 19.9 U/l.

Thus, hepatotoxic reaction in the dynamics of the first induction chemotherapy course were observed in 28.6% of patients without functional liver condition violation and in 100% of patients with concomitant NASH. The identified liver injury was characterized by a combination of cytolitic and cholesstatic syndromes with maximum activity in patients of group II.
High accuracy of soluble Axl in the differential diagnosis of chronic liver diseases and hepatocellular carcinoma

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Introduction: Diagnosis of hepatocellular carcinoma (HCC) at early stages allows curative therapies, whereas treatment options at later stages are very limited. State-of-the-art diagnosis of HCC by ultrasonography and determination of serum α-fetoprotein (AFP) levels shows moderate sensitivity and limited specificity, thus highlighting the need for more accurate biomarkers in the diagnosis of early stage HCC. In this multicenter study we assessed the potential of soluble Axl (sAxl) as a diagnostic biomarker of early HCC and cholangiocellular carcinoma (CCC) as well as examined the value of sAxl in the differential diagnosis between chronic liver diseases (CLDs) and HCC.

Methods: Levels of sAxl, a cleavage product of the receptor tyrosine kinase Axl, were analyzed by enzyme-linked immunosorbent assay in 814 serum samples from centers in Europe and China.

Results: Analysis of sAxl showed significantly increased levels in HCC as compared to healthy controls. Receiver operating characteristics (ROC) curve analysis revealed high sensitivity and specificity of sAxl in very early stage HCC (BCLC 0) and early HCC (BCLC A) compared to AFP. HCC patients negative for AFP displayed significant sAxl serum levels and combination of sAxl and AFP improved diagnostic accuracy in very early HCC patients. Differential diagnosis revealed high levels of sAxl in HCC versus CLDs derived from non-alcoholic fatty liver disease (NAFLD/NASH), autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC). These CLDs categorized by fibrosis and cirrhosis scoring showed accurate values of sAxl in the differential diagnosis between fibrosis/cirrhosis and HCC. Interestingly, sAxl failed to be elevated in CCC and in secondary hepatic malignancies derived from colorectal carcinoma. Furthermore, independent stress testing revealed storage and temperature stability which corroborates the potential of sAxl as valuable diagnostic biomarker.

Discussion/Conclusion: In summary, sAxl is a stable serum biomarker showing enhanced levels in HCC but not in CLDs, CCC or secondary liver malignancies.
Long-term UDCA therapy in the patients with primary biliary cirrhosis

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**Introduction:** Primary biliary cirrhosis (PBC) is a progressive cholestatic liver disease leading to development of liver cirrhosis. Ursodeoxycholic acid (UDCA) has been reported to be a safe and effective therapy for patients with PBC. The aim of this study was to determine a favorable effect of UDCA on clinical, biochemical and histological features of the disease.

**Methods:** Twenty-nine patients with biochemical and histological proven PBC received 15 ± 2 mg/kg/day UDCA for a minimum period of four years. The biochemical parameters of cholestasis and hepatocellular damages were compared every two months, and fine-needle liver biopsy was performed before and after every two years of the therapy.

**Results:** UDCA therapy was associated with significant improvements in serum biochemical liver tests (aminotransferases, alkaline phosphatase), serum bilirubin level, immunoglobulin levels and blood coagulation factors. UDCA also markedly improved clinical symptoms of the disease (jaundice, pruritus, fatigue). The beneficial effect of UDCA on the liver histology was assessed in 24 out of 29 patients. Improvement in some histological features was found in 12/29 patients, but not in histological stage.

**Discussion/Conclusion:** Our results strongly confirm that long-term therapy with UDCA in PBC improves biochemical and clinical variables, and delays histological progression of cirrhosis which leads to prolongation of transplant-free survival after 4 years of the treatment.
High prevalence of HDV infection in Mongolia

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Introduction: Mongolia has one of the highest prevalence of hepatitis B and C. Consequently, leading mortality rates of liver cirrhosis and hepatocellular carcinoma in the world. In clinical practice it is thought that HDV infection is on the rise. However, HDV infection was not formally studied in Mongolia.

Aim of study: To study the prevalence of HDV infection in Mongolia

Method and subject: Study subjects were chosen based on two-stage cluster random sampling method. Total of 1158 “healthy” subjects (20–70 ages) were enrolled in this study. 499 (43.1%) of them men and 659 (56.9%) female. All participants on-site tested for HBsAg using rapid tests (CTK Biotech, San-Diego, US). Also, 5–10 ml of blood was drawn from antecubital vein and sera were separated following a standard protocol. Rapid test positive tested subjects’ serum specimens were tested for HBsAg, anti-HD-Ab and HD-Ag by enzyme-linked immunosorbent assay (Diasorin, Italy). All anti-HDV positive serum tested for HDV-RNA by RT-PCR.

Results: The overall prevalence of HBsAg among study subjects were 10.6% (123/1158). From 123 HBsAg-positive subjects 83 were tested positive for HD-Ab (67% of HBsAg-positive population and 7.2% of total population) and 8 subjects were tested positive for HD-Ag (6.5% of HBsAg-positive population). From 83 anti-HDV positive tested serum, there was positive tested HDV-RNA in 51 serum. This mean is that prevalence rate of HDV infection 4.5% in total population.

Conclusion: Prevalence of HDV infection is alarmingly high in Mongolian population. It indicates that there is an urgent need for concerted action from all stakeholders within the Mongolian healthcare system.
The role of clinical scores and hs-CRP level in NAFLD progression

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Non-alcoholic fatty liver disease (NAFLD) is a clinical spectrum that includes simple fatty liver or steatohepatitis with varying degrees of inflammation, progressing to fibrosis and finally to cirrhosis and hepatocellular carcinoma. High-sensitivity C-reactive protein (hs-CRP) is a marker of inflammation and some studies have shown a potential role of hs-CRP in differentiating simple fatty liver from NASH.

Introduction: Aim of our study was to correlate hs-CRP level with 2 scores related with simple fatty liver: fatty liver index (FLI) and NAFLD liver fat score (NAFLD-LFS) and NASH predictive score – GHOLAM score (reference value 8.22).

Methods: We included 50 patients with NAFLD, 18 males and 32 females with mean age 56.4 years. 28% patients were overweight, 62% were obese and 10% had normal weight. We practice liver biopsy in all patients. Blood samples were collected to determine: aminotransferases, glucose, albumin level, GGT, platelet count, hs-CRP. In all patients we calculated BMI, WC, FLI, NAFLD-LFS and GHOLAM score, than we correlated with histological samples and hs-CRP level.

Results: After the examination of histological samples we found: 2 patients with steatosis < 5% so we classified them as S0, 38% patients had S1, 34% had S2 and 24% had S3. We found significant correlation between the degree of steatosis and metabolic syndrome (p = 0.00018), aminotransferases levels (p < 0.05) and hs-CRP (p < 0.005). We calculated FLI and NAFLD-LFS and we found a significant correlation with histological samples (pChi < 0.0001; pFisher = 0.0049). With sensibility > 95% and specificity = 100% these scores are very useful to predict the presence of steatosis. hs-CRP correlated statistical significant with steatosis scores (p < 0.005) and histological classification of steatosis. GHOLAM score was greater than 8.22 in all patients, so we can't make any difference between the patients with or without NASH using this score. hs-CRP did not correlate with GHOLAM score or presence of inflammation.

Discussion/Conclusion: In our study hs-CRP was a predictive marker for the degree of steasosis but not for the presence of inflammation. Steasosis scores were useful in clinical practice but NASH score was not predictive for inflammation.
Osteoporosis and chronic inflammation in NAFLD obese females

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Bone mineral density (BMD) is influenced by both intrinsec and extrinsec environmental factors. Hyperleptinemia is commonly observed in obese and it seems to be related with proinflammatory effect. High-sensitivity C-reactive protein (hs-CRP) is also, a marker of inflammation.

Introduction: Aim of our study was to correlate leptin and hs-CRP level with BMD in obese females with or without NAFLD.

Methods: We included obese females in postmenopausal period for at last one year: 54 with NAFLD and 56 without NAFLD, age, waist circumference (WC) and body mass index (BMI) matched. Exclusion criterias: diabetes mellitus, chronic use of corticosteroids, supplementation with calcium products, secondary obesity due endocrine diseases, renal disease, alcohol intake, smoking, cardiac disease, previous fractures. All patients underwent clinical examination, laboratory test (lipid profile, hepatic enzymes, leptin, hs-CRP) and lumbar spine BMD was measured by DEXA.

Results: In NAFLD group mean age was 49.5 years, BMI 32.5 ± 3 and WC 99 ± 5 cm, in second group mean age was 51.3 years, BMI 30.3 ± 3 and WC 97 ± 5, without statistic significance between the two groups. Leptin level was 8.7 ng/ml ± 1.2 in second group and 15.2 ng/ml ± 5.1 in NAFLD group, with significance statistic differences between the two groups, but values were still in normal range in both groups. BMD was lower in NAFLD women and osteoporosis in NAFLD group seemed to be associated a more severe liver disease. In NAFLD group the highest levels of serum leptin were found in moderate or severe steatosis with osteoporosis and we found a positive correlation with BMI and WC (p = 0.000 and p = 0.002). In the other group, leptin level had no significant differences in relationship with BMI, WC or decreased BMD.

hs-CRP had high level in NAFLD group and we found a significant independent association of hs-CRP with BMD scores in this group and no relationship in the other group, supporting the role of an inflammatory state which may accelerate loss of bone mass in patients with NAFLD.

Discussion/Conclusion: In our study, both hs-CRP and leptin were correlated with decreased BMD in NAFLD group, but high hs-CRP level was an independent significant factor for osteopenia/osteoporosis in NAFLD group.
Intestinal microflora in patients with non-alcoholic fatty liver disease

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The interest in non-alcoholic fatty liver disease (NAFLD) has risen due its high prevalence in elderly patients. NAFLD is frequently associated with obesity. It is characterized by liver pathology resulting from excessive accumulation of fat in hepatocytes. It normally occurs in 2 forms: steatosis or non-alcoholic steatohepatitis (NASH).

Introduction: We have monitored the prevalence of steatosis and NASH in patients with and without obesity and examined the intestinal microbial landscape in these patients.

Methods: A total of 60 patients were examined (37 women and 23 men) aged between 25 and 68 years. Alcoholic and viral causes of chronic liver disease were excluded. Complaints of patients included discomfort in the right subcostal area, bloating and weakness. NAFLD was diagnosed by abdominal ultrasonography, showing hepatomegaly and vascular changes. The laboratory analyses showed ALT/ST elevation up to 2–4 times as well as increased bilirubin, GGT, and lipid levels. Changes in the intestinal microflora were examined by bacterial cultures of feces.

Results: Overweight patients with steatosis and group of patients with obesity of 1–2 degrees had decreased number of lactobacilli as well as growth of clostridia and candida species. Patients with NASH had a reduced number of bifidobacteria and lactobacilli as well as growth of proteus species and staphylococci. Based on the BMI (body mass index) the patients were categorized into 4 groups: Group 1 – normal BMI – 14 people (control); Group 2 – overweight patients – 18 people; Group 3 – first degree obesity – 16 people; Group 4 – second degree obesity – 12 patients. Steatosis was found in 75% of patients in group 2, 80% in group 3, 81% in group 4. NASH was found in 10%, 13% and 18%, respectively. In controls only 5% of patients had steatosis. Overall, the study revealed a direct correlation between steatosis, NASH, and BMI.

Discussion/Conclusions: Obese patients often have NAFLD, predominantly as steatosis and impairment of the intestinal microflora, especially in patients with NASH. Therapeutic approaches to cure NAFLD include probiotic agents to to improve the intestinal microflora.
Hepatocellular carcinoma (HCC) characteristics in patients with chronic HBV-related liver disease

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**Introduction**: Chronic Hepatitis B Virus (HBV) infection is one of the leading causes of hepatocellular carcinoma (HCC) development in Turkey. We aimed to study the HCC characteristics developed in patients with HBV-related chronic liver disease.

**Methods**: Patients admitted to our outpatient clinic between January 2006–2014 and diagnosed as HCC were evaluated retrospectively. Patients who had chronic HBV-related liver disease and HCC were included to the study. The HCC characteristics in study group were determined.

**Results**: We evaluated 324 patients diagnosed with HCC and 188 (58%) of those had HBV-related chronic liver disease. In HBV group, 89 patients were under follow up and having HBV treatment properly. The mean follow up between the diagnosis of HBV-related chronic liver disease and HCC development or detection was 77.5 months. On the other hand, 72 patients were diagnosed with HBV-related chronic liver disease and HCC on the first admission. Remaining 27 patients had HBV as well as accompanying infections (HCV, HDV) or chronic ethanol usage. Portal vein thrombosis were detected in 40, hepatic encephalopathy were detected in 15 and distant metastases were detected in 19 of HBV-related HCC patients. The chemo-embolization and RF ablation were the most common treatment modality of HCC and the mean survival time was 8.6 months after HCC diagnosis.

**Discussion/Conclusion**: HBV is leading cause of HCC development in our country. Chronic HBV-related liver disease patients, even under the follow up has high ratio of HCC development. The mean duration between diagnosis of chronic HBV-related liver disease and development or detection of HCC was less than 7 years. The ratio of chronic HBV and HCC diagnosed on first admission was also high. HCC screening programs should be strictly applied in HBV patients.
Endocannabinoids in chronic alcoholic liver disease

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Introduction: Cannabinoid receptors CB1 and CB2 are implicated in the development of chronic liver diseases. However, the mechanisms by which the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) contribute to ongoing liver damage in alcoholic liver diseases (ALD) are incompletely defined.

Methods: Anandamide (AEA) and 2-arachidonoylglycerol (2-AG) were measured by gas chromatography and mass spectrometry (GC-MS) in plasma from healthy individuals and ALD patients. Gene expression was assessed by TaqMan PCR. In vivo, liver fibrosis was induced by combination of ethanol and CCL4 for 5 weeks in C57BL/6 mice, which were treated with inhibitors of fatty acid amid hydrolase (FAAH, URB937), monoacyl glycerol lipase (MAGL, JZL184) or vehicle control for 4 weeks. Liver damage was assessed by ALT, AST and GGT levels. Collagen content was measured by hydroxyproline determination and Sirius Red.

Results: AEA and 2AG plasma levels were significantly higher in patients with ALD, whereas FAAH and MAGL mRNA in liver biopsies were appr. 2- and 10-fold downregulated, respectively, compared to healthy controls. Statistical analysis revealed ALT, AST and alcohol levels as predictors of high AEA among alcoholic patients (p < 0.05). The active metabolite of ethanol – acetaldehyde (AA) slightly inhibited enzymatic activity of MAGL, reflected by a reduced amount of hydrolyzed 2AG. In peripheral blood mononuclear cells AA showed similar effect by reducing MAGL mRNA. In vivo, inhibition of FAAH and MAGL in alcohol-received mice did not change collagen content (hydroxyproline), but modified fibrosis- and inflammation-related gene expression.

Discussion/Conclusion: Chronic alcohol consumption may induce endocannabinoids AEA and 2AG levels via the blockage of endocannabinoid degradation enzymes activity what might result in concomitant modulation of hepatic inflammation and fibrogenesis.
Hepatic and extrahepatic autoimmune constellations

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Aim: We have studied, in patients with overlap syndrome (autoimmune hepatitis/primary biliary cirrhosis), the coexistence of certain autoimmune extrahepatic syndromes. The genetic or immunological pathogenesis underlying these associations has been studied on a large scale, but has so far failed to provide an adequate answer.

Methods: Clinical and biological extended investigations have been made on 7 patients with overlap syndrome in order to detect possible autoimmune extrahepatic syndromes. The diagnosis of these extrahepatic diseases was confirmed before, during and after diagnosing the hepatic autoimmune disease.

Results: Of the 7 female patients, aged 45–74, 4 had autoimmune extrahepatic syndromes. 3 patients had two autoimmune extrahepatic syndromes each, and 1 patient associated a single autoimmune disease. 1 female patient had psoriasis and psoriatic arthropathy, and another patient had autoimmune thyroid disease and hemolytic autoimmune anemia. Autoimmune thyroid disease and vitiligo were the autoimmune diseases associated with the overlap syndrome in the third female patient. Celiac disease was the concomitant autoimmune condition in another female patient.

Conclusions: Extrahepatic autoimmune conditions in patients with autoimmune hepatic diseases are relatively frequent. Autoimmune thyroid diseases are predominant among the patients under study. It is necessary to follow up the patients with hepatic autoimmune diseases and to detect potential autoimmune hepatic syndromes in order to prescribe adequate treatment and to monitor their evolution.
Normix alone vs. Normix + L-ornithine-L-aspartate for the treatment in patients with minimal hepatic encephalopathy

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Introduction: Minimal hepatic encephalopathy (MHE) represents a common complication present in well-compensated cirrhotic patients that impairs patients' daily functioning. L-ornithine-L-aspartate (LOLA) has been shown to be useful in improving blood ammonia in cirrhotic patients with MHE. This study evaluated the effects of LOLA treatment in patients with MHE.

Methods: This was a prospective case-control study. Thirty-seven patients with MHE were recruited to the study. They were assigned to two groups and received either 2 g LOLA twice a day + 1200 mg Normix (n = 18) or 1200 mg Normix alone (n = 19) for 90 days. The primary efficacy measures were changes in ammonia, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl-transpeptidase, albumin, alkaline phosphatase, prothrombin time, urea and bilirubin. Clinical and laboratory assessments, psychometric tests were performed for all patients at the baseline and at the end of the study.

Results: At the end of the study period, between the two groups, we observed a significant difference in ammonia (p < 0.001), aspartate aminotransferase (p < 0.001) and alanine aminotransferase (p < 0.001). No significant difference was observed in γ-glutamyl-transpeptidase, albumin, alkaline phosphatase, prothrombin time, urea and bilirubin. Psychometric tests results were significantly improved at the end of the study as compared to the baseline.

Discussion/Conclusion: This study shows that LOLA + Normix was superior to Normix alone for the treatment of MHE in cirrhotic patients and is associated with significant enhancement in the laboratory assessments.
Bone metabolism proteins (fetuin-A, osteoprotegerin and α-Klotho) in patients with alcoholic liver cirrhosis

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Introduction: One of the liver cirrhosis complications is hepatic osteodystrophy, which includes osteoporosis and more rarely osteomalacia. Fetuin-A, osteoprotegerin and α-Klotho protein regulate bone metabolism.

Aim: The aim of this study was to evaluate the concentrations of fetuin-A, osteoprotegerin and α-Klotho protein in patients with alcoholic cirrhosis in different stages of the disease. We sought to demonstrate that fetuin-A, osteoprotegerin and α-Klotho could be used as markers of the severity of cirrhosis.

Methods: Fifty patients with alcoholic liver cirrhosis treated in various hospitals of the Lublin region were randomly enrolled. The control group consisted of 18 healthy individuals without liver disease, who did not drink alcohol. Serum levels of fetuin-A, OPG and α-Klotho were measured by ELISA kits.

Results: The level of fetuin-A was significantly lower in patients with alcoholic liver cirrhosis compared to the control group. The level of osteoprotegerin was higher in patients with alcoholic liver cirrhosis than in controls whereas the level of α-Klotho was comparable in the cirrhosis and control groups. No statistically significant differences in concentrations of fetuin-A, OPG and Klotho protein were demonstrated according to type of liver cirrhosis. The study findings revealed a significant negative correlation between the level of α-Klotho protein and CRP in the group with alcoholic liver cirrhosis.

Discussion/Conclusion: The concentration of fetuin-A is lower whereas that of OPG is higher in the group with alcoholic liver cirrhosis as compared to the control group. Fetuin-A, osteoprotegerin and α-Klotho may be not a good indicator of liver cirrhosis severity. Fetuin-A and osteoprotegerin can be used in the diagnosis of liver cirrhosis.
Audit of the management of ascites in a large Scottish district general hospital

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Introduction: Symptomatic ascites frequently leads to admissions in our hospital. Scotland has one of the highest mortality rates from chronic liver disease (CLD) in Europe. To assess whether management of this frequent complication of CLD could be improved, we audited abdominal paracentesis: ascitic fluid should be sent for: cell count, culture, sensitives (blood culture bottles and universal container), protein, albumin and cytology (if indicated). We aimed to audit spontaneous bacterial peritonitis (SBP) treatment and prophylaxis. Further data collected: demographics, cause of ascites, consent documentation, site, aseptic technique and diuretic use.

Methods: Audit of patients undergoing abdominal paracentesis (diagnostic/therapeutic) and ascites management on a gastroenterology ward over one month. Data was collected using a clinical research form based on audit standards (British Society of Gastroenterology and local guidelines).

Results: Episodes of abdominal paracentesis: 23, 100% caused by cirrhosis (mean age 56). Seven SBP cases were identified and treated. Five ascitic samples were not sent to microbiology in blood culture bottles (all sent in universal containers). Some samples not sent for protein or albumin. Four samples met the criteria for cytology but were not sent. Two patients wrongly not prescribed SBP prophylaxis. Grade of ascites and site of paracentesis inadequately recorded (n = 4). Compliance with aseptic technique and diuretic guidelines: 100%.

Discussion/Conclusion: Potentially 276 cases of ascites are treated per year in our unit. Ascites is generally well managed but there is room for improvement. Inoculation of aspirate in blood culture bottles and criteria for SBP prophylaxis needs highlighting within the team. Cirrhosis is our leading cause of ascites and routine requests for cytology to investigate malignancy is currently not part of our protocol. Recommendations: poster for ward doctors working in gastroenterology and audit of antibiotic sensitives in our patient population.
HBV cccDNA form in serum samples and liver biopsy samples of chronically infected patients

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Introduction: The HBV genome exists in two different forms: covalently closed circular DNA (cccDNA) and a partially double stranded relaxed circular form (rcDNA). There have been some reports that free cccDNA that is normally found in the infected hepatocytes can occur in the serum as an early signal of liver damage. The aim of this study was to investigate the presence of cccDNA in serum and liver biopsy samples of chronically infected patients (CHB).

Methods: The study group consisted of 41 patients. Serum and liver biopsy samples were collected at the same time point for each patient. HBV DNA was extracted with the use of QIAamp DNA mini kit with changes (carrier DNA was added to the starting material). Next, rolling circle amplification (RCA) was done to amplify cccDNA. RCA products were then digested with SpeI enzyme that cuts only once in HBV genome. Digestion products were analyzed on a 1% agarose gel.

Results: HBV cccDNA was detected in 1 serum and in 25 liver biopsy samples. cccDNA positive serum sample was taken from the naïve patient with the liver biopsy stage and grade 1. HBV serological markers, viral load, hematological variables were not correlated with the presence of cccDNA in liver samples. This form was detected more often in patients with increased ALT level however this wasn’t statistically significant.

Discussion/Conclusion: In this study we demonstrated that cccDNA form may be found in serum samples of CHB patients. However, further investigations are needed to explain the correlation between the serum cccDNA presence and the response to antiviral therapy.
**Upper gastrointestinal bleeding: Non-variceal vs. variceal hemorrhage**

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**Introduction:** Despite advances in upper gastrointestinal bleeding (UGIB) management, it remains a serious problem in clinical practice, with high mortality in both variceal and non-variceal bleeding, unchanged in the past 5 years. Objective of the study was to appreciate the characteristics of acute upper gastrointestinal bleeding (AUGIB) due to esophageal varices compared with non-variceal acute bleeding.

**Methods:** We evaluated 637 patients admitted in Institute of Gastroenterology and Hepatology, St. Spiridon Emergency Hospital, Iasi for AUGIB during one year period (2014). A comparison between AUGIB from esophageal varices and non-variceal causes was made, regarding mortality rate, number of hospitalization days and number of blood transfusions needed.

**Results:** A total of 637 patients with confirmed AUGIB were admitted: M/F – 73.13%/26.07%, mean aged 56.5 ± 8.12 years. The mortality rate during the hospitalization was 14.75% and it was significantly higher in patients with AUGIB from variceal bleeding compared with non-variceal causes (22.38% vs. 11.04%, p = 0.004). Rebleeding occurred in 8.84% of patients. During hospitalization time, rebleeding rate was higher in AUGIB from variceal causes (15.69% vs. 5.50%, p = 0.004). Average hospitalization days was 7.82 ± 6.96 days, significantly higher in patients with AUGIB from esophageal varices compared with non-variceal causes (8.88 ± 5.80 days vs. 7.37 ± 7.36, p = 0.025). During hospitalization, 65.83% of patients needed blood transfusions (76.57% at patients with AUGIB by esophageal varices compare to 60.50% of patients with AUGIB with non-variceal causes) (p < 0.001). Average of blood units was 0.64 ± 0.48 units (0.79 ± 0.41 units in AUGIB by variceal causes vs. 0.58 ± 0.49 units in AUGIB due to non-variceal causes, p ≤ 0.001).

**Discussion/Conclusion:** Non-variceal bleeding is the most common cause of AUGIB. In hospital mortality, rate of rebleeding, blood transfusions and average hospitalization days are higher in patients with variceal hemorrhage.
Iron deposition in the liver in patients with non-alcoholic fatty liver disease, who had died from cardiovascular causes

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Introduction: Iron overload (IO) is considered as one of possible mechanisms of non-alcoholic fatty liver disease (NAFLD) progression and it is also a risk factor of the cardiovascular events. Our aim was to determine the frequency of morphological signs of hepatic IO, associated with metabolic syndrome (MS) and insulin resistance (DIOS/IR-HIO) in patients with NAFLD, who had died from cardiovascular events.

Methods: In our study were enrolled 80 cases patients with MS and histological findings of fatty liver in autopsy. Exclusion criteria were: pre-existing alcohol abuse and clinically diagnosed liver diseases. An evaluation of hepatic iron was done according to Deugnier Y et al. (1992).

Results: Among 80 cases of autopsy in 75 (93.8%) the accumulation of fat was more than the minimum criterion of NAFLD (> 5%). Hemosiderin deposits in the hepatic lobules have been found in 23 cases (28.8%; 95% CI: 18.8–38.8). The sum of the hepatocytic iron score (HIS) was graded from minimal value to mild. In one case value of HIS was high (26). Isolated parenchymal iron overload in 7 cases, mesenchymal iron overload in 5 (all of them with sinusoidal localization). Others cases were mixed, both mesenchymal and parenchymal iron deposits. Fibrosis was found in 60 cases (75.0%; 95% CI: 65.6–84.4), predominantly in portal area of lobules: F1 – in 29 cases (36.3%; 95% CI: 25.8–47.8), F2 – 10 (12.5%; 95% CI: 6.2–21.8), F3 – в 1 (1.3%; 95% CI: 0–6.8), F4 (cirrhosis) – 5 (6.3%; 95% CI: 2.1–14.0).

Discussion/Conclusion: Our study demonstrated high frequency of IR-HIO (28.8%, 18.8–38.8) and fibrosis (75.0%; 95% CI: 65.6–84.4), including 5 cases of cirrhosis among patients with pre-existing MS, who died from cardiovascular events without ante mortem diagnosed liver diseases.
Rational approach to the choice of the treatment of anthracycline-induced liver injury

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Ursodeoxycholic acid and ademethionine an effective combination for the treatment of anthracycline-induced liver injury.

The programmatic polychemotherapy (PCT) is the primary method of leukemia acute (LA) treatment. The success of the PCT of LA depends on the using of the adequate doses and intervals of administration of cytotoxic medications. Liver injuries on the background of PCT are the limiting factor for the PCT in its entirety. The application of anthracycline antibiotics is associated with the risk of development of the drug-induced liver injury (DILI).

The purpose is to improve the effectiveness of treatment options of DILI, induced anthracyclines.

We examined 54 LA patients (38 – LA myeloid, 16 – LA lymphoblastic), in which the dynamics of the PCT with doxorubicin during induction and consolidation of remission developed of DILI. All patients received ursodeoxycholic acid (UDCA) 20 mg/kg 60 days in combination with ademethionine 1200 mg/day jet i.v. 10 days of the transition to 1200 mg/day orally 50 days.

On the background of PCT increased activity of alkaline phosphatase (ALP) in 2.7 times (209 ± 22.9 IU/l vs. 77.4 ± 10.8 IU/l; p < 0.05), gamma-glutamyl transpeptidase (GGT) – in 4.3 times (94.5 ± 10.39 IU/l vs. 21.9 ± 2.42 IU/l; p < 0.05), bilirubin – in 4.8 times (58.1 ± 8.71 IU/l vs. 12.1 ± 1.33 IU/l; p < 0.05), ALT – in 2.1 time (54.8 ± 4.9 IU/l vs. 26.1 ± 3.65 IU/l; p < 0.05), AST – in 2.9 times (57.1 ± 6.86 IU/l vs. 19.7 ± 2.36 IU/l; p < 0.05) was found relative to healthy. Under this condition in 2.5 times decreased of argynase blood activity and in 1.9 times increased the concentration of molecules of average weight (MAW).

After 30 days of starting treatment decreased the activity of ALT, AST in 1.9 and 2.1 times respectively, ALP, GGT, total bilirubin in 1.4, 2.3, 2.8 times respectively. At the 56th–60th days of treatment were normalized indices of cytolytic and cholestatic syndromes in 44 (81.5%) patients. Established correlation between the reduction of clinical symptoms of cholestasis and ALP (r = +0.76), GGT (r = +0.85) activity. Increased in 1.7 times of the argynase activity on the background of decreased in 1.5 times the MAW level, reflecting the increase of the detoxication processes. This allows to prescribing the PCT in full compliance with the mode of administration of cytostatics.

Thus, the combination of UDCA and ademethionine in the high doses is an optimal approach to treatment and prevention options of DILI, induced by anthracyclines.
Relationship between immunoglobulins superfamily molecules and histologic changes in non-alcoholic fatty liver disease

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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), platelet-endothelial cell adhesion molecule-1 (PECAM-1) plasma levels and histological changes in non-alcoholic fatty liver disease (NAFLD).

Methods: 40 patients with histologically proven NAFLD were examined. The control group included 60 healthy volunteers. Blood concentration of ICAM-1, VCAM-1, PECAM-1 were carried out by means of ELISA. Diagnostic value of parameters defined their sensitivity (Se), specificity (Sp), positive (PPV) and negative predictive value (NPV), accuracy (Ac) which expressed in percentage. Statistically significant values were considered for \( p < 0.05 \).

Results: Plasma levels of ICAM-1 were higher and plasma levels of PECAM-1 were lower in severe liver steatosis than in mild steatosis. Levels of ICAM-1 and VCAM-1 in blood were higher in high histological activity (NAS-II \( \geq 5 \)) than in minimal hepatic morphologic changes (NAS-II \( \leq 5 \)). Parameters of ICAM-1 \( \geq 774 \) ng/ml were associated with increased risk of NAS-II \( \geq 5 \) in NAFLD (OR = 6.8; 95% CI: 1.6–28.9). Se, Sp, PPV, NPV and Ac of ICAM-1 \( \geq 774 \) ng/ml for detection of NAS-II \( \geq 5 \) were 82.6, 58.8, 73.1, 71.4, 72.5, accordingly. Levels of all immunoglobulins superfamily molecules increased with intensifying of hepatic fibrotic changes and were maximal in fibrosis 3. Patients with ICAM-1 \( \geq 1445 \) ng/m (OR = 10.4; 95% CI: 1.9–56.0), VCAM-1 \( \geq 7250 \) ng/ml (OR = 74.7; 95% CI: 6.8–819.5) and PECAM-1 \( \geq 74 \) ng/ml (OR = 8.6; 95% CI: 1.5–49.4) characterized by higher risk of severe fibrosis. Se, Sp, PPV, NPV and Ac of ICAM-1 \( \geq 1445 \) ng/m, VCAM-1 \( \geq 7250 \) ng/ml and PECAM-1 \( \geq 74 \) ng/ml for detection of severe fibrosis were 66.7, 83.9, 54.5, 89.7, 80.0; 88.9, 90.3, 72.7, 96.6, 90.0 and 77.8, 71.0, 43.8, 91.7, 72.5 accordingly.

Conclusion: The relationship of immunoglobulins superfamily molecules and histologic changes in liver testifies to their involvement into processes of inflammation and fibrogenesis in NAFLD.
Therapeutic efficacy and side effects of peroxisome proliferator-activated receptor-gamma agonists for non-alcoholic steatohepatitis-associated metabolic disorders depend on genetic polymorphism

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Introduction: Peroxisome proliferator-activated receptor-gamma – NR1C3 (PPARG) plays an important role in various biological processes including lipid and glucose metabolism. PPARG agonists have been widely used in treatment of different metabolic disorders and non-alcoholic steatohepatitis (NASH) decreasing steatosis, inflammation, and fibrosis. However, several studies indicate significant side effects of PPARG agonists leading to partial removal from the market. The aim of the study was to clarify the perspectives for individualized therapy with thiazolidinediones.

Methods: 249 patients with hypertension, dyslipidemia, metabolic syndrome participated in the study. Among them 50 patients with NASH were selected to form study group. PPARG agonist pioglitazone administered 30 mg daily during 50–51 weeks. Genetic polymorphism (Pro12, Pro12Ala, Ala12Ala) of PPARG gene determined by PCR. Genotypes were: Pro12 (n = 32, 64.0%); Pro12Ala (n = 14, 28.0%); Ala12 (n = 4, 8.0%) Liver biopsies performed prior and after study.

Results: Pioglitazone improved glycemic control and glucose tolerance (p < 0.001), normalized liver aminotransferase levels as it decreased AST by 42.1 ± 1.17% p = 0.014; ALT by 57.5 ± 1.37%, p < 0.001; decreased hepatic fat by 54.6 ± 2.09%, p < 0.001; and increased hepatic insulin sensitivity by 48.5 ± 1.63% p = 0.006. Administration of pioglitazone caused improvement in histologic findings with regard to steatosis, ballooning necrosis, and inflammation. In 4 (8%) Ala12 patients no reliable changes were observed, except glycemic control and glucose tolerance. Reduction in fibrosis did not change significantly. Statistically insignificant weight gain and mild lower-extremity edema developed in 2 subjects with Pro12Ala genotype, no other side effects were observed.

Discussion/Conclusion: Administration of thiazolidinediones leads to metabolic and histologic improvement in most patients with NASH while not influencing liver fibrosis. However, individual response may be affected by Pro12Ala polymorphism of PPARG gene. This study shows that carriers of Ala genotype whilst comparatively rare among NASH patients are much less sensitive to PPARG agonists' therapy.
Metabolic profile, inflammation and endothelium in obese patients with hepatic steatosis and hypertension depend on genetic polymorphisms of candidate genes

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Introduction: The main cause of hepatic steatosis (HS) is non-alcoholic fatty liver disease representing the hepatic component of the metabolic syndrome. The risk factors for HS are clearly established, the genetic basis of HS is largely unknown. The aim of study was to investigate the possible role of PPAR-γ2 gene Pro12Ala polymorphism and ACE gene I/D polymorphism on metabolic profile and cytokines in obese patients with HS and AH.

Methods: Study included 154 obese HS patients with AH (87 male, 67 female, age 50.06 ± 7.34). HS duration – 1–5 years, AH – 3–21 years. Metabolic disorders analyzed with body mass index (BMI), glycemia, immunoreactive insulin (IRI), total cholesterol (TC), low and high density cholesterol (LDL-C, HDL-C), triglycerides (TG), C-peptide (CP) levels and HOMA-IR index. TNF-α and leptin plasma levels were assessed by ELISA. Genes' polymorphism of PPAR-γ2 (Pro12Ala), and ACE (I/D) alone or in combination were studied with PCR.

Results: Differences of BMI, plasma glucose, IRI, HOMA-IR, CP and leptin are independent from ACE gene genotypes (p > 0.05). Pro-allele carriers of PPAR-γ2 gene have higher BMI than AlaAla carriers (32.7 ± 2.1 and 27.9 ± 1.1 kg/m² vs. 25.6 ± 0.8 kg/m², accordingly (p < 0.05), leptin level – 14.3 ± 0.41 and 8.6 ± 0.25 ng/ml vs. 3.7 ± 0.22 ng/ml, (p < 0.001), glucose level – to 10.2% and 10.9% accordingly (p < 0.05); CP level was higher in ProPro-genotype than in Ala-allele carriers to 15.7% (p < 0.05). Risk group of dyslipidemia are ProPro-genotype carriers of PPAR-γ2 gene with higher level of TC, TG and LDL-C to 16.4%, 17.3% and 27.9% (p < 0.05) and lower level of HDL-C in women to 25.6% (p = 0.038). Lipids levels are independent on ACE I/D polymorphism. Baseline TNF-α plasma levels did not significantly deviate between genotypes of PPAR-γ2 gene, but D-allele carriers (I/D+DD) of ACE gene had higher baseline TNF-α plasma levels (91.61 and 109.11 pg/ml, accordingly p < 0.01).

Discussion/Conclusion: Metabolic disorders have strong association with PPAR-γ2 Pro-allele (carbohydrates) and ProPro-genotype (lipids) In HS hypertensive patients. Presence of D-allele of ACE gene associates with reliably higher level of TNF-α plasma levels.
Inhibition of endotoxin-lipopolysaccharide alleviates its pro-carcinogenic effect

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Introduction: Multiple clinical and experimental data support the role of inflammation as a key performer in development of hepatocellular carcinoma (HCC). Previous studies showed that endotoxin – lipopolysaccharide (LPS) is both angiogenic and immunosuppressing, thus promoting metastatic growth (MG). However, there is insufficient data regarding LPS inhibition as a possible therapeutic and prophylactic option. We hypothesized that anti-LPS therapy may have anticarcinogenic effect in part decreasing MG.

Methods: Murine model including 3 groups (25 each) of adolescent mice was used. Metastatic process was modeled by i/v injection of 200 µl spontaneously metastasizing mammary adenocarcinoma cell culture suspension. Control group (CG) animals received 200 µl sterile saline intraperitoneal (i.p.), experimental group 1 (EG1) – 200 µl suspension of 10 µg LPS per mouse, experimental group 2 (EG2) – same plus 20 µg at 0.5 ml anti-LPS monoclonal antibodies. MG evaluated histochemically within lung metastases.

Results: EG1 showed significantly higher (p < 0.001) MG compared with the control. MG was characterized by 61.2% higher mitotic index (MI) in the EG1 and 42.3% lower apoptotic index (AI). MI/AI ratio in the EG1 was 3.2 times higher (p < 0.001) than control. LPS injection resulted in reliably (p = 0.002) higher levels of serum VEGF than in control with strong positive correlation (r = 0.971) between circulating VEGF and LPS levels. Addition of anti-LPS monoclonal antibodies significantly decreased MG, MI and increased AI with respective change of MI/AI ratio. VEGF becomes insignificantly higher than in control whilst LPS concentration decreased reliably (p = 0.014).

Discussion/Conclusion: Despite the well-established role of LPS as pro-inflammatory, pro-proliferator and pro-neovascularization factor, its role in carcinogenesis remains under evaluated. Our findings show that targeted anti-LPS therapy may impact tumor growth due to prevention of neovascularization and inflammation as well as inducing apoptosis.
Pro12Pro-genotype of PPAR-γ2 gene significantly increases the risk of non-alcoholic fatty liver disease

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Introduction: Non-alcoholic fatty liver disease (NAFLD) associates with abdominal obesity (AO) and includes hepatic steatosis (HS) and steatohepatitis (NASH); in 2–12% it can progress to fibrosis and cirrhosis. NASH prevalence in general population is about 10–20%. Nowadays, genetic and molecular mechanisms of NASH/HS are still unclear and need further investigations. The aim is to analyze the association of NASH/HS in obese patients with genetic polymorphisms of angiotensine-convertine enzyme (ACE, I/D) and Peroxisome Proliferative Activated Receptor-γ2 (PPAR-γ2, Pro12Ala).

Methods: Study included 110 patients with AO I–III grade severity: 80 female, 30 male, mean age 52.9 ± 4.25; 17.3% patients with HS, 82.7% with NASH. Alleles of genes ACE (I/D) and PPAR-γ2 (Pro12Ala) were studied with PCR method. AO signs determined according to ATP III, NCEP criteria. Control group included 50 AO patients without signs of NAFLD.

Results: Analyzed genes genotypes’ distribution confirmed the higher probability of NAFLD onset in D-allele (ACE) and Pro-allele (PPAR-γ2) carriers of moderate-severe AO patients vs. II-genotype carriers (73.9% and 80.0% vs. 56.0%; p < 0.000) and Ala12Ala genotype (100% and 78.4% vs. 56.9%; p < 0.000). The mutant D-allele and insertion-allele of ACE gene ratio in study and control group didn’t differ reliably (p > 0.05): for I-allele 46.4% vs. 54%, for D-allele 53.6% vs. 46% (p > 0.05). However, frequency of Pro12-genotype in NAFLD patients was 1.3 times higher (OR = 1.86, 95% CI: 1.10–3.43; p = 0.045) and 12Ala-genotype –2.7 times less (OR = 0.34, 95% CI: 0.13–0.84; p = 0.023) than in control group subjects.

Discussion/Conclusion: Pro12Pro-genotype of PPAR-γ2 gene significantly increases the risk of HS/NASH in obese patients; 12Ala-genotype can play protective role. I/D polymorphism of ACE gene do not associate with NASH/HS in subjects with metabolic syndrome.
Is there a link between the HBV-DNA viral load value and liver stiffness in inactive HBs carriers?

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Introduction: Chronic hepatitis B virus (HBV) infection is important public health problem (approximately 350,000,000 persons are estimated to be HBV infected). In the case of inactive carriers it is possible that viral replication restarts, with the evolution to chronic hepatitis. Nowadays, in these patients liver injury severity can be assessed by non-invasive means such as transient elastography (TE) or biological assay (e.g. FibroTest-ActiTest).

The aims of the study were to evaluate whether liver stiffness (LS) is influenced by viral load in inactive HBs Ag carriers and to evaluate LS values in these patients compared to normal subjects.

Methods: We studied 69 inactive HBs carriers (22 women – 38% and 47 men – 62%, mean age 43.4 ± 14.2 years), defined using the following criteria: persistent normal AST and ALT serum levels for a 6-month period, HBsAg-positive, HBeAg-negative and HBV-DNA load < 2000 IU/ml (< 10,000 copies/ml). None of the patients was HCV, HDV or HIV coinfected. The control group included 50 healthy subjects.

Results: In the inactive HBs carriers group the average liver stiffness measurements (LSM) was 5.62 ± 2.1 kPa vs. 4.9 ± 1.2 kPa in healthy subjects (p < 0.001). Patients with undetectable viral load presented an average LSM of 4.9 ± 1.9 kPa, significantly lower than in patients with detectable DNA (but < 2000 IU/ml) 6.6 ± 2.2 kPa), (p < 0.001 – ES). Furthermore, in 7 cases (10.1%) LSM were higher than 7 kPa (including these patients as having significant fibrosis – F ≥ 2).

Discussion/Conclusion: In our group LSM were significantly high both in inactive HBs carriers versus healthy subjects (p < 0.001– ES), as well as for the ones with viral load < 2000 IU/ml versus non-detectable HBV carriers (p < 0.001) suggesting that low viral load can induce fibrosis. On the other hand, LS values increased with higher viral load but not significantly (p = 0.435). Furthermore, in the inactive HBs carriers with LSM higher than 7 kPa the morphologic evaluation of liver fibrosis is worthwhile in these cases.
The effect of bioflavonoids on liver monooxygenase system in rats with CCl4-induced liver damage

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Introduction: Reactive oxygen species are important in the pathogenesis of several chronic hepatopathies. Chronic administration of carbon tetrachloride (CCl4) is widely used as an animal model of liver injury induced by reactive radicals. Bioflavonoids are known to have antioxidative effect.

Aim of study: to follow the effect of Pycnogenol®, mixture of polyphenols, mainly phenolic acids and procyanidines, on cytochrome P-450 enzyme activities in liver of animals after CCl4-induced liver damage.

Methods: Male Wistar rats were divided into four groups: control group – animals without any treatment, PYC – animals received Pycnogenol (50 mg/kg body weight) daily during 10 weeks, CCl4 – animals received CCl4 two times per week during 10 weeks, CCl4 + PYC – animals received CCl4 two times per week and 50 mg of pycnogenol/kg body weight daily during 10 weeks. In sera of experimental animals we determined the activities of ALT, AST, cholinesterase and levels of triacylglycerols. In liver tissue we determined the enzymatic activities of cytochrome P-450 as aniline hydroxylase, ethoxycoumarin O-deethylase and p-nitroanisol O-demethylase.

Results: The activities of ALT and AST in sera were significantly increased in animals with CCl4-induced liver damage. The administration of Pycnogenol® with CCl4 showed significantly higher activities of both enzymes. The administration of Pycnogenol® alone showed moderate induction of cytochrome P-450 in comparison to controls (approx. 20–25%). The enzymatic activities of cytochrome P-450 were significantly decreased in liver of CCl4-animals. The results in group CCl4+PYC were worse than that in group with CCl4 alone.

Discussion/Conclusion: The results of our study showed no hepatoprotective effect of Pycnogenol® on CCl4-induced liver damage. One of the possible explanation of worse results in group CCl4+PYC is the induction of cytochrome P-450 by Pycnogenol®. Higher activities of cytochrome P-450 probably produced higher amount of reactive radicals from carbon tetrachloride which was followed by more significant damage of liver tissue.
Effect of polyphenolic extract on liver steatosis and fibrosis after CCl4-induced liver damage

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Introduction: There is no doubt that reactive oxygen species (ROS) play an important role in the pathogenesis of some chronic hepatopathies, particularly in cases of alcoholic and toxic liver diseases. Chronic administration of carbon tetrachloride (CCl4) is widely used as an animal model of liver injury induced by ROS. Bioflavonoids are known to have antioxidant effect. Pycnogenol® is a concentrate of polyphenols, mainly phenolic acids and procyanidins.

The aim of study: to follow the effect of Pycnogenol®, French maritime pine (Pinus maritime) bark extract on fibrosis and steatosis in liver of animals after CCl4-induced liver damage.

Methods: We have four experimental groups: control group – animals without any treatment, PYC – animals received pycnogenol (50 mg/kg body weight) daily during 10 weeks, CCl4 – animals received CCl4 (1 ml 50% CCl4/kg body weight) two times per week during 10 weeks, CCl4+PYC – animals received CCl4 two times per week and 50 mg of pycnogenol/kg body weight daily during 10 weeks. Liver steatosis and fibrosis were determined through quantitative histomorphometric analysis. Triacylglycerols were determined in liver tissue spectrophotometrically.

Results: There were significantly increased steatosis and fibrosis determined through histomorphometry in liver tissue of animals with CCl4-induced liver damage. There was also significantly increased content of triacylglycerols in liver of CCl4-group. The results showed statistically significant positive correlation between histomorphometrically determined grade of steatosis and content of triacylglycerols determined spectrophotometrically. But the pathological changes were markedly worse in group with CCl4+PYC than in group with CCl4 alone.

Discussion/Conclusion: Our results didn’t show any hepatoprotective effect of Pycnogenol® in animals with CCl4-induced liver damage. The administration of Pycnogenol® paradoxically aggravate steatosis and fibrosis in liver of experimental animals.
Liver disease progression in the German HCV(1b)-contaminated anti-D cohort after more than three decades

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Introduction: To date, there are only a few long-term studies with a known date of Hepatitis C Virus infection, which include all infected people without bias. According to the initial reports it was assumed that after 20 years, 30% of patients would have developed cirrhosis of the liver. However, these unfavorable results were found in liver centers where only patients with progressive liver damages were treated. After the anti-HCV treatment has become more effective and the interferon-related side effects have ceased to exist, the question now is whether even in a previous relatively benign natural course of HCV(1b) infection, the prognosis would be worse with increasing age and therefore the therapy should be strongly recommended now.

Aims and methods: Between August 1978 and March 1979 it had come to the administration of 14 hepatitis C-contaminated anti-D immunoglobulin batches to 2867 East German women to prevent Rh isoimmunization. This HCV cohort is of particular interest because there are only a few international events with known HCV infection point of time that would allow precise statements about the spontaneous course. Our data were collected in 15 study centers in East Germany since the beginning and repeatedly published: After 25 years, the cirrhosis rate was only 0.5%. The Leipzig anti-D-cohort as part of the total cohort includes 356 women, of whom now 181 were followed up after 35 years.

Results: After 35 years, 85% of the 181 women in the HCV ELISA were positive. 33% were viremic (HCV-PCR-positive). Only 11 (8.3%) of viremic women had liver cirrhosis, 7 (5.3%) suffered from advanced fibrosis. In the last 15 years a continuous but slow rise of advanced fibrosis score was observed. Up to now no HCC has been diagnosed. Since 1978 6 HCV RNA-positive women of the Leipzig cohort died (1 HCV-related; 5 by extrahepatic causes); 8 women died after spontaneous viral clearance (negative HCV-PCR) as a result of cardiovascular, oncological and other diseases. Overweight and obesity accelerate disease progression to advanced liver fibrosis and end-stage liver cirrhosis.

Conclusion: Young women without comorbidity eliminate HCV(1b) infection spontaneously in approximately half of the infected cases. After 35 years, a continuous low progression with regard to final states such as cirrhosis, HCC or death could be confirmed in this cohort. Patients with self-limited HCV infection or SVR after antiviral treatment were protected from progressive liver disease and showed the best clinical long-term outcome. That means that in the group with an even longer life expectancy and despite the previous benign course the IFN-free HCV therapy should be strongly recommended too.
Long-term follow-up of AIH children who completed at least 6 months course of budesonide and azathioprine therapy

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Introduction: Budesonide with azathioprine was tested in patients with AIH between 2003 and 2009 (BUC-38-AIH). Before budesonide formulation was approved for AIH therapy patients who had completed budesonide regimen within clinical trial continued further standard of care prednisone and azathioprine therapy. The aim of this study is to present the data of patients switched from budesonide to standard of care treatment.

Methods: This is retrospective analysis of 15 patients (M – 3, F – 12) with AIH diagnosed at the age 7–16 (mean ± SD 11.2 ± 2.8) years who participated in BUC-38-AIH study. 6 patients received budesonide and azathioprine as the initial AIH treatment and 9 subjects were switched to budesonide and azathioprine from previous standard of care immunosuppressive therapy due to AIH exacerbation. Within BUC-38-AIH protocol patients received 6–12 months course of budesonide and azathioprine therapy. After study completion patients continued standard of care AIH treatment for 1.5–6 years (3.5 ± 1.7) until they reached 18–19 years of age and were transferred to adult hepatology clinics. Liver function tests, IgG, gamma-globulin, liver biopsy results, treatment and BMI at the final pediatric visit were analyzed.

Results: Laboratory results elevated at the beginning of budesonide trial were markedly reduced at the end of budesonide treatment and remained stable at the final pediatric visit respectively: ALT 395 ± 387; 61 ± 99 and 49 ± 44 U/l; gamma-globulin 24.6 ± 6.7; 16.1 ± 2.0 and 16.9 ± 6.0 g/l and IgG: 2388 ± 715; 1606 ± 265 and 1642 ± 330 mg/dl. Grading of inflammation in liver biopsy improved from 2.5 ± 0.92 before budesonide treatment to 0.86 ± 0.7 at the end of pediatric observation and staging respectively from 2.0 ± 0.85 to 1.3 ± 1.0.

At the final visit at pediatric site 7 patients continued steroids and azathioprine, 6 patients received azathioprine monotherapy and 2 patients were off medication (one due to full and long term AIH remission and one due to pregnancy). BMI at the final pediatric visit ranged from 17.7 to 33.3 kg/m² (22.5 ± 4.2).

Discussion/Conclusion: Patients who completed budesonide therapy remained stable until the end of observation in pediatric site.
Surgery in post-hepatitis liver carcinoma

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The aim: To optimize results of liver carcinoma treatment after viral hepatitis.

Materials: We observed the treatment results of 148 patients with post-hepatitic liver carcinomas. The main methods used to verify the diagnosis were computed tomography, ultrasonography, puncture biopsy with following morphological study and definition of viral hepatitis markers. We determined during anamnesis that 93 (62.8%) patients were suffering from HVC and 55 (37.1%) from HVB. T1N0M0 stage was observed in 13 (7.3%) patients, T2N0M0 in 49 (33.8%), T2N1M0 in 46 (31.6%), and T3N1M0 in 50 (34.5%). The tumor was localized in the right side of liver in 77 (53.7%) patients, in the left side in 56 (38.2%) patients and in both sides (bilobar) in 13 (8.0%) patients. Hepatocellular carcinoma was established in 79 (55.9%) patients, cholangiocellular carcinoma in 41 (27.9%), malignant hemangiothelioma in 19 (12.5%), and hemangiopericytoma in 7 (3.7%). Right-side hemihepatectomy was performed in 49 (34.6%) patients, left-side hemihepatectomy in 37 (25.7%), trisegmentectomy in 26 (17.6%), bisegmentectomy in 15 (9.5%), atypical liver segment resection in 7 (4.4%), and paramedian bilobectomy in 12 (8.0%).

Results: Following analysis of the obtained results, complications, divided into local and total complications, were observed in 24 (16.2%) patients at an early post-operative period. 13 (8.8%) patients developed liver insufficiency followed by encephalopathy and renal insufficiency, and 11 (7.4%) developed post-operative right-side pleuropneumonia. The most commonly observed local complications were biliousness in 7 (4.2%) patients and bleeding in 5 (3.0%) patients. General complications most common for extensive resection of liver following hemihepatectomy or paramedian bilobectomy were observed in 10 (10.2%) patients. Development of biliousness and bleeding had no correlation with the volume of surgery. 12 (8.1%) patients died during surgery, 7 (4.7%) of which due to acute hepatorenal insufficiency with the development of heavy encephalopathy, 4 (2.7%) of which due to bilious peritonitis and 1 (0.8%) of which due to bleeding in the liver.

The remote results were tracked in 109 patients. One-year mortality existed in 18 (16.5%) patients, corresponding to a 1-year survival rate of 91 (83.5%). A three-year survival rate was established in 69 (63.3%) patients, and five-year in 43 (39.4%) patients. A study of the correlations showed that average life expectancy (ALE) depended on the type of surgery and the most positive factors noted after hemihepatectomy and stood at 47.1 + 1.0 months. 4 patients experienced a relapse of the disease, 3 (2.7%) of which after tri- and bisegmentectomies and 1 (0.7%) after a segmentectomy.
Chemoembolization and endoarterial chemotherapy in hepatic carcinoma

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The aim: To determine the results of chemoembolization (ChE) and endoarterial chemotherapy (EChT) in primary hepatic cancer (PHC).

Materials: The treatment results of 108 patients with PHC were analyzed. T3N0-1M0 stage of PHC was established in 37 (34.2%) patients, T4N0-1M0 in 41 (37.9%) patients and T4N0-1M1 in 30 (27.7%) patients. The tumor was localized in one part of liver in 42 (38.9%) patients and in both parts in 66 (61.1%) patients. Hepatocellular carcinoma (HCC) was determined in 53 (49.1%) patients, cholangiocellular carcinoma (CCC) in 39 (36.1%), and hepatic hemangiendothelioma (HHE) in 16 (14.8%). ChE of the hepatic artery was performed on 47 (43.5%) patients using the Seldinger technique with 60–80 mg of doxorubicin and a jodolypol + metallic spiral. EChT was performed on 61 (56.5%) patients for 120 hours using the FAC combination. The results were based on 4 criteria.

Results: Chemotoxicity after ChE was degree 0 in 23.4% of patients, degree 1 in 51.0%, and degree 2 in 25.5%. Following EChT, toxicity was degree 0 in 45.9% of patients, degree 1 in 37.7% and degree 2 in 16.4%. Partial regression of the tumor size was observed in 55.3% of patients and stabilization in 38.3%, while progression was established in 6.4% of patients. The regression was observed in all patients with HHE and in 10 out of 23 patients with HCC. The toxicity results after EChT were better than after ChE, but partial regression was increased following EChT in comparison to ChE.

We performed a liver puncture biopsy 3–4 weeks after treatment on 31 (65.9%) patients following ChE and on 37 (60.6%) patients following EChT. The first stage of pathomorphosis was observed in 13 (27.6%) and 14 (37.8%) patients respectively. The second stage was observed in 15 (31.9%) patients following ChE and in 19 (51.3%) following EChT.

Analysis has therefore shown that ChE is the method of choice in the treatment of HHE. ChE and EChT are more effective in the treatment of PHC. After treatment we observed high degrees of pathomorphosis in HCC and HHE.
Doppler flow study for the assessment of the liver hyperemia

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Introduction: Liver congestion impairs liver function and may cause liver damage: hepatomegaly, abnormal hepatic tests, ischemic hepatitis and finally cirrhosis. Clinical symptoms of hepatic hyperemia – soft liver edge, smooth surface, pulsation are not always present. Laboratory tests are not optimal for assessment of liver congestion. Among numerous imaging methods, sonography is the most useful in clinical practice (non-invasive, low cost, commonly available). The two-dimensional USG presentation is useful for assessment of liver hyperemia (hepatomegaly, veins dilatation, decrease of the respiratory movements of the vena cava inferior, liquid inside visceral cavities, and others). The pulsed Doppler flow pattern for grade of the liver hyperemia has not been well determined.

Patients and methods: 35 patients suffering from cardiac failure (III–IV NYHA classification) with chronic insufficiency of tricuspid valve were examined by Doppler method – color and pulsed Doppler. We examined portal flow, middle hepatic vein flow and hepatic artery flow. All patients were observed clinically. Results of Doppler examination were compared to two-dimensional USG presentation and to clinical observation – physical examinations, period of disease, laboratory tests, cardiac sonography, X-ray examination. Others liver diseases were excluded. We compared the results of Doppler flow analysis to a group of 50 patients without right cardiac pathology.

Results: The abnormal hepatic vessels flow was diagnosed in 30 patients. There were: different degree of the pulsatility spectral portal flow – below zero line (biphasic) in advanced cases, different degree deformation of hepatic veins flow – biphasic flow. The arterial flow was normal.

Comments: The presence of the hepatic veins flow abnormality, reflexes abnormal liver – heart relations come across in advanced cardio-hepatic insufficiency. Biphasic flow in hepatic veins is one of the symptoms of advanced tricuspid valve insufficiency. The Doppler pulsatility of portal flow is associated with right atrial pressure and with advanced left ventricle insufficiency but is not typical for liver hyperemia on its own. The relationship between shapes of portal spectrum and veins spectrum deformity has been not established.

Conclusions:
1. Doppler assessment of hepatic veins flow and portal flow are important factors for examination of the liver hyperemia.
2. Hepatic veins flow deformity and portal pulsatility flow analysis allows to assess the grade liver hyperemia by Doppler method
3. Doppler symptoms of the advanced liver congestion are: biphasic hepatic veins flow and increased pulsatility portal flow.
4. The relationship between hepatic veins Doppler flow deformity, and two-dimensional USG abnormality and clinical hepatic changes are not clear.
ITU escalation and renal replacement therapy in decompensated liver disease – Utility or futility

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Introduction: Liver-related mortality continues to increase in the UK with alcohol remaining the leading cause. A recent NCEPOD report highlighted deficiencies in the acute care received by patients with decompensated ALD, including early management and access to specialist review and ITU care. In our institution, a large DGH, we have a dedicated HDU/ITU and 2 hepatologists. We sought to assess outcomes and predictors of survival of patients admitted to ITU with decompensated CLD and utility of mechanical ventilation (MV) and renal replacement therapy (RRT).

Methods: We interrogated a prospective ITU-admissions database and identified 64 patients with decompensated CLD of any aetiology admitted between 2008 and 2013. We conducted a case note analysis collecting data on demographics, aetiology of CLD, cause for decompensation, Child’s and MELD scores, interventions received and 30-day and 1-year mortality. We compared outcome to previous study between 2003–2007.

Results: Of 64 patients, 42 (66%) were male. 55 (86%) had ALD. Mean age was 47.7 for ALD and 50.8 for non-ALD. The most common precipitant was UGI bleed (27%), sepsis (20%) and alcoholic hepatitis (17%). AKI was present in 32 (50%; 55% ALD vs. 22% non-ALD; p < 0.05). The Child's score was A in 4 (6%), B in 9 (14%) and C in 42 (80%). The mean MELD score was higher in ALD (27) vs. non-ALD patients (22). The mean creatinine and bilirubin were both higher in ALD vs. non-ALD (51 vs. 109 and 184 vs. 84, respectively). 29/55 (53%) patients with ALD had prior contact with hepatology services vs. 7/9 (79%) for non-ALD. 28 patients (44%) were ventilated and 10 (16%) received RRT (all ALD patients).

The 30-day mortality was 58% for ALD and 66% for non-ALD with 1-year mortalities of 71% and 77%. Overall, survival to hospital discharge was 20/64 (31%).

The best predictor of survival was escalation to ITU within 48 hours 17/24 (71%) vs. 7/40 (17.5%) (p-value < 0.05). ALD patients > 60 did not survive. Prognosis was better if previously under hepatology service. Receiving either MV or RRT were not predictive of a worse prognosis. As expected, higher MELD score also predicted poorer outcome.

Overall survival of ALD patients of 40% over this study period is favourable compared the previous study period (29%). There was an increase in the number of admissions from 35 to 55 patients over the same period.

Discussion/Conclusion: Outcomes for patients with decompensated CLD including ALD are improving and ITU escalation should be offered early to all appropriate patients. Ventilation or RRT should be considered as not always predictive of poor outcome. The best chance for survival was in patients escalated within 48 hours and those who had been under the care of hepatology prior to presentation.
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Highlights from Hepatology 2015: From Chronic Hepatitis to Hepatocellular Carcinoma

October 14 – 15, 2015
Konzerthaus Freiburg
Freiburg, Germany